U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

WORKSHOP ON UNDER-RECOGNIZED CO-OCCURRING

CONDITIONS IN ASD

Tuesday, September 23, 2014

The Interagency Autism Coordinating Committee (IACC) convened a science workshop on Under-Recognized Co-Occurring Conditions in ASD in Bethesda, Maryland, at the National Institutes of Health, 35 Convent Drive, Building 35, Room 620, from 9:03 a.m., until 5:00p.m., Thomas R. Insel, *Chair*, presiding.

PARTICIPANTS:

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

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

ANSHU BATRA, M.D., Our Special Kids

JOSIE BRIGGS, M.D., National Center for Complementary and Alternative Medicine (NCCAM)

SALLY BURTON-HOYLE, Ed.D., Eastern Michigan University

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

JUDITH COOPER, Ph.D., National Institute on Deafness and Other Communication Disorders (NIDCD) (representing James Battey, M.D.)

PARTICIPANTS Continued:

JOSE CORDERO, M.D., M.P.H., University of Puerto Rico

JAN CRANDY, Nevada State Autism Treatment Assistance Program

GERALDINE DAWSON, Ph.D., Duke University

TIFFANY FARCHIONE, M.D., U.S. Food and Drug Administration (FDA)

ALAN GUTTMACHER, M.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

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

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

DONNA KIMBARK, Ph.D., U.S. Department of Defense (DoD)

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

ROBERT RING, Ph.D., Autism Speaks

JOHN ROBISON, College of William & Mary

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

EXTERNAL PARTICIPANTS:

EVDOKIA ANAGNOSTOU, M.D., University of Toronto

ASHURA BUCKLEY, M.D., National Institute of Mental Health (NIMH)

DANIEL COURY, M.D., The Ohio State University

LISA CROEN, Ph.D., MPH, Kaiser Permanente Northern California

ANJALI JAIN, M.D., Lewin Group

ISAAC KOHANE, M.D., Ph.D., Harvard University

BETH ANN MALOW, M.D., M.S., Vanderbilt University

ROBERT K. NAVIAUX, M.D., Ph.D., M.S., University of California, San Diego

MUSTAFA SAHIN, M.D., Ph.D., Harvard University

LAWRENCE SCAHILL, Ph.D., M.S.N., M.P.H., Marcus Autism Center, Emory University

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

JUDY VAN DE WATER, Ph.D., MIND Institute, University of California, Davis

JEFFREY WOOD, Ph.D., University of California, Los Angeles

PROCEEDINGS:

Dr. Thomas Insel: I'm Tom Insel, the Chair of the IACC, and I want to welcome all of you to this workshop. I'll make some introductory remarks, but it may be best just to get us all introduced to each other, because there are a number of people around this U-shaped table who don't know each other, I suspect, and also it will give you good training in how to use your microphones.

So we'll start over here with Alice and we can go around the table that way. This is a new building and a new PA system, so you have to get a little bit used to it.

Dr. Alice Kau: I'm Alice Kau. I'm in program staff, the Eunice Kennedy Shriver National Institute of Child Health and Human Development. I'm sitting in for our Director, Dr. Alan Guttmacher.

Dr. Isaac Kohane: I'm Zack Kohane from Harvard, and if Alan was here I would say that if you don't like anything I say, he's responsible because he interviewed me when I was a medical student applying for a residency program and he

made the mistake of admitting me to Children's Hospital residency program.

Dr. Matthew Carey: I'm Matt Carey, the parent of an autistic child and a public member to the IACC for the next seven days.

Dr. Lisa Croen: Good morning. I'm Lisa Croen. I'm an epidemiologist from Kaiser Permanente, Northern California.

Dr. Judith Cooper: Good morning. I'm Judith Cooper. I'm the Deputy Director of the National Institute on Deafness and Other Communication Disorders here at NIH. I'm sitting in for Jim Battey, our Director, and I also coordinate the autism program for NIDCD, primarily in the area of language.

Dr. Beth Malow: Good morning. I'm Beth Malow. I'm from Vanderbilt. I'm a neurologist and sleep specialist.

Dr. Ashura Buckley: Good morning. I'm Ashura Buckley. I'm a staff physician at NIMH and a child neurologist and sleep specialist.

Dr. Sally Burton-Hoyle: Good morning, I'm Sally Burton-Hoyle. I'm from Eastern Michigan

University. I run a master's program to train teachers who work with folks with autism and a college support program for individuals with autism spectrum disorders.

Dr. Carlos Pardo-Villamizar: Good morning. I'm Carlos Pardo from Johns Hopkins University, Division of Neuro-Immunology and Infectious Disorders. I am a clinical neurologist and neuropathologist working in different aspects of clinical neuro-immunology.

Dr. Judy Van de Water: Hello. I'm Judy Van De Water. I am at University of California-Davis at The MIND Institute and I'm an immunologist working in autism.

Dr. Donna Kimbark: Hello. I'm Donna Kimbark. I'm with the Department of Defense Autism Research Program.

Dr. Laura Kavanagh: Good morning. I'm Laura Kavanagh. I'm with the Health Resources and Services Administration.

Dr. Anshu Batra: Good morning. I'm Anshu Batra. I'm a developmental pediatrician in Los Angeles in private practice, and I have three

kids, one of whom is on the spectrum for autism. He's 17. He just had his birthday a month ago. I'm happy to be here.

Dr. Robert Naviaux: I'm Bob Naviaux from the University of California-San Diego. I'm a human geneticist and mitochondrial metabolic disease specialist.

Ms. Lyn Redwood: Hi. I'm Lyn Redwood. I'm Vice President of the Coalition for Safe Minds. I'm also the mom to a 20-year-old young man who previously had PDD-NOS, who's in his second year of college now.

Dr. Mustafa Sahin: Mustafa Sahin from Boston Children's. I'm a child neurologist.

Mr. John Robison: I'm John Robison. I'm an autistic adult. I'm an IACC Committee member and I'm a neurodiversity scholar at William and Mary.

Dr. Evdokia Anagnostou: Evdokia Anagnostou from University of Toronto and I'm a child neurologist.

Dr. Lawrence Scahill: Larry Scahill from Emory University Marcus Center, where I run the clinical trials program.

Dr. Daniel Coury: I'm Dan Coury. I'm a differential behavioral pediatrician from Nationwide Children's Hospital.

Dr. Jose Cordero: Good morning. I'm Jose Cordero, Dean of the School of Public Health in the University of Puerto Rico and member of the IACC.

Dr. Anjali Jain: Good morning. I'm Anjali Jain from the Lewin Group. I'm a pediatrician and health services researcher.

Dr. Susan Daniels: Good morning. I'm Susan Daniels. I'm the Director of the Office of Autism Research Coordination at NIMH and I'm the Executive Secretary of the IACC.

Dr. Insel: We've got a really distinguished group. I'm delighted that all of you could come. This is, for those of you who haven't been here before, a new building, the newest building on the NIH campus. It's the Porter Neuroscience Center, which was launched, inaugurated in April of this year, and home to some 80 different laboratories, many of which work on problems highly related to autism.

This is also the day of our annual Science Festival, so there's a lot going on, on the NIH campus, as you probably saw as you came onto the campus, but delighted that all of you could make it here, some from quite far away.

My Co-Chair for this subcommittee, Gerry Dawson, will be here I think momentarily. But I think we'll go ahead and get started without her. By way of introduction, the first thing to say to those of you who are my colleagues on the IACC is that this is not an IACC meeting. Even though we have plenty of oral and written comments from the public and we're webcasting and we have many of the same people around the table, this truly is a workshop. That means that this is a time for us mostly to listen and ask questions.

The workshop itself was organized by the Basic and Translational Research Subcommittee that Gerry and I have been co-chairing for a couple of years. We have been wrestling with this general topic of co-morbidities for some time. Part of this was discussed within the IACC full committee and other points raised by the subcommittee. It took a

while, actually, to fix on what the agenda should be. To frame that a bit for you, I think we struggled with what we thought were three needs that we had heard about, both from the public and from members of the IACC: one being the absence of guidelines to guide clinical care for kids on the spectrum and for adults on the spectrum beyond what we have currently for sleep, a little bit for GI problems, and for seizures.

As we talked about the wish to develop guidelines in the IACC, and getting the American Academy of Pediatrics involved and other groups that could help with this, because IACC is not the place to develop guidelines, it became clear that we don't have the evidence base that people would need to do that. So one aspect of this meeting was to think about what that evidence base could look like and where it would come from and what sorts of studies would need to be done. Then we had two other issues that we grappled with, one being the sense that came to the fore, I think as a major topic, and that was the continuing challenge of sort of undetected or under-recognized co-

morbidities. Calling them co-morbidities by itself was a bit of a struggle, but because we weren't sure to what extent these were just symptoms of certain aspects of autism or certain subtypes or whether they were, like the renal complications of diabetes, something that often traveled with autism. We talked a lot about what those would be, and the again concern that we heard from so many parents that when their kid would develop one or another serious medical issue that it would be treated as -- it would be ignored or neglected because the clinician would say: Oh, but they have autism, so it must be just part of autism, rather than getting the care they needed. So a lot of concern with that and then the third issue was this sense that some of the people on the subcommittee had that by engaging in a deep discussion about co-morbidities we could get into the etiology, pathophysiology of autism, perhaps not all of autism, but that certain kinds of autism would be revealed by trying to understand something about the biology and the co-morbid symptoms or biomarkers that might emerge in

studying this group broadly. So we kind of wrestled with all of those issues. I think you'll see from the agenda that there's a little bit of all three of them. Again, we're not going to do guidelines, but we are going to ask what do we know and what do we need in order to move forward in areas other than the three where we have some guidelines? There's going to be a major focus on these undetected or underreported, under-recognized co-morbid issues that come up, that travel with autism. Then towards the end of the day, the hope is that we will have more time to talk about does this help us understand something about mechanisms of disease or etiology. The way we've set this up is hopefully to have rather brief presentations -- Gerry, welcome. My Co-Chair and I will be assiduous about the time, so we can make sure there's plenty of time for discussion.

As I said, the IACC is really here mostly to listen and ask questions and to draw you out as experts, so we can have a deeper understanding of the problems that drove us to this workshop. So it'll be, hopefully, more of a conversational day

and we'll have a chance to get each of you to say a bit more in these discussion sections.

So to just kind of organize the day a little bit, one of the things that the planning group wanted was an overview from some of the large health studies, large health care studies and large population-based studies, to get a sense of this issue from 30,000 feet: What are the major co-morbid medical/psychiatric issues that we should be concerned about in this population.

We thought we would follow that with perspectives from a wise clinician, who will hopefully give us some direction about how we should be thinking about the clinical burden and the clinical opportunity. I should mention at the outset, because I think it will come up, that we're likely to talk quite a bit about psychiatric co-morbidities, and I know that these used to be called behavioral problems. I just wanted to stress at the outset as the head of NIMH that today we recognize anxiety, depression, and ADHD as brain disorders and as neurodevelopmental disorders every bit as much as we think that way

about autism itself. So putting them into that context I think will be important, because they're not so much mental disorders or behavioral problems, but another aspect of brain circuitry not functioning in quite the right way. We've got a second panel that will review some recent insights about those particular co-morbidities, and then we'll break for lunch. After lunch we're going to hear public comments. You should have all received copies of both the oral and written comments. I think some of these were in fact intended for the IACC and not specifically directed at today's workshop. But as you will see, many of them address service needs and some address the vaccine issues, some recommend specific causal and environmental factors. That's really -- none of those are likely or should be in the agenda today. What we really want you to do, though, is to look carefully -- at least members of the IACC should review these comments, even if we don't have time to discuss them today. We won't have a lot of time, given how much we want to cover within the workshop. So I hope and I want to

implore you -- and I think Gerry will help in this -- to remain focused on the topic of co-morbidities so we can fulfil the charge we have from the IACC to be able to respond to that particular issue of those that are under-recognized or undertreated. We'll follow the public comment period with two additional panels, one on sleep and neurological disorders, another on metabolic and immune disorders. And hopefully, if everybody abides by the schedule; we'll have enough time for about an hour at the end of the day for a general discussion.

Just one other comment, since it may be on some of your minds. What happens to the IACC? The members of the IACC will finish their term of duty next Tuesday, in one week. So this is actually the last event for this particular committee. The Congress has approved and the President has signed the CARES Act, which will reinstate an IACC, but we'll go through that process of nomination and charge and reforming the committee over the next few months. My hope is -- obviously, there won't be any time between now and next Tuesday to do

justice to the minutes from today and to actually formulate any kind of a summary or report. But we can do that, even after September 30th, and we'll make sure that that's available on the IACC web site, and it will come back to the new committee when that new committee convenes next year. I should just introduce or have her introduce herself, my Co-Chair here, Gerry Dawson. Do you want to say just a word? We did introductions already.

Dr. Geraldine Dawson: Is this on?

Dr. Insel: That's the main reason for doing introductions.

Dr. Dawson: Welcome, everyone. I'm Gerry Dawson, Professor of Psychiatry and Behavioral Science and now Psychology and Neuroscience at Duke University and Director of the Duke Center on Autism and Brain Development. I just want to welcome everyone here. We're so excited about today, and just to say that this is a topic that is of tremendous interest to parents. We've heard so much about this topic in the public comments that we've received and also the IACC members.

So we've really been looking forward to this. I was just looking at the group of people that are presenting today, and so pleased that all of you were able to come. I know that it's going to be a really exciting set of presentations and discussion.

We hope to learn more about how to improve quality of life by addressing medical co-morbidities, but also have better insight into neural mechanisms and full-body mechanisms and how these may play a role in etiology, but also development in autism. So with that, I think we're ready to begin.

Dr. Insel: Any questions before we launch?

[No comment]

Okay, let's make sure that -- are all of our technical glitches resolved at this point, so the webcast is fully working? Do we know that? Can we get that up?

[Contractor]: The webcast is working. The conference call, though --

Dr. Insel: The conference call?

[Contractor]: The conference call we're still

working on.

Dr. Insel: That means that people have the video, but not audio, is that right? Do we have any idea how long it will take to get the conference call working?

Dr. Jain: Should I wait a few minutes?

Dr. Kohane: I just checked. It has audio.

Dr. Insel: On the webcast, right. Okay, so people can join by webcast. Thanks, Zack. Given the time, I think we better move on and then you can let us know.

[AV Tech]: Dr. Insel, we can call the operator on the conference call and tell people to go to the webcast.

Dr. Insel: Thank you, great. It's a pleasure to introduce Dr. Anjali Jain, who is a general pediatrician and Vice President at the Lewin Group. Lewin Group is a health and human services research and policy group in Falls Church, Virginia. I think, rather than taking any more of your time, Anjali, welcome, and we'll turn this over to you.

Dr. Jain: Good morning. Thank you for inviting

me to speak here. I wanted to note that we had a huge discussion about what to call these conditions and ultimately settled on "co-occurring conditions." So that's one possibility.

I've discussed our study before and I can certainly spend the entire time talking about the study overall. So I'm going to assume that you'll ask questions if you need to and I'll just give a very brief overview of what we affectionately call the Health Outcomes Study.

It consists of four tasks. Most of what I'm going to be presenting today is really from the first two tasks. The Task A is really to just look at the data.

This is a large health insurance claims database or administrative database. The first part was to identify children with autism as well as their family members, and also identify a control group or comparison group of children and their family members. Part of that, of course, was to validate their ASD diagnoses using a chart study. In Task B we compared overall just very descriptively the health outcomes of children with

ASD and without ASD, as well as that of their family members. And Tasks C and D looked more at utilization patterns as well as etiologic list factors, which I won't be discussing here today.

This is the OptumInsight Research Claims Database. The group involved was us at Lewin and Optum, which is our parent company now, as well as Craig Newschaffer and his colleagues at Drexel University, was the main core of the team. We had medical and pharmacy claims and linked enrollment information from 1993 to present. For this particular, the results I'm presenting today, are results from 2001 to 2010.

The database itself is geographically diverse across the U.S. It's fairly representative. It has a little more in the Northeast and the South compared to the West, for instance. It also is linked to an associated demographic marketing database, so we are able to get person and household-level data on socioeconomic characteristics, as well as, a match for some of the other basic socio-demographic characteristics for the population.

This just gives you a sense of the numbers, which start out very large and get smaller pretty quickly, but still end up quite sizable. The database overall during this time period has about 62 million individuals. This is adults and children. And if once you require them to have about six months of coverage or more, that number cuts down to about half or 30 million. 9.5 million or so of those are kids, meaning they are in the database from age zero to age 20 at the beginning of their follow-up period. We were not, explicitly not studying Rhett's syndrome and CDD, so we took out the children who had any of those diagnoses. We ended up with about 46,000 children who had evidence of ASD. And what I mean by evidence is that they had at least one claim with an ICD-9 code for one of Asperger's, autism, or PDD-NOS codes.

We also pulled their siblings and parents, as well as a three to one comparison group and their siblings and parents. And because they're on the same health plan, we were able to do that and get some family-level characteristics. I will be

presenting a little bit of that data very briefly.

Based on the chart validation, we decided for most of our multivariable analysis and more detailed analysis that we were going to stick to children who had a more definite diagnosis of ASD, and those are the kids who had at least two claims with an ICD-9 code that fell into the appropriate categories. So those kids we're calling likely autism versus the others are probable or possible autism. So you'll just see that terminology used in the next few slides.

To look at co-morbidities or co-occurring conditions, the first thing we did is we used the ART clinical classification software, which basically breaks down groups of ICD-9 codes into various categories. In general, this slide -- I'm not going to get into it in detail, but basically shows what we'll continue to show, is that children with autism, either likely or possible, had greater rates of almost every group of conditions compared to the comparison group. Some of the codes that fall into these various categories are not very intuitive and so we did

look at groups of codes separately, as well as developed our own sort of working model for a clinical co-morbidity index to use in children, and I'll present those results shortly.

Looking first at some of the mental and behavioral health co-morbidities, as you can see here -- the likely group -- again, this is two claims, so they sort of more definitely have an autism spectrum disorder. The possible group are the ones with only one claim, probable are the group all together, or a total ASD, and here's the comparison group.

As you can see, the numbers are large. And if you just compare total to comparison, you can see that the prevalence in the data set of anxiety, attention deficit, bipolar, all of these disorders, are much higher prevalence than in the comparison group. I don't think that there's any huge surprise here.

One thing you might note is that the rate of intellectual disability is quite low compared to what we think it probably is, and I think that's a function of these being medical claims and so

intellectual disability is just not well coded. So we don't expect that to be a very reliable estimate.

So this is -- we were searching for an appropriate index of clinical co-morbidity in children and actually didn't find much. A lot of that has to do with children not having a lot of necessarily mortality or morbidity at a very high rate during childhood. The best thing we found was something called the CCC, or Clinical Co-morbidity Index, which is used for children who had spent a lot of time in the hospital itself.

We decided to modify that and break it down into an ordinal scale for each of these categories. There was an additional category of developmental disorders that we took out because that was a disease of interest, of course. And we looked at the overall co-morbidity. This was mostly needed and useful in our study so that we were able to control for some of these other conditions when we were looking at other health outcomes as well as utilization.

Here we also grouped co-occurring conditions

or co-morbidities into several different categories, and these have their own set of ICD-9 codes. I do have some handouts that list those codes if anyone is interested, but for these main groups of conditions we compared children with ASD to comparison groups, and again found much higher rates of infectious diseases, neurological, neurodevelopmental disorders, mental health conditions, metabolic dysfunction, autoimmune disorders, congenital and genetic disorders, and gastrointestinal and nutritional disorders.

Again, not all of this is surprising or known, but one of the things that I think such a large and heterogeneous data set does for us is it sort of narrows the range of prevalence of these conditions, because if you looked at the literature previously you would get something like between 9 and 80 percent of children have X. So I think this gives us a little bit more of a handle on what the kind of norm is.

Something like infectious diseases, it is not immediately obvious why children with autism would have them in such a greater quantity. So those

were some of the maybe under-recognized conditions that we don't quite understand, but might give us a handle on what's going on. The co-morbidity score was low across the board, but, as you can see, it was still much higher in children with autism compared to the comparison group.

This is siblings. So these are all the siblings of the children with ASD compared to the siblings of the comparison group. The children themselves, as well as the children themselves in the comparison group, were not included in this, in this analysis. As you can see, the siblings also have higher rates of just about everything, not close to what the children with autism have, but still considerably higher. I think that this kind of is provocative in the sense that it starts to give us a sense of what might be biologic, what might be environmental, what might be going on, and are these the same conditions that they're having with their siblings or are they different issues. So I think that this data can be explored further and certainly the ideas can be.

Again, their co-morbidity score was also

higher, but only a little bit higher. We did some more detailed analysis, and this is actually now published as a paper, looking at injuries in children with autism, and we confirmed what's been shown in the literature, basically is that children with autism have more injuries than children without. However, what we found in our analysis is that a lot of that difference is really explained by co-occurring conditions. So that really makes you think twice about how both intervention as well as the mechanism of the injury -- for any injury experts, injuries in children vary hugely by age group. So we did do a more detailed analysis on injuries in children with autism by age group compared to those without, and indeed found that injuries are much higher in the younger kids compared to other children without autism, but they're actually much lower in teenagers. A lot of that is explained by fewer motor vehicle accidents.

One of the things that was really perplexing about how to adequately control is this issue of surveillance bias. Children with a chronic

condition like autism are getting more health care and, sure enough, in our data set on average the children with autism had a longer continuous enrollment period. Their enrollment period on average was about three years in the data, whereas the comparison group was about two years.

One of the problems with any study of co-occurring or co-morbid conditions I think is trying to understand the extent to which things are being picked up versus occurring. So one of the things we did is we just -- this is a very crude marker, but we used preventive visits as a marker of health care users and found that, at least for the chronic conditions, it didn't change the results significantly.

However, when we looked at things like otitis media and pneumonia surveillance bias seemed to play a huge role in terms of how often they're picked up. So I think in any sort of further research of co-occurring conditions we need to pay really close attention to this issue and the extent to which we're diagnosing things versus they're actually occurring at increased rates.

This is just some of the geographic differences that I wanted to have available in case anyone asked questions. But here you can see that the enrollment times, for instance, vary quite a bit.

Just a couple questions – one of the things that I think such a large and heterogeneous descriptive database does is it allows us to potentially observe what's going in in terms of the occurrence of co-morbid conditions, as well as potentially use some of the newer data mining techniques to try to get a sense of the degree to which there might be clinically meaningful subgroups of children where conditions are clustering together, and that might help us to understand both autism itself and its manifestations, but also particularly how to intervene appropriately in different groups of children.

Then I already brought up the extent to which some of the patterns of co-morbid conditions in families might be helpful for us to understand both etiology and the ability to intervene.

How am I doing on time? Okay?

Dr. Insel: Yes. You've got a minute or two left.

Dr. Jain: Okay, thank you.

Dr. Insel: All set. Thank you.

[Applause]

Thanks, Anjali. We'll come back with questions at the end when we've got some time for the whole panel.

Our next speaker is Lisa Croen and, as you heard, Lisa already introduced herself as a senior research scientist in the Division of Research, Kaiser Permanente-Northern California. She's Director of the Autism Research Program there and well known to most of the people in the room through her work on epidemiology and many other areas. Welcome.

Dr. Croen: Thank you. I'm going to talk -- this is a nice companion to the last speaker -- of a similar kind of study design, looking at co-occurring conditions, psychiatric and medical conditions, among adults with autism. Just a very quick background—we know children, and we're

learning today and many of us know already, children with ASD have increased rates of medical and psychiatric visits, everything from GI problems to sleep disturbances to seizure, mitochondrial conditions, infection, allergy, asthma, and psychiatric disorders. Children -- the rates of autism, the prevalence is going up dramatically. We all know this. The latest figures are one in 68. And kids become adults, and so we need to find out what's happening with autistic adults, there's not much information.

There have been a few studies. One in particular that was large, that Dr. Kohane, I think will speak about in his study that included some adults. Most of the studies of adults have been very limited in size and scope and age group. They focused on the younger adults. So what we did is use the data that are collected routinely as members of Kaiser come in for their routine care. It's a very large database. The membership in Northern California is about three and a half million, both kids and adults. And we looked at the health status of adults with an autism

diagnosis, autism spectrum disorder diagnosis.

This study also looked at health care utilization and we also did a survey of the adult providers, which in those last two I won't be speaking about, but maybe in the discussion period I can bring some of that up, because what the providers told us about their knowledge and experience with autism was very critical, I think, to where we need to move the field forward.

I'll be focusing on the health status. Briefly, the study was designed to look at adult members who are 18 or older, who are members of Kaiser Permanente-Northern California for at least nine months per year over a five-year period. So this addresses some of the surveillance bias issues that Dr. Jain just mentioned. We only focused on people who had the same amount of membership, almost a full membership over a five-year period.

And we identified adults with an autism spectrum disorder diagnosis. This is based on ICD-9 codes recorded in their medical records. We required at least two diagnoses in their medical

record any time through the end of the study period. And we sampled, randomly sampled a control group, a comparison group. These were the same adult members in the same study period who never had an ASD diagnosis recorded in their record. They were matched to the cases on the total length of KPNC membership, sex, and age. So it's a fairly -- the opportunity for diagnosis between these two groups we tried to equalize as much as possible.

In terms of defining their health status, we looked at all conditions recorded in the electronic medical record in this five-year period between 2008 and 2012. We used a variety of different strategies to come up with diagnostic categories, using first of all validated algorithms that used a combination of ICD-9 codes, lab results, and medications that other investigators had developed for specific conditions that they study within our population. So these had been validated against with chart review against, using -- looking at medical records and comparing to clinical exams.

We also have a very large and longstanding

cancer registry and diabetes registry. So for those conditions we linked our study population to those registries to determine cancer and diabetes prevalence. Then for other conditions we based groupings on this PheWAS, this Phenome-Wide Association Studies, which essentially takes all of the ICD-9 codes and comes up with a way of grouping them into specific conditions. Then we had -- in terms of determining obesity, we used the body mass index that was calculated at each office visit in this five-year period and took the highest one that had been measured over this five-year period. We also had self-reported alcohol and smoking. Again, that is asked of each patient when they come in for their care, so this is: Do you currently smoke, do you currently drink?

So, a little bit about the population. We identified about 1500 adults with an ASD diagnosis and ten controls or comparison adults for every case. That's 15,000. The mean age of this population was about 29, but about a quarter were over 35 and about 10 percent were over the age of 50. So I think this population is older than other

populations that have been reported on in terms of adults with autism.

We have a pretty diverse group in terms of race and ethnicity. About three-quarters, 75 percent were men and the other 25 percent were women, which is what we would expect.

In terms of the clinical, the phenotype of the autism, about a third, 37 percent, had a diagnosis of autistic disorder, another 30 percent Asperger's syndrome, and the other third you couldn't tell from the record; it was a combination. Over the course of the many diagnoses there were autism and ASD and autistic disorder, so it just wasn't clear what exactly the diagnosis was. In this population, in terms of intellectual disability, almost 20 percent, 19 percent of this population, had in there an indication in their medical record of an intellectual disability. Again, I think this is probably an under-ascertainment, for the reasons that Dr. Jain mentioned. These are medical records and intellectual disability is often not recorded in these records.

Now I'm going to show you a series of bar graphs that look like this. Just to orient everybody to the graph, we have percent along the vertical axis, the Y axis, and a specific condition along the horizontal or X axis. So these are basically the rate or the percent or the prevalence of a condition. In the blue bar are the adults with ASD and in the red bar it's the comparison group.

Also, in addition to comparing just the straight-up percent of these conditions between the case group and the control group, we did a multivariable analysis where we estimated an odds ratio. This is after adjusting for sex, age, and race-ethnicity. So these are adjusted. And so an OR of 3.7 means that the cases were 3.7 times as likely to have an anxiety diagnosis recorded in their medical record as the comparison group, and this is after adjusting for any differences between the two groups of sex and age and race-ethnicity.

And so, what you'll notice as I go through these is that there's a substantial excess or

increased rate of almost every condition that we looked at in the autistic adults compared to the comparison adults.

This first slide summarizes the individual psychiatric conditions that we looked at. There's two take-home messages here. One is that the overall -- look at the height of the bars, and looking at just the prevalence of the condition is really strikingly high.

These, again, are based on -- not based on self-report, but based on medically recorded diagnoses by physicians. So for example, anxiety occurred, was diagnosed in about 29 percent of the autistic adults versus maybe 8, 9 percent in the non-autistic adults.

So 29 percent anxiety diagnosis, 25, 26 percent depression diagnosis, and you can go on down the line here. Schizophrenia or Schizophrenia disorders were 8, 9 percent diagnosed in the autistic group, obsessive-compulsive disorders 8 percent. Suicide attempts were on the order of about 3 percent in the autistic adult population and this was about a fivefold higher rate compared

to the non-autistic adults. So a quite high burden of psychiatric conditions.

Interestingly, drug and alcohol use -- these are again diagnoses of abuse or dependency -- were significantly lower in the autistic group than the comparison group.

In terms of some conditions we have seen reported over and over again in children, the same conditions show up as being in excess in adults. Gastrointestinal disorders -- and this was a whole slew of different conditions; I just grouped them into one big category here -- nearly 35 percent of autistic adults were diagnosed with some kind of gastrointestinal disorder in this five-year period and it's significantly elevated compared to the controls.

Allergy was quite common. Autoimmune diseases were common. Asthma; sleep disorders -- we'll hear a lot more about that later -- were quite common and almost two times as likely to be diagnosed in the autistic adults as the non-autistic adults. And thyroid disease also was significantly elevated. These are all significantly elevated,

the ones I've shown here, statistically significantly. In terms of metabolic conditions, these -- and I think this is of special interest for this meeting because these are -- most of the data that are published have not addressed obesity. There's a growing body of research showing obesity is more common in children and adolescents with autism. We find also significantly higher rates of obesity in adults as well.

Hypertension, dyslipidemia, diabetes, these are often conditions that occur and are diagnosed later in life and we don't have much data on this yet. We're finding that very high rates of these kind of chronic, serious medical conditions that are often precursors to other, more serious lifelong conditions, significantly higher rates in adults with autism. These are other medical conditions that were less common, but again sort of across the board, across every system; we see significantly increased rates in adults with autism.

Here's - neurologic conditions. As expected,

epilepsy-seizure disorder was quite a bit more common in the autistic adults, other disorders of the central nervous system. Stroke, Parkinson's, and dementia, all occurred much less frequently, but again significantly elevated in the autistic adults. Again, like the alcohol abuse and dependency - this is the self-reported alcohol and tobacco use, and we see significantly reduced rates of smoking and alcohol in autistic adults, which is very interesting, and we know that these behaviors are often risk factors for things like hypertension and obesity and some of these other chronic health care conditions, and yet these specific behaviors were much less common in the autistic population.

These were the only -- of all of the conditions we looked at, these were the only conditions that were significantly less common, commonly diagnosed, in the adults with autism. Infection was a little bit less commonly diagnosed, migraine headaches, genitourinary disorders, and cancer. The cancer finding I think is very interesting. I don't know what it means.

The numbers were very low, so it was hard to really go into this in depth. We did try to look at age at first diagnosis of cancer and stage at first diagnosis of cancer and there was a little bit of an indication that the stage at which the cancer was first diagnosed was more advanced in the autism group than the non-autism group.

But this again, I take this with a big grain of salt because the numbers were fairly low. But I think this is, in terms of looking further into etiology and what may be shared between autism and non-autism, this might be an area to look at. Am I running out of time, Gerry?

Dr. Dawson: Yes.

Dr. Croen: Okay. So, in summary, there's evidence for increased rates of many of these health conditions. We do know there's some evidence for common biologic causes. There's been some nice genetic work looking at susceptibility, at SNPs and polymorphisms that are similar across several psychiatric disorders, including autism. We know obesity is a risk factor for several chronic conditions and we see obesity as very high

in this population.

I think we can say pretty certainly that the communication and social impairments and sensory issues may impede preventive health and early diagnosis and timely treatment, and this would be an area for further research. I think it's clear that nutrition and exercise are very much related to health and the need for some health education and lifestyle interventions early on in life to make sure that children enter adulthood with good nutrition and exercise regimens to reduce some of these risk factors for chronic illnesses.

And then better integration of people with ASD into all aspects of society, to reduce the social isolation, and discrimination and which we know the social isolation can be related to many of these diseases, especially anxiety, depression, and the psychiatric problems.

These are some research opportunities that I think we have before us, understanding all of the different implications -- social, health care access, and biologic mechanisms -- that underlie the increased rates of these medical and

psychiatric conditions. And understanding how physicians investigate and manage chronic disease in adults with ASD. Then finally, coming up with some improved strategies for delivering health care to this population is very much needed. That's it. Thank you very much.

[Applause]

Dr. Insel: Thanks very much. A lot more to talk about so looking forward to the discussion section. A pleasure to introduce Zack Kohane from Harvard Medical School. He's a Professor of Pediatrics and Health Sciences and Technology. He's the Co-Director of the Center for Biomedical Informatics at Harvard, as well as Director of the Harvard University Countway Library of Medicine and Director of the Children's Hospital Informatics Program, and many other things.

Dr. Kohane: Thank you very much. I'm very excited to be here, just already listening to the first couple of talks. I'm just fascinated to be able to participate in this meeting where we're looking at all different aspects of this beast, this beast, this collection of symptoms and

pathologies that make up this thing that we call autism. I think in some ways we're very much like where we were when we called heart failure dropsy and did not understand that it was an infectious myocarditis and there was an atherosclerosis-based heart failure, that there was a traumatic heart failure, that there was structural proteins that were aberrant, and we were all calling that heart failure. Similarly, we call all these different things autism. Just listening to all these talks already -- and I'm sure there'll be more like it today – to get a feel for these other aspects. I should say, by training I'm a pediatric endocrinologist and I have a Ph.D. in computer science. So I was very both active in this committee, this National Science committee that put out a report -- that is, by the way, freely available -- called "Precision Medicine," and I was influenced by it, because it said if we can actually just layer multiple perspectives on the patient, from the microbiome to exposures to the genome to clinical data, we're going to much better understand medicine and be able to dissect,

just like heart failure, a multitude of diseases into their heterogeneous components.

And, my own take on that same message we recently published as a Viewpoint in JAMA, were I think in autism and neurodevelopment diseases we need to take this perspective -- this figure is in the JAMA article -- where there's actually a much larger ecosystem of data, showing the blue-shaded areas, is stuff that falls into our health care system, which is important, some of it's structured, some of it's unstructured, and as you'll see in my own work, which I've done a lot with it, and we've heard from our other speakers.

But there's also the registry, there's claims data. There are also a number of other data sources from ancestry.com to Zillow to club memberships to blogs and tweets, which are incredibly revealing. And because I'm enthusiastic, I don't have time to tell you some of the things that my faculty has done just in categorizing autism using the social web. But that's for another time. But this is just to think expansively about the available data. It's not

just the one percent of our lives that we spend in health care systems; we have a much broader membership in life. My view of precision medicine is simply this:

What is the probability of disease, given findings? And the smaller the error bars around that probability estimate, the more precise we are; and the more useful it is the closer it is to zero or to one. That's an ideal for precision medicine.

Now, not being a neuroscience researcher, when I first entered this field at Harvard, when I went to the neurobiologists this is what they told me was autism. They were not wrong, because in fact there are a multitude of single families where you found individual problems, mutations in the synapse. And there's no question the synapse is involved in many learning disabilities for many patients.

But they have not accounted for even a small plurality of the cases of autism. But nonetheless, when I went around this is what I saw. So when I did a gene expression study, which is looking at

the RNA, the genes that are turned on in patients with autism, looking at the blood, something that we published many years ago, my grad students started making fun of me. Not that they never do that just for no reason at all, but here they made super-fun of me, because we were looking at white blood cells. And they said: Zack, what did you expect to see? There's a lot of Chemokines and all these immunological signals. This is, after all, the blood.

I said: Wait a sec, wait sec. We're also seeing long-term potentiation and neurotrophin signaling as being differentially expressed. And you know, yes, it's the blood and its white blood cells, so yes, you're going to see an immunologic signal, but it's different between the kids with autism and the controls. And we did several studies where this was reproducibly the case.

But I was still mystified and irked by my students, so then I did what my students should have done before attacking me, which is -- I read the literature. It turns out there's a wide literature that reflects the immunological aspects

of autism, and I'm not here to say that it's the only aspect, but I just want to broaden our discussion, because back home all you hear about is the synapse. So this is just to try to push the pendulum in the other direction.

So I was very impressed by this study by Vargas in 2006 where they looked at brains of kids with autism versus controls, unfortunately all sudden death like car accidents, and they showed that the microglia, the macrophages of the brain, were massively up-regulated. And then I looked into other studies and it showed the expression program in the brain, including studies by Geschwind that showed there was an immunological signature as well as a neurotrophin signature. I saw that the late Paul Patterson, who recently passed away at CalTech, had a beautiful mouse model where when you put into the mother agents which cause a sterile inflammation the pups that are born look just as autistic as any mouse model, genetic mouse model of autism. If you look at CSF and the peripheral blood, there's a very interesting, immunologically distinct, signal.

Also, if you look at all of Denmark -- it's not my work -- mothers with rheumatoid arthritis and fathers with type 1 diabetes are much more likely to have kids with autism. If you look at all of Finland -- so these are comprehensive, complete unbiased studies -- mothers with a high gestational CRP, much more likely -- a measure if inflammation -- much more likely to have autism. If there's intra- and peri-partum infection, much more likely to have autism. And I told you about the mouse models.

Here's a quick comment about our ecosystem. The one hat that Dr. Insel mentioned that I wear proudly is I'm a librarian at Harvard Medical School, and I went through the literature around autism looking at genetic disorders either associated with the synaptic function or associated with immunological function. Those are papers -- this is the open access literature -- they're noted "N" and "I." As you can see, they're non-overlapping.

But even worse, the literature cited by the immunological genetics studies and the literature

cited by the neuroscience genetics studies are really over tens of thousands of papers that don't reference one another. So this tells you what a split we have in our community and how, by not taking the big data, comprehensive view, we allow our communities to engage in shouting matches with each other without actually having looked at each other's, or at least being willing to acknowledge each other's, literature.

One of my endeavors of the past few years has been to look at electronic health record data from large health care systems. We've built something called I2B2, which you can look up under I2B2.org, which is free software which is now used by over 100 academic health centers in the U.S. about three dozen internationally. This now allows us to also create real-time queries across academic health systems. So with eight health centers, coast to coast, we did this quick study with 13, almost 14,000 patients with autism. We found that they were only about half a percent of the hospital population, so it's probably an underestimate.

We had an unusually high male to female ratio. I can't explain that. But, importantly, they had 5,000 diagnoses other than the autism-related diagnoses. I want to point out that -- I'm not going to summarize that paper except to say that there were rare things that are great research agendas: Why is it the fact that 25 percent of kids with dystrophin mutations have autism? I don't know. It's interesting. But all these things popped out, in addition to all the co-morbidities you just heard about so far.

But we saw many, many such findings in this data set, 3 million lab measurements on 3500 measurement types and a bunch of medications. But one of my postdocs by the name of Finale Doshi, who has a meteoric career -- she graduated two years ago with a Ph.D. in computer science at MIT, did two years of postdoc with me, and then immediately -- and in that process, by the way, had two kids -- and then just got accepted a tenured position at the School of Engineering and Applied Sciences at Harvard. Superwoman.

And so what she did was to use her same

information theoretic techniques, which look a lot like gene expression clustering, on our data. She said, given the fact that we have 50 years of data on these kids, I'm going to look at these kids as a time series and I'm going to break up each of their six-month blocks in their life -- each of their 50 years into six-month blocks, and for each six-month block I'll simply say, did they have one of those 5,000 co-morbidities. I give them a one if they have that co-morbidity and zero if they don't. So you have a little bit string corresponding to their co-morbidities in that six months. And then I'm going to march that out for all 50 years, and then I'm going to cluster the patients together, just like you do in gene expressions, in fact using the exact techniques that we use for gene expression studies; are there clusters of patients who come together? What we found was pretty interesting.

This is showing the network of hospitals involved. So there was one subgroup. Now whereas in our other previous studies we showed there was a 20 percent, 22 percent epilepsy-seizure

prevalence, there was a subgroup, distinct subgroup that had over 80 percent seizures. So this is a group that's characterized by seizures. There was another subgroup that was characterized by otitis media -- you heard about it -- infections, viral chlamydial infections, and -- not shown here because it's much lower prevalence; it isn't on the same scale -- highly increased inflammatory bowel disease, and a variety of GI disorders.

Incidentally, when I talked to my truly beloved colleagues' in developmental medicine what they told me was: Oh, yes; brain's bad, tummy hurts. Which after the fact seems incredibly dismissive. And I'll show you what we looked at subsequently.

Then there was another subgroup which had this huge, 60 percent, prevalence of things like ADHD and anxiety, corroborating what you just heard. These are independent studies across these multiple health care systems. Not shown here because it's a much lower scale, schizophrenia as well. So I want to point out what we have here:

three distinct groups. Now, there's other groups that overlap, but these are three distinct subgroups that have distinctive biological, clinical pathologies. They look like different diseases.

So I want to ask you – we posted the…earlier, oh, this is just to show that between the Children's Hospital and Wake Forest, two very different systems, the co-morbidities look the same. So despite all the confounding, different doctors, different hospitals, different patients, it looks the same. It's amazingly reproducible. And since I have access to these multiple hospitals, I can tell you this is amazing reproducible, especially for something that's not recognized.

I should point out that when I first published an earlier paper I had an experience which I'd never had before in my life, which is a bunch of parents sending me very passionate emails, both positive and negative, and they all said either, thank you for identifying what I've always known about my kid, or why didn't you find this sooner

because I've known this all my life. That was for me pretty persuasive, because the way I was trained is parents really know what's going on with their kids and doctors tend to be one step removed.

So here's a quick thought experiment. Autism is a common disease with a prevalence of one percent. Let's say the causal variants are one percent, one percent frequency, so middling low, and the relative risk is 2, which is on the high side. Then with 80 percent power we need 23,000 kids with autism. These are the arguments which argue for larger and larger cohorts of autism. But what if ASD is really ten diseases? And there are many reasons why it could not be clinically noticed. If you saw a thousand kids with autism, you'd only see ten with inflammatory bowel disease. Highly significant, but you'd never register it cognitively. So if you had ten pediatricians, each with a thousand kids, they'd never see it. So many reasons it would not be clinically noticed.

So then the causal variants might have 10

percent frequency and with the same power you'd only need 2300 subjects. But if we treat autism like heart failure, being one disease, it would be like doing a case control study on heart failure and saying, what are the causative variants causing heart failure and lumping all the heart failures I told you about into one. It would never work because we're trying to get some signal out of something incredibly heterogeneous.

So let's use the biology and the clinical findings to pull out the cases. I can't show you the stuff that we're doing with IPS cells to actually find sub-phenotypes in expression space, but it's the same game: Can we find the subgroups where we can actually boost the signal?

Here's an interesting thing. Until recently, we had to go with the genetics first because it was so much more expensive. We always think of genetics as being expensive, but guess what the average price for a good phenotype to NIH is between 1,000 and $3,000. So if you can use electronic health records and high throughput phenotyping using high-speed processing, we can

now start doing on millions of patients these kinds of analyses that were previously impossible.

Ah. So Finale said: Zack -- and I told everybody this -- I went to talk to Lenny Rappaport; he doesn't think that this is a real thing, this thing with inflammatory bowel disease. So I said: Okay. Go to my buddy Athos, who is a GI specialist, and let's go and look at the records of the kids with IBD -- sorry -- with autism and IBD, as per our search.

What she found was not IBD diagnosis, but pathology-proven IBD, like the highest level, the highest standard of definition, IBD was higher. So we actually looked at the cases. What was interesting, there was also enrichment for a set of cases that were incredibly, horrible, raging colitis and enteritis that did not make the criteria for IBD. It's some other biology, but it doesn't make the criteria, but it's there and no one's calling it IBD because it doesn't meet the criteria.

But it's torturing the kids. Think about that. Ah. So this is we have a collaboration with Aetna

and, using Wake Forest or Boston Children's, wherever you look at, the enrichment, the prevalence of IBD is higher than any of the most generous estimates of the Crohn's Colitis Foundation. So no matter what population you look at, no matter how you slice it, it's higher.

And I'm just looking here at one disease. I assure you we're going to see this in all the different other diseases. But it's so easy to ignore.

So in summary, the conventional wisdom regarding the cause of autism is incomplete, divided, and obscured by the fact that we all by our human nature end up down the rabbit hole once we find a hypothesis. And although I'm a big fan of hypothesis-driven research, on the other hand premature focus can put it on blinders. Phenotype-first strategies may massively accelerate discovery of the genetic architecture. There is a lot of shared pathobiology across autism and I haven't had time to share it, but for example we've looked at gene expression all of these co-morbidities. It's mighty interesting around the

toll-like receptor pathway.

And there's a lot of undiscovered heterogeneity in this distinctive pathobiology within conventionally labeled diseases, of which autism is a great example. So what I'm arguing for is an aggressively ecumenical approach to integrative data analysis. That's I think what IACC actually seeks to promote and that's why I'm so excited to be here.

Here's a plug. Sorry for the chopping. NHGRI, but mostly NIMH, in its wisdom or whatever, has decided to fund a project that we put in for a Center of Excellence in Genomic Science with Roy Perlis from MGH. Basically, we're going to take this systematically. We're going to take electronic health record-defined phenotypes for which we have -- and we're going to do it with both classical phenotyping and dimensional phenotyping -- and we're going to look at both those patients that we have in a bio bank, a special bio bank which I'll describe, and all the other neuropsychiatric patients, so we can compare it to them. And we're going to take those patients

in the bio bank, where we have the fibroblasts, and we can create both induced neurons and pluripotent neural progenitor cells, and we're going to look at their transcriptome, we're going to look at their epigenome.

We're going to do CHIP-SEEK, so looking at histone marks, and we're going to look at not only the standard transcriptome, but all the non-coding transcriptome as well. And we're going to come up -- and we will perturb this transcriptome in these neuron cells, in these neurons, and actually come up with a probabilistic model that links, that attempts to link back the responses to the drugs, the position in this multidimensional precision medicine stack, of going all the way from the phenotype through the transcriptome, epigenome to the genome -- there's also whole-genome sequencing -- to see if we can have some explanatory/predictive capability.

Meanwhile, we'll have Mike Greenberg, Department Chair of Neuroscience, working on the same neurons, depolarizing them, to see if we can actually see activity-dependent changes in the

epigenome and transcriptome, which is a long way to say we fully believe in this ecumenical approach. Thanks to generous funding by NHGRI and mostly NIMH, we're going to be able to attack this systematically. For those of you who are interested, I'm glad to take more questions later.

I just want to thank a fairly large cast of characters. Thank you very much.

[Applause]

Dr. Insel: Thanks, Zack. We'll get back to questions fairly soon, hopefully. Obviously, there's a lot to talk about. Our final speaker in this session will be Dr. Daniel Coury, who is Chief of the Section on Developmental and Behavioral Pediatrics at Nationwide Children's Hospital and a Professor of Pediatrics and Psychiatry at the Ohio State University College of Medicine.

Dr. Coury: Good morning. It's a pleasure to be here. I really have enjoyed the presentations so far. I think everyone's getting a good idea that autism is not simply a mental or neurologic disorder; it's really a whole body disorder. I'm

going to share some data that we have from the Autism Speaks Autism Treatment Network, to give you a little more feel for this. The network -- you've heard from Dr. Jain about some database from the health care area, from Dr. Kohane from a large medical database. We are more of a cross-sectional database.

The information that we have from 14 sites across North America, the network has an emphasis on the medical conditions that occur in children with autism spectrum disorders. A lot of what has driven the development of the network has been this belief that it is more of a whole-body disorder. We also have generous funding from HRSA to serve as the Autism Intervention Research Network on Physical Health, which helps us to do additional research, as well as develop evidence-based guidelines for care.

A lot of our work has already been reported in a supplement to the journal Pediatrics in November 2012. I encourage you to look that over. It has open access at that link there. We have actually over 6700 children with data at this time in our

network. I'm going to briefly report on some of the co-occurring conditions and symptoms. You heard a lot of this from both Dr. Kohane and from Dr. Croen's presentations. We see a lot of GI disorders, a lot of nutritional symptoms, partly due to variations in diet preferences and in use of supplements that these families use in an attempt to treat or improve their children's health.

We have a lot of complaints about motility issues from both extremes, either explosive diarrhea or severe constipation. In some of the written comments that we've received here today, I saw a number of families complaining about that as well. Epilepsy is a concern; sleep disorders, and we're going to be hearing both of those in a lot more detail later today; immune conditions, which are also going to be addressed, and we've heard a little bit from Dr. Croen about mental health conditions as well. When we look at the GI disorders reported across the Autism Speaks Autism Treatment Network, again you see here some of the data, any problems in the past three months and

then chronic conditions, continuing to have symptoms across the past three months, in these two categories. So we see that there was a lot of problem with constipation and diarrhea, the chronicity of these conditions; abdominal pain, other GI symptoms, nausea, symptoms of bloating; and then overall, "any GI problem" being reported in over half of the patients. So it is a significant concern.

This also raises another concern or a problem with assessing this and a problem that we've heard from families, where again that their physician was dismissive about this: My child has all these GI problems. Yeah, we see that in autism. And so nothing is done, when in fact a fair amount could be done. The other problem with autism, a communication disorder, problems with social interactions and verbal and nonverbal communication, is accurately identifying issues such as abdominal pain or nausea. Many times this is not well expressed. It relies on parental belief or understanding of their child. Parents are the experts of their child. But these can be

difficult to interpret and understand.

A little more regarding GI disorders and this is similar to what we were just seeing from Dr. Kohane. We look at numerous studies that have been done over the last 15 years looking at GI problems. Is it really more of a problem in autism or is it as prevalent and simply not recognized compared to typically developing people? Few of these studies have comparison groups. In those that do have a comparison group, all of them find the rate of GI problems far greater in people with autism than in the comparison group, and at least one of these also had a comparison group of other developmental disabilities to look at.

As Dr. Jain I think mentioned earlier, a range of 9 to 90 percent; that's very helpful, isn't it, in managing this and answering this question? So some of the things that we're hearing this morning are going to help us, hopefully, get a better understanding of that.

Seizure disorders in children with autism. And at the time we did this, we had 2500 children in the registry. We had about 16 percent at that time

with epilepsy. We found no differences according to their ASD diagnoses, Asperger's, autism, or PDD-NOS, nor gender. We did see higher rates among white children and Latino populations and higher rates in children who have an IQ lower than 70, which was consistent with some prior reports in the literature.

Parents also reported that their child had skill loss or regression to some extent. That was higher in children with seizures. So you start seeing that these children are having a bigger picture, that it's not just neurologic, but there may be other aspects associated to this. What we've also seen in our population is that the children with seizure disorders among the population of children with autism have a higher rate of GI problems and of sleep problems. So this is difficult to fully explain unless you take a whole-body approach to this. They also have lower Vineland Adaptive scores and some of their Child Behavior Checklist scales, which pertain to symptoms such as anxiety and over-activity, are also different.

Sleep disorders. I'm very pleased we've got a really good group talking about sleep later today. Previous reports have ranged from well over half to over three-fourths of children with autism having sleep problems and approximately half that rate in children without autism. In one of our studies that was published in that supplement, where we looked at about 1200 children, we categorized these as good sleepers, mild sleep problems, and then moderate to severe sleep problems, and that was occurring in -- about over half were having some degree of sleep problems.

We do see a lower incidence of sleep problems as these children get older. We also see that the sleep problems are associated with an increased rate of daytime behavior problems. This is one of the areas that we are trying to better tease out. If we treat the daytime behavior problems, can we have better sleep? If we better address the sleep problems, can we improve daytime behavior? I know that my own behavior improves when I get good sleep, and we believe that's true for people with autism as well.

Psychiatric symptoms, we heard a little bit about this. ADHD is reported in 40 to 78 percent of children with autism, and we get a lot of reports of this in our registry information as well, 37 percent scoring in the clinical range on the attention subscale, 14 percent on the aggressive subscale, and about 22 percent on the hyperactivity subscale of the Child Behavior Checklist, which is a well-validated instrument.

This is a non-color version of Dr. Kohane's overlapping boxes and squares. It might be easier to understand. But it has -- this is an effort to show you -- and this comes from the National Survey of Children's Health -- the prevalence of some symptoms, such as ADHD, behavior-conduct problems, depression, and anxiety in the general population through this National Survey of Children's Health.

When we look at how frequent these other conditions are and then how many of them have a co-morbid behavioral condition and how many have a co-morbid physical health condition, we see that the autism group is dramatically different from

other groups of mental health or behavioral health disorders. So again, there's something more here, autism or autisms.

When we look at the use of medication -- and what we have found is that the best predictor of medication use in our children with autism is the presence of one of these co-morbid behavioral or psychiatric diagnoses. So the children who have ADHD as a co-morbid diagnosis or have anxiety as a co-morbid diagnosis are more likely to be receiving medications.

When we look at our registry -- and at the time that we looked at this we had about 2700 children reviewed -- the number of children in the under six age group was about 1500 and about 10 percent were on some medication, a psychotropic medication. As we get older, we have higher and higher rates of medication usage, and this has been seen in other reports that have been done, indicating that by the time we hit our teen years about two-thirds or more of adolescents on the spectrum are receiving medication, psychotropic medication directed at treating some of their

symptoms.

When we look at -- if you've seen some reports of our overall findings in the registry, which is roughly 20 percent, it's far less than what you see in other reports, and it's because we are picking up a larger percentage in our registry of younger children. Medications that are used are the typical medications you might expect for these symptoms of hyperactivity or anxiety and then the atypical antipsychotics, which are increasingly used to treat what is referred to as "irritability"; and alpha-agonists are also used for treatment of either sleep problems or ADHD symptoms. The co-existing psychiatric diagnoses are a lot smaller than you might have expected, and part of that we believe is again the young age of our population -- we don't diagnose depression in many three-year-olds -- but also up until the DSM-5 technically speaking you weren't allowed to give any of these other diagnoses because it was the child's autism -- again, almost a dismissive approach to the problem.

Many of these children are treated without

having a clear diagnosis, so there's a lot of symptomatic treatment in our population. I do want to acknowledge the folks who are involved with the ATN and the ARP through the Clinical Coordinating Center, my colleagues Jim Perrin, Brian Winklosky, Kirsten Klatka, Karen Kuhlthau, Alix Nozzolillo, and Jessie Figueroa, as well as our help from Autism Speaks and our funders.

I had a couple of other comments I wanted to make that really follow up with Dr. Kohane's comments. Parents are the experts on their children and we need to listen to them, and many times we see parents saying: My physician hasn't listened to me. So we've tried very hard to make physicians more aware of this. We've seen that simply treating these problems as you would in any other child, can be effective a good number of times. But then we run into those problem ones, the ones that are unusual, that we can't figure out. So a lot of this is validating common wisdom.

If we would use good clinical sense, we can have good outcomes for many of these children. Parents are the experts, and try not to be so

dismissive. So one of the things I like to remember is what Yogi Berra once said: "If I didn't believe it, I wouldn't have seen it." And we need to think about that when we're looking at the whole problem. Thank you.

[Applause]

Dr. Insel: Well, those are terrific presentations to begin the discussion. There are a few people who have joined us since we did the introductions. I just want to make sure we capture everybody who's here. Alison, I think you came in later. Maybe we can just go around and those who didn't have a chance to introduce themselves could do that now.

Ms. Alison Singer: I'm Alison Singer. I'm the Co-Founder and President of the Autism Science Foundation and I am the mother of a 17-year-old daughter with autism, and I also serve as legal guardian for my now 50-year-old brother with autism.

Dr. Insel: Tiffany, I think you --

Dr. Tiffany Farchione: Hi. Tiffany Farchione. I am the Acting Deputy Director of the Division of

Psychiatry Products at FDA.

Dr. Josie Briggs: I'm Josie Briggs. I'm the Director here at the NIH of the National Center for Complementary and Alternative Medicine.

Dr. Jeffrey Wood: I'm Jeff Wood, an Associate Professor of Educational Psychology and Child Psychiatry at UCLA.

Dr. Robert Ring: I'm Rob Ring. I'm the Chief Science Officer at Autism Speaks.

Dr. Insel: All right. Let's open this up for discussion. We've got about 15 minutes or so. So let's start with Dr. Naviaux.

Dr. Naviaux: I have a question for Lisa Croen related to the co-occurring use of atypical psychotic medications and anticonvulsants and their potential confounding role in the prevalence estimates of obesity, dyslipidemia, and diabetes.

Dr. Croen: Thanks for bringing that up. I got the same question from Rob as I sat down. Yes, it's a very good point. We know that many of these medications that people take for epilepsy and psychiatric conditions are known to increase weight gain and have lipid problems associated

with them. So that's something that we have to look at.

We have looked separately at medication use among the cases and controls and, as you'd expect, there are much higher rates of psychotropic meds and antipsychotics, for example, and we need to look at how much of the increased prevalence of the medical conditions can be accounted for by that excess medication use.

Dr. Insel: Jose Cordero.

Dr. Jain: May I add a comment to that?

Dr. Insel: I think Jose had his hand up and then we'll come around, Anjali.

Dr. Cordero: Hi, Lisa. This question is for you, too. Very interesting data. I'm glad that you have such a distribution in terms of race and ethnicity. I wonder if you could comment if you had a chance to look at differences in terms of co-morbid conditions, something like what Daniel described, in terms of epilepsy in whites and Latinos? Any other differences that may be interesting and may shed some light on the heterogeneity observed here?

Dr. Croen: Yes. We did see some differences, and I'm not going to be able to tell -- there were so many different conditions that we looked at and there were differences. But actually, in diabetes, for example, there were some differences in prevalence across the different race and ethnic groups, but I don't remember exactly what they are. But, surprisingly, many of the conditions had similar prevalence across race-ethnicity. So it was the case that most of the time it didn't, but there were a few conditions where there was quite a bit of variability.

Dr. Kohane: I should point out that for type-1 diabetes, which obviously is a very different pathophysiology, we saw an increased rate of type 1 diabetes in the kids, increased risk in the kids with autism relatively. And that's hard to be compounded, because if you don't treat it – you go down.

Dr. Insel: Anjali.

Dr. Jain: I was just going to comment that in some of our work we looked at psychotropic use and there is an incredibly high rate of polypharmacy.

So it's not just one medicine with side effects. It's often the combination of medications, and we don't know how those interact to cause all kinds of side effects. We know almost nothing about that.

Dr. Insel: Why don't we start at this end with Anshu and we'll just come around.

Dr. Anshu Batra: I wanted to thank all the speakers. This was absolutely wonderful. And I wanted to thank Susan and staff for organizing the speakers today. I as a pediatrician, a developmental pediatrician, this resonates with me in terms of looking at the whole child approach. So I'm very excited about having this presentation.

My question is to all the speakers. Now that we've identified these tendencies, how -- what can you do to guide me as a pediatrician in the community to now treat my patients? What guidelines, what approaches can I take home to then use for my patients?

Dr. Kohane: I'd like to just jump in. I think that, if nothing else, this suggests the model for

other complexes for kids, for example the kids with mild dysplasia. We have the neurosurgeon -- we have a team. I think that what this does is, both for the payers as well as for the providers, to start thinking about what are the teams we need to put in place.

So pediatrics is all about anticipatory guidance, right, so anticipatory guidance for the health care system, which is this is what we can expect. Don't let the parent bounce around with tummy aches on their kid until something bad happens. Don't wait until there is an anxiety -- just have assessments. It's going to be cheaper and certainly a better experience if the mother is not the first one who has to, or the father push this to the pediatricians. Instead, have the pediatricians both recognize it and have a team in place to actually take care of it.

I think in terms of health care economics and outcomes, that's what we need. We have a few, but only a few, successful models of that in some complex diseases for kids.

Ms. Redwood: My question was very similar to

Anjali's. The presentations were excellent. I could ask each of the speakers at least an hour's worth of questions. But what we really need as a committee is concrete next steps, because we hear from these families over and over and over again that these medical conditions are being ignored, they're not being assessed, they're not being treated. I think all of us could agree that the data that was presented today is just the tip of the iceberg. I know with my own son, he suffered needlessly with many of these underlying co-morbidities, and my concern is we don't have this on the radar screens of our general pediatricians and our physicians and clinicians who are providing care. So what can we do as a committee to get this information more widely disseminated? How can we develop clinical practice guidelines that just incorporate an assessment to ask that question: Is your child sleeping during the night?

Are they having problems with constipation and diarrhea? And then where do we go from that to really evaluate them, because many of these are subtle and they're overlooked, and we see the

behaviors, but we're not looking at what the causal mechanisms might be for that. So that's what we really need to know today.

Dr. Malow: I wanted to expand on that. I was going to bring up the discrepancy where Lisa Croen showed us, I think it was 18 percent sleep problem prevalence in the claims data, but you pointed out the 50 to 80 percent report that parents have. I don't think sleep is unique. I think GI is another really good example of that.

So I think figuring out a way to understand that discrepancy -- we have some idea in sleep. It may be the behavioral problems are eclipsing and overshadowing, so the pediatricians never get to sleep because they're hearing about the behavioral issues.

But those and other co-occurring conditions could actually be drivers of the behavior. And then I think the other thing is we need to figure out tools to give the pediatricians, because they're so busy and they have to do so many different things, the last thing they want to do is open up Pandora's box and hear about sleep

problems or GI problems or something else if they're not equipped to actually treat them. So I think we need to think about what we can do to help the pediatricians and other health care providers address the issues that are brought to them.

Dr. Insel: John.

Mr. Robison: I think that we should, at least I would hope, we would all be able to agree that these co-occurring conditions are the rule and not the exception in autism. And yet they are not a part of any of the recognized definitions of autism, and I think one of our fundamental problems here is that not enough medical practitioners are aware of how common these co-occurring conditions are. I guess I'd like to see our committee take some kind of definitive action, maybe in doing something with NIH or with HRSA or CDC, to take steps to make our medical professionals in America more aware of the high likelihood of these co-occurring conditions, because here we have a situation where effective treatments for many of these things currently

exist.

And what I took away from all of these excellent presentations is that a great many children and adults are suffering needlessly because people say, that's their autism, or they ignore it, it's just not recognized. And yet we have tools now to help, but we are not deploying them. I think that's a really important point that I hope we can act on.

Dr. Insel: Dr. Coury.

Dr. Coury: I agree with you completely, John. There is work going on, as I mentioned, the Autism Intervention Research Network on Physical Health. The funding from HRSA and MCHB for that, part of that is set aside or earmarked to conduct and develop best practice guidelines and evidence-based practice guidelines.

As you've heard, there is no evidence. So currently these are consensus expert guidelines based on what there is in the literature. Then what we are doing across the network is testing these guidelines to see how frequently they do work. So far, regular standard treatments will

work. As Dr. Anshu down the way here mentioned, a lot of it is knowing that the problem is there in the first place.

So we are working hard to get physicians to add these to their regular screening in evaluating these children. Just as we know with a child with Down syndrome that they're at increased risk for low thyroid, for atlantoaxial subluxation, for developing leukemia, and so physicians monitor for that as they follow a child with Down syndrome, we're pushing to specifically ask those questions about constipation, diarrhea, any unusual spells, sleep problems, and so forth, and then working on that.

So there is funding and there is work currently going on through the AIR-P Network.

Dr. Insel: Could we just have you unpack that a little bit? Because I think what you're hearing from the members of the committee is the interest in how do you take this to scale. It's really great that in the four presentations we heard you're sort of seeing that the best case scenario -- and Anjali, you even used the term

"surveillance bias," like there might even be too much in the case, because there's such a focus on health care for these kids. And yet all of us know, because we've heard this over and over again from public comments at these meetings, that in fact in the real world of practice these things are neglected.

So if you could just give us a better sense of what that pathway, as maybe it was followed for Down syndrome, to actually get those kinds of screening materials to every pediatrician in America? Who does that and what are the steps to make that happen?

Dr. Coury: It's a long, arduous pathway. It doesn't happen overnight. Physicians are notoriously slow to change. So the problem is that we have to have the evidence, it has to be presented as a best practice or clinical guideline, and for that to be acceptable to physicians it needs to come from a credible source, such as the NIH or from their own professional societies, whether it's pediatrics, neurology, or whatever, the AAP, the AAN, and so

forth.

We have to have that stamp of credibility for them to do that. The next thing is dissemination and, as you heard me say, we've been doing the standard dissemination routines of publishing, having conferences, and trying to get the word out through that. That is also a slow process. We're using more technologically savvy methods such as webinars, but people don't always log into those.

The next step is really getting out and changing practice. The good news is that across the medical specialties maintenance of certification is in place and a requirement for that is quality improvement, showing that the clinician is actually changing their care and improving their care. So our next step is trying -- because autism has become such a prominent concern, trying to get practices to change and developing ways that they can change how they are identifying and managing these children in their practice. So we're starting to get out in there hand to hand, right on the ground with them.

Dr. Jain: I'd like to take issue with that a

little bit, in the sense that I think that it's not okay to -- we need to take those steps and they do take a long time, but I also think we need alternative pathways to get there. The fact is the kids are getting treated, but they're not getting treated well necessarily, but they're getting treated with medications, with treatments. So there is collective wisdom out there that I think we should work hard to make available as the best available evidence until we know differently. I also think that some of the advocacy organizations and the groups like: Patients Like Me, where patients are in direct communication with each other about what works best for them, can be leveraged to get more immediate information about what is the best of the evidence telling us to do.

Dr. Dawson: One of the really great deliverables, sort of speak, that has come out of the AIR-P are the toolkits for physicians and also for families. I wonder about the idea of having a toolkit that really is focused on anticipatory guidance around these conditions for pediatricians -- of course, you're linked to a great advocacy

organization -- and just trying to get the information out through that route.

Dr. Coury: That is one of the pathways, and we are working on that. The American Academy of Pediatrics is in the process of revising their guidelines, which came out in 2007. So they're already being revised as we speak.

Dr. Kohane: At the suggestion of annoying all my colleagues, would it be feasible to, once the AAP or some other organization endorses it, to actually generate a little card for parents to come and give the pediatrician and say: These are the Academy guidelines for autism? Because I know that parents do that always now with genetic tests. And after the pediatrician gets over the embarrassment of actually not being up to date on that, they actually do what they can to help. So I think parent-driven advocacy for the guidelines, not going over the organization, but immediately once an organization adopts it, to actually have the parents be the armed vehicle for that change in behavior of the clinicians, might be the best.

Dr. Cordero: I think that that would be very

helpful. I think the challenge is that we need a little bit of a systems change also, because what happens if you look at all the co-morbid conditions? Some are GI, some are psychiatric, and basically you're talking about different people that traditionally are in different places. We need to find a way to have more of a multidisciplinary approach for parents, instead of having to go today and say, well, line one of the card if you go to the neurologist, line two to the GI person, so that everyone would be in the same place. I think that some of the groups, like ATN, is trying to do that. But we need to have a more comprehensive, multidisciplinary approach to working with I don't knows that have autism.

Dr. Insel: I'm mindful of the time, and we're right at our break time. Obviously, there's a lot more to talk about. I think we'll come back to many of these issues. Like Lyn, I have about an hour worth of questions that I've already scribbled down. But we'll have time at the end of the day to circle back to some of those. Let's take a break and reconvene right at 11:00 for the

next session.

(Whereupon, the workshop participants took a brief starting at 10:45a.m. and reconvened at 11:00a.m.)

Dr. Insel: I want to make sure we don't fall too far behind on the schedule. So if you'll take your seats -- thank you -- I'll turn it over to Gerry Dawson.

Dr. Dawson: Welcome back, everyone. We're now beginning the part of the day where we're going to delve in more deeply into a few of these areas. We're going to start with psychiatric disorders, and we've got a really great group of complementary speakers.

Our first speaker will be Larry Scahill, who is a Professor of Psychiatry at the Marcus Autism Center. Larry.

Dr. Scahill: Thank you. How do you do? I wasn't nervous until I got here. Those first four talks were outstanding, and so data-driven.

And I don't have much data. I have lots of data, but that's not the presentation for today. For the sake of my chair, Barbara Stahl, I'm

Professor of Pediatrics. I've changed, I know; in Pediatrics.

Dr. Dawson: So it's wrong on here.

Dr. Scahill: The Marcus Autism Center is a rather remarkable place. We see about 5,000 children a year. A very high percentage of them, autism spectrum, and the rest of them have various types of developmental disabilities. It's a wonderful, wonderful place, and we are growing the research portfolio over the past few years.

Disclosures: I've just gotten used to doing this. These are companies that, believe it or not, have an interest in autism and that's why we talk to them. Most of our funding comes from the NIMH.

So briefly, what I'm going to talk about is outcome measurement, because I'm a very practically oriented person, a clinical trials person, and I'm very interested in the outcome measurement. If you can't measure it, you can't really study it. And then a little bit about our Autism Speaks Task Force; and a big interest of mine is the patient, or in our world parent, reported outcomes; and then a little work that

we're in the midst of, an NIMH grant to develop anxiety measures in children with autism.

Director Insel said it right at the beginning. I'm a little bit shaky on this notion of co-morbidity. I've been thinking about the co-occurrence of anxiety, the occurrence of anxiety in children with autism, for the past 14 years or so. And I came to that through work that I had been doing at Yale University in Tourette's syndrome. Tourette's syndrome, like autism, has lots of features. It's defined by tics, but there's often repetitive behaviors, OCD, ADHD. And a lot of times those other components were a bigger deal than the tics themselves.

So we didn't really talk too much about co-morbidity. We talked about what's the biggest problem and trying to focus our attention to that. So I kind of brought that notion to the work in autism.

To underline, our practical charge here is we've been studying through NIMH multi-site work, mostly through the research units on pediatric psychopharmacology, for a number of years. Our

first publication was back in 2002. It's not the last century, but almost.

You see the targets here. These are targets that we have measures for. If we had some other brilliant drugs out there for targeting other things, we'd have a challenge on how to measure it. So we really have to keep ourselves working on outcome measurement. What makes a good outcome measure? It's got to be relevant. That's obvious, that's really obvious. It should measure a separate and measurable construct.

Again obvious, but you'd be surprised. If you start looking at measures, they often do not accomplish those simple two tasks. The distribution should be orderly. That means that we should be able to talk about the mean and the standard deviation, because when we talk about change we're talking about oftentimes in standard deviation units, so we need to understand something about the mean and the standard deviation. We've done some wonderful work with observational measures and what do we find? The standard deviations are bigger than the means.

That's not too good.

It be great to have normative data, and when I say "normative" I mean in developmental disabilities; I don't mean in the general population, because that's going to help us interpret those means and standard deviations. Otherwise, we're hard pressed to know what they mean.

Internal consistency: Much is made of this. Professor Cronbach is probably the most cited paper. His 1951 paper is probably the most cited paper in all of psychology and psychiatry. But, it's important, but a little noise is okay. Good test and retest. We learned from the Autism Speaks Task Force that, surprisingly, we don't know a whole lot about the commonly used measures, how do they behave in the absence of intervention. That's test and retest. If you don't have good test and retest, you've got a very noisy measure. You've got to have that. And it's sort of the Goldilocks thing: It can't be too long and it can't be too short. It can't be too narrow. So it's got to be just right. It's got to have coverage, but it

can't take an hour. We want handy-dandy, but we also want coverage.

Sensitivity to change, that's obvious, but you really don't know until you've got a good treatment to test because if it doesn't change you don't know if it's the treatment. Autism Speaks Task Force, there were three of them. This is the paper that was published in JADD. Some of the folks that were on that committee are here right now today. It was a very interesting enterprise. The issue of co-morbidity was threaded throughout that discussion. I commend you to that article.

So, the committee could not identify a measure that was ready for prime time. So we identified three that looked like they have some promise, they're so-called appropriate with conditions. The comment on your far right is the conditions that kind of emerged. If a measure is going to work in this population, it's got to work across the full range of IQ. I shouldn't say it has to. It would be good if it did. And if it doesn't, that narrows the scope of its application. So no good measures just yet. This, fortunately, has helped us focus

on this and move forward.

We learned a lot from this monograph from the FDA. If you haven't stumbled on this, this is well worth looking for. They don't mention autism in this whole monograph. This is really about outcome measurement. It says if you want to have a claim of a drug or a device and you have a new outcome measure, you better develop it along these lines or you're going to have a hard sell at the FDA. And what's good about it is it's on the money. It is -- they really have offered a road map on how to build an outcome measure.

Here's the conceptual problem for me. If it is the case that anxiety disorders are no different in children with autism or typically developing children, then just measure anxiety, and if you're going to develop a medication or a treatment for it, it should be relevant to typically developing children, children with autism, and so forth.

But if it's not the case, if it's not simply that this child is unlucky and his two conditions, we need to think a little differently about it. This may be what I would call the complication

model, which is that the presence of autism increases the risk of evolving a condition that we could label anxiety. It's sort of like if you play football and you have a bad knee and you start walking funny, then suddenly you've got a hip problem. It's related. It's not an accident.

That's a sort of blended and amplification type of situation. More and more, that's the way I'm thinking about it. Convergent model: There are people that wonder -- and I don't think we can dismiss it out of hand -- that anxiety might be actually part of autism. This is a comment going right back to Leo Kanner, that he used such terminology.

What I can tell you -- I don't have time to present the data -- on measures of anxiety, we have children with autism in fairly large samples who are low on anxiety, some who are in the middle, and some are high. So I'm not really convinced about the bottom, but I don't think we should dismiss it.

A practical problem: We have to disentangle anxiety from ASD. Social avoidance, for example;

because some people with autism may not be that interested in interacting with other people, so they're avoidant. Is that the same thing as being anxious about interacting with others? Could it be that social avoidance over time makes a person not very good at social interaction, so then it becomes a socially anxious kind of a thing?

Cognitive language delay: I was interested that in the wonderful talks we heard earlier, I didn't hear much about developmental disabilities like language delay. But I suspect, especially with the new frame in DSM-5, that language disorders will emerge as an important area. But even children who don't have cognitive delays may not have the best use of language.

So getting the child to tell you about their internal experience may be difficult. It may be that there is some blending of anxiety in children with ASD. So for example, I had one mother explain to me that her child is very insistent on routines at breakfast and various routines throughout the day. And I thought, yes, I've heard that before. But the mom went on to say that it's not just that

she is insistent on these things; she's always on the lookout for whether this is going to be some deviation in the routine. That's starting to sound a little more like anxiety to me.

Blurry boundaries: This is true in typically developing children as well. Children with separation anxiety often have generalized anxiety. Children with generalized anxiety often have social anxiety. So that's true with typically developing children. Given some of the issues we just talked about in children with ASD, those blurring boundaries are probably going to be even a bigger deal.

I'll tell you my wish: My wish is that we are not going to focus on specific anxiety disorders in children with ASD, that we're going to focus on anxiety and we come up with an outcome measure that is not seven items of this and four items of that. We have this wonderful NIMH grant and we use the FDA monograph as a template. We started with six focus groups with parents. We asked the parents to tell us about what they thought were manifestations of anxiety.

It's been said here a couple times, parents are the experts of their children. They told us a lot. We learned a lot from them. We have now taken those 600 pages of transcripts and we've pulled out items - more about that in a minute. We're now going to take those items and put them on the web and hopefully we'll get 900 families to fill them out, and we'll start doing a factor analysis and the like.

Once we're done with that, we're going to bring in about 90 to 100 children for face-to-face evaluations to look at that measure and also a revised interview measure that's been around for typically developing children with anxiety.

Finally, we're going to try and take the children with high anxiety and compare them to children with low anxiety and look at biomarkers like heart rate variability.

So what did the parents tell us? They told us many, many things, and I've boiled this down really to one slide, perhaps unfairly. They told us that they noticed changes in their child's behavior in certain situations. I really

appreciated their observation that they were talking about change the child's behavior, and you can see what it says on the slide.

We asked them to tell us about the behaviors, not just the triggers, and they told us things like requesting for reassurance. Now, that's in typically developing children as well. Avoiding behaviors because of the situations where this distress was observed; and what we came to call child coping behaviors. These are the behaviors that the child resorted to when they encountered these triggering situations. For an outcome measure, the money is mostly in observable behaviors, I think you'd agree.

So we took those 600 pages. I'm only showing a few. You can read them. I won't read them out. I just give you an example of how you go from testimony from the parents that was often rambling, sometimes right on the money, sometimes -- we had to boil it down. We had to boil it down to simple items that could be read off and scored on zero to three. This is just a few examples. I went to the middle of the pack of the 52 items and

just made a slide out of it. We'll have altogether 71 items that we're going to ask parents to comment on, on a simple zero to three scale.

So, put those on the web. We're hoping that we get a dimensional parent-rated measure. We're hoping that it is in the neighborhood of 30 to 35 at best items. We are then going to do assessment of the children and look in a more fine-grained way how this maps to other measures, to establish reliability and validity, and then we're going to do this heart rate variability. The heart rate variability, we've now collected pilot data. We can measure this in children with autism. I think it's a very cool possibility.

These are our collaborators at Emory: Karen Bearss, who is a psychologist that moved from Yale down to Emory with me, and our good friends at Ohio State, and our good friends at CHOP in Philadelphia. Thank you very much.

[Applause]

Dr. Dawson: Thank you, Larry. I'm sure there'll be many questions at the end. Our next speaker is Jeff Wood and he's Associate Professor

and a Clinical Child Psychologist from UCLA. I know Jeff has done a lot of work in the area of treatment of anxiety, so we're looking forward to hearing you.

Dr. Wood: Well, thanks for having me today, and nice to see you all. I'd like to start by first thanking the organizations that have helped to fund my research, Autism Speaks, NICHD, and NIMH, without which I certainly would not be here.

We have already discussed the issue of psychiatric co-morbidity in detail today, and I am citing yet one more slide of previous research by Leyfer and colleagues, which shows in their structured diagnostic interview study using the KSAD's that children with ASD generally had at least one co-morbid psychiatric diagnosis, if not more. Only about 27 percent in this study did not.

Today I want to talk first conceptually about some emerging thinking in my lab about the possible reasons for some of this co-morbidity and then move on in the second half to discuss the treatment research that we've been working on.

One of the really puzzling characteristics to

me in my work on the co-morbidity of anxiety in ASD has been - why the rate of anxiety is so high in children with ASD? And inn searching for reasons, ultimately we've been looking for both environmental as well as interpersonal factors that might explain the linkage. One interesting possibility which we've been exploring with our data with children with ASD is that possibly executive functioning deficits are related to the anxiety issues that are experienced with some children with ASD. In general, executive functions are related to basic cognitive abilities such as inhibiting impulsive responses and shifting cognitive sets and thinking about stimuli in a different way in an adaptive sense and executive function deficits have generally been with many psychiatric disorders, especially ADHD, but also schizophrenia, mood disorders, and anxiety disorders in the general population.

These deficits are very pronounced in people with ASD as well and it seems that there may be a common linkage explaining why there is such an extent of co-morbidity in children with ASD in

terms of these exact same diagnoses. So preliminary research in my lab has been looking at these linkages and indeed finding correlations between executive functions as measured by simple tasks, such as reversed number responding and other types of cognitive tasks and scores on parent-reported measures such as the CAS-E on anxiety, ADHD severity, mood symptoms, and so forth and seemingly, there may be some important linkages that should be further investigated.

There's some other research that's been published in the literature already in ASD, one which linked executive functioning deficits with psychotic spectrum disorder symptoms such as illogical thought in children with ASD, in other words that there is greater executive functioning deficits in children with ASD who have more psychotic symptoms in the form of illogical thought.

So, this is a very preliminary set of findings. These are not published in my laboratory yet. But again, in sharing sort of our thinking about how to understand these co-morbidities this

is one important direction that we feel the field may need to go in. It's also interesting to consider that this notion of autisms as a multitude of variably caused disorders may be very helpful in understanding why some people do and others do not have certain co-morbidities in autism.

A parallel and very interesting set of work has been done in the field on psychopathy, particularly in adults, which has used phenotyping and basically personality trait psychology to understand two extremely distinct pathways to the development of psychopathy, one of which involves essentially extremely low levels of neuroticism and fearfulness and the other of which involves very high emotionality, high neuroticism, and poor emotion regulation and poor executive functioning. There are brain correlates that have been mapped onto these sorts of subtypes of psychopathy and different clinical outcomes that are linked with them as well.

So in additional area of interest, I think, is to identify at a phenotypic level are there

patterns of traits that individuals with ASD have which may ultimately help to explain why certain people have high risk for some co-morbidities, particularly psychiatric ones, and other people have risks for others or no co- morbidities whatsoever.

Along these lines, some initial genetic research has been suggesting that some of the same markers for co-morbid psychiatric disorders, such as anxiety and depression, which are present in people without ASD are also present in people with ASD who have the same co-morbidities. I would point to Ken Gadow's work as one example of excellent research in that field. At any rate, a model that Ken and I published a few years ago in trying to understand some of the co- morbidity effects also looks at environmental factors.

This is the model and, in short, we're focusing on ASD-related stressors which may produce greater susceptibility to in particular anxiety, but other kinds of mood symptoms too, such as anger and depression. The basic idea is that having ASD often produces very specific daily

stressors for individuals that other people don't necessarily experience.

Some examples are social confusion and unpredictability of social encounters, peer rejection and victimization experiences, prevention of accessing preferred activities, for instance during school. So the idea is that there is a long, decades-long, body of research showing that daily stressors that are frustrating to people increase anxiety, anger, and other negative mood symptoms and if people with ASD are experiencing a high level of daily stressors then it might follow that there is heightened anxiety and other types of mood symptoms that are correlated with this.

A dissertation study that's recently been completed in my lab has found both measuring stress at the parent report level and at the cortisol level is indeed linked with higher levels of these types of mood symptoms as reported by both children and parents. The interesting question to ask is, is there a linkage then between this increased level of emotionality and

negative mood and some other, more distal effect such as increased social avoidance and avoiding coping and reactive and aggressive coping on the part of children that may explain even a broader swath of psychiatric symptoms, for instance those in the disruptive behavior domain. This has yet to be determined, but our model would predict it and we're trying to investigate that further.

Very briefly, we've also been interested in the idea that Dr. Scahill brought up about the differentiation between anxiety and autism symptoms per see. In a paper published in my lab using structural equation modeling, we essentially found that the severity of ASD symptoms as indicated by things like the ADOS and the ADIR and the SRS had essentially an almost zero correlation with constructs related to anxiety, separation anxiety, social phobia, and total anxiety based on child, parent, and clinician report. This was done mainly to investigate the idea that there is this overlap and yet to what extent do anxiety severity and autism severity actually travel together in the autism population? This one study suggests

that it may be a fairly low level of covariance.

Moving on to the treatment research that I've been doing -- and I realize I don't have much time -- we've been studying cognitive behavioral therapies for both the co-morbidity of anxiety and OCD in children with autism and youth with autism, but also more recently CBT or core autism symptoms themselves and we had found in earlier work that CBT, when adapted carefully to people with ASD, seemed that it was having some impact on parent-reported autism symptoms. So we followed these early studies up with larger studies using observational measures of autism symptom severity to determine whether CBT might be useful in actually addressing the core features of autism, such as perspective-taking, low social motivation, repetitive behaviors, and so forth.

In doing so, we have been concurrently developing a measure to try to personalize the measurement of outcomes in this very study or set of studies. The idea here is that parents identify three top problems that their children are experiencing within the realm of autism symptoms

and then they rate these problems continuously throughout treatment, and ultimately we want to know if these three top problems can be improved, personalized to each child with CBT; and secondly, if that improvement is related in any way to broader improvement on more traditional measures like the SRS and the ADOS and so forth.

We've been using videotaping in the home to try to validate this particular measure. Our report is due to Autism Speaks in a few weeks and fortunately, there is good news. There is a lot of convergence between independent coding of these problem behaviors and parents' coding of the behaviors on a daily basis. So the measure looks promising. We don't know how it's going to perform as a measure of treatment outcome yet, but that is coming up.

In the future, it feels like CBT may be a worthwhile treatment approach to continue to assess and potentially disseminate. I recently have published an article on potential implementation plans for any evidence-based intervention into schools and community health

clinics, due to the dire need of creating access to good quality interventions in our communities and not just leave them in our research centers. So this is in press in Behavior Therapy.

I feel that currently the treatments that I've been developing are too preliminary to actually be moving to an implementation stage. However, with the help of NICHD we are currently testing CBT in a more stringent clinical trial versus an active alternative CBT treatment for the anxiety co-morbidity specifically. This is a three-site trial and we may have a clearer idea of how beneficial CBT for children with autism might be at the end of this trial, as well as the ones funded by NIMH and Autism Speaks for core autism symptoms.

My final point is that I think, looking towards the future, investigating genetic, neurologic, psychophysiological, neuropsychological, and personality substrates of co-morbid psychiatric disorders in ASD may be very beneficial in understanding better how similar are these co-morbidities to the same types of symptoms that are in the general population. Two examples

of this type of research might be functional neuroimaging of people with and without high anxiety in the context of ASD, how much does the brain look similar to people who have high anxiety that don't have ASD, for example; and second, pursuing this idea that executive functioning deficits and stress may predict greater co-morbidity concurrently and over time seems like a fruitful direction to perhaps pursue. Thank you for your time.

[Applause]

Dr. Dawson: Thank you, Jeff. Our last speaker for this section is Evdokia Anagnostou. Evdokia is a Senior Clinician Scientist and Associate Professor at the Bloorview Research Institute at the University of Toronto. Evdokia.

Dr. Anagnostou: I took the long way, I am sorry. My job today -- it's a pleasure to be here and I appreciate the invitation. My job today is to just challenge us a little bit on the constructs, on the definitions of constructs. I want to disclose my bias. I am a translational trialist, so my funding is in figuring out what it

would take to take the emerging genomic findings, the emerging basic science findings, and get to novel compounds or all compounds that we have solved that would actually target those mechanisms. So this is my bias and this is the lens by which I see these issues. You'll see how this becomes a little tricky, in effect.

There's been lots of nice data presented on prevalence. I just have this one up just to remind us that it matters when we look. For the first two talks, you saw the discrepancy between the prevalence -- the discrepancy in prevalence in OCD and anxiety. If we're looking at a population that has a mean age of seven, obviously OCD will not be a very prevalent co-morbidity, but if we look at 30-year-olds -- this is the cohort that -- UCLA viewed the cohort from the eighties and it has been followed and classified with the DSM-IV criteria -- then the rates of those co-morbidities look much higher.

It also makes a difference a little bit whether we look at codes, which actually make it possible to do very large-sized research, or

whether we actually use expert clinicians to administer structured interviews and actually make expert diagnoses, which was in this case. So you'll see a little bit of a discrepancy, although not that much. You see that in adults with ASD who have childhood diagnosis of ASD we have almost 70 percent chance of a lifetime occurrence of a co-morbid neuropsychiatric disorder, with anxiety disorders leading in terms of numbers, followed by OCD. These are 30-year follow-ups, so these are 30-something year olds in terms of the means. Some increased prevalence in expansive mood problems and psychotic disorders, but still remain lower than the other problems. And the depression data in this particular cohort has been challenged a little bit.

It's an interesting discussion to have. You'll notice this particular study did not look at ADHD co-morbidity, just because it's not part of the instrument that they used to identify co-morbid conditions.

The other thing that has been reported before and people in the room have actually reported on

this before, is that age is not the only thing that matters. IQ and language ability also matters. In this particular cohort -- and it's very consistent with previous data -- there's a much lower prevalence of anxiety and depression in people who have lower IQ's or have language difficulties. This brings me to the issue that I'm going to start discussing, because I'm not going to give you a prevalence talk. The issue is, is it that people with intellectual disability have neurobiology distinct from people who don't have intellectual disability that makes them less likely to have internalizing disorders, or is it that the way we measure internalizing disorders is more likely to identify those disorders in people who have higher IQ's and higher language ability and therefore we are missing people with the same biological construct in the group of people who have IQ's below 70?

So this becomes this discussion of constructs. So we have high co-occurrence of several neuropsychiatric conditions, more than we expect by the general population numbers. Is it that the

constructs that we have for these diagnostic -- and I don't mean to be facetious about this, but is it that our diagnostic constructs actually do not map onto biological constructs and therefore when we look at co-occurrence this is a moot point because the constructs that we are looking at are not additive because they're not distinct biological entities? Is it that the measurement produces confusion because we're not quite clear what we're calling anxiety -- this has been discussed by the two previous speakers -- in the population, depending on their IQ, their language, and the biological substrate? And what does all this confusion mean for treatment development?

Again, excuse my bias, but my bias would be medication development, new medication development, how do you translate from basic science to treatment knowing this?

I'm just going to bring a couple of examples. Our original -- I'm at the University of Toronto. Most of our funding -- we have some American funding, but most of our funding is Canadian. What we have argued with the Canadian funding agencies

is to give us the room to consider that the diagnostic constructs are not valid, period. So then we basically were able to get funding to create a large biomarker core that recruits children who have ASD, ADHD, intellectual disability, OCD Tourette syndrome, and a bunch of rare symptoms that we typically associate with autism, and create a series of platforms for characterization, but that are diagnosis agnostic. So, all the kids get the same genomics, the same imaging, the same phenotyping for behavior and cognition, and the same electrophysiology.

Then the question becomes, are we validating using this biological system the existing constructs or are we saying that biology does not map to these constructs? So it's just a very early example of this. Lots of data now to suggest that ADHD and ASD have overlapping genomic architecture. This is a candidate gene astrotactin, which is an interesting gene because it does -- it's important for migration, glial-guided migration.

The original cases were reported and they were

intellectual disability, and then a couple of cases were reported and they were ASD. So we combined our cohort with the large cohorts, genomic cohorts that we have access to, and looked at what are the phenotypes that are described for this rare variant, right? And we're getting overlapping deletions and duplications. By the way, there was some debate at some point whether the duplications and deletions would predict different symptoms, and we're not getting that. So, overlapping duplications and deletions will give you in our hands ASD, ADHD, intellectual disability, a little bit of schizophrenia, a bit of bipolar, a bit of schizophrenia with epilepsy. Right? That's a single gene. And there is data now across a variety of those genes.

So what does it mean to have co-occurring ADHD and ASD when the same genetic variance will produce both symptoms? This co-occurring construct is becoming a bit difficult to interpret. In addition, when we look at the rare cases -- we have 46 now cases across -- and we look at what the clinicians put as phenotypes in the database,

the most common diagnoses are ASD, ADHD, intellectual disability, language delay, anxiety, and OCD, so our whole neurodevelopmental neuropsychiatric spectrum captured by a single type of mutation.

I don't want to make it too simplistic. There are variations in the expression of this particular mutation depending on where the cut points are and all of that. But the point is it's very easy to start from a very -- from a single or similar genetic, early genetic difference, and end up with a variety of those neurodevelopmental disorders so one problem.

The second problem is a measurement problem. I'm a neurologist. I'm a little bit cruder than the previous two presenters. So this is the clinical dilemma in the neurology clinic: Does the kid who comes in with generalized anxiety from the general population, who has persistent worries that she cannot control, but they may be unreasonable, have the same anxiety with the low-functioning kid who is not verbal, whose parental report is that he's pacing, he's hyper-aroused, he

has irritability, and he melts down all the time around transitions?

Both get an anxiety diagnosis, but is the biological construct of those two anxieties the same thing? And how do we do translation if we call both anxiety, but we do not know that the biological construct for those two things is the same thing.

And then in an effort to clarify that, we're asking whether biology studies can clarify those questions. Again, I'll show you a little bit of early data, and I don't mean to be simplistic. This is just to see our thought process in this biomarker core. It has already been noted, there is another well-known signature and a signature for anxiety in the general population. Yes, the different anxieties have a slightly different signature, but, you know, going with the generalized anxiety concept for the purpose of this demonstration, we know that we have another drive for this specific brand, we have increased sweating, increased heart rate, and cutaneous vasoconstriction, and we know we can measure that,

as was mentioned before. So we can look at heart rate and heart rate variability and electrodermal activity to measure these things. Our question is, if we describe anxiety in terms of self-report, which in autism is impaired because of communication difficulties, IQ, and introspection difficulties, and if we measure anxiety based on behavior, which is a bit also problematic because behaviors that we used to call anxiety come from all kinds of different constructs in ASD, so irritability for example, can we use physiological measurement to clarify the construct? That is the question.

And we do the same thing with imaging. We have a similar pipeline that we do with imaging. This is a little bit of early data. If you look at heart rate, if you compare ASD to controls -- there are about 440 kids at this point in the sample -- there we go. You get increased heart rate compared to controls in all kids with ASD, and you get a bit of -- this is a paradigm where the kids do two tasks that are anxiety-provoking. This is a task where the presentation of the

stimuli gets faster and faster and faster and everybody gets really anxious, and this is a public speaking task. Then they are doing a series of tasks that require cognitive load, but they are not particularly anxiety-provoking. So there's an attention task, a stop signal, and a social cognition task. You'll see across these tasks you get higher heart rates in the kids with ASD versus controls, but you get a statistically significant difference at baseline and you get a dumping response during the public speaking tasks. You see that, although there is a trend across, this is not a general phenomenon. You don't get it across all domains. You get it around the anxiety tasks, and baseline. For heart rate variability, right now we're not getting very much yet. It could be that we separate these later. I'll show you in a bit. But heart rate variability seems to be putting out other cognitive load tasks.

Then if you look at electrodermal activity, you get controls and you get ASD and you get again this pattern that's consistent with increasing pathetic load. So the question now is, if we split

these kids with ASD to high anxiety and low anxiety kids, would we see a difference in pattern like that? Now, we have a measurement issue, and I'm not even going to go there because Larry spoke about it in detail. So we're as good as our measure, so this is the CBCL anxiety. We're looking at kids are high anxiety versus lower anxiety versus controls.

Clearly, the kids who have higher anxiety look different than the controls, and this is a signature that we see in the generalized anxiety literature. There's nothing atypical per se with this particular pattern, except the kids who have autism who are not supposed to be having anxiety still have this increased arousal pattern, increasing sympathetic tone pattern. So now we have a construct problem again. Is it that our measure is not sensitive enough to pick all the kids who have anxiety and we're only picking the kids who have extreme levels of anxiety and very high sympathetic tone, or is it that the measure is doing just fine, but that the pattern, which is a signature of anxiety in the general population,

is not particularly specific for anxiety in ASD, in which case we have a biological construct problem? In either case we have a construct problem. Right? So what we are doing right now is we are adding groups here, so we have all the kids in the general population with all the different anxieties to figure out what their patterns look like, and we're adding numbers, and we have an imaging core that goes at the same time. But this is again to highlight, we can talk about measurement and we can talk about treatment, but we are not quite sure what our constructs are. We're not quite sure what the construct of anxiety is in this population.

This is my last slide. I would argue that this construct confusion is a critical problem for drug development. And again, this is my bias, but take it as is. If, let's say, anxiety in the general population and anxiety in ASD is the same biological construct, we don't have a problem of medication development. There are plenty of medications that are effective for generalized anxiety in the community, and the main problem we

have that we have to deal with is an access problem: How do we get kids with autism into mental healthcare systems?

The same thing -- you don't have to think just biology. You can think cognitive constructs, too. So in the case of ADHD -- I like this because I see in clinics -- if the attention deficits of ADHD in the general population, which tend to be difficulty in sustaining attention and stopping, are the types of attention deficits we get in ASD, we're good. But if the types of attention deficits that we get in ASD are shifting and orienting and other kinds of problems in the attention pathway that are not typical of ADHD, then we have a construct problem that would make it unlikely that our medications that were developed for ADHD in the community will actually be as effective for kids with ASD. So I would say we need to resolve this issue.

This is a gap in the literature of co-occurring conditions, if you want to call them that, because we need to figure out whether we actually need drug development for these co-

occurring conditions because the constructs are distinct, biologically distinct, or whether we actually are dealing with a common biological construct that exists in the community, that we have treatments for, and it's about service delivery.

The last thing I'm going to put there, just for food for thought, especially in the presence of regulatory agencies, is what do we do with this problem where our genomic information has no sensitivity or specificity for our diagnostic constructs, or vice versa, the diagnostic construct is not showing sensitivity or specificity for the biological pathway? So if we are thinking drug development, we have to, based in the current regulatory context, think about developing drugs for specific disorders. But if the biology we are targeting with the drug development is not specific or sensitive for a specific disorder, then is our regulatory climate the right context to develop effective drugs that make big changes in kids and adults' biology, functional of life, and quality of life?

I'll stop there.

[Applause]

Dr. Dawson: Well, thank you to all three speakers. It's a very interesting session because you really get the sense of this field being at an early stage where we're really grappling with some basic constructs and lots of questions. So I'm sure that the group has many questions, so I'll open it up. Yes, Lyn.

Ms. Redwood: I'm sort of confused. One of the questions I had was with regard to these outcome measures, especially the heart rate variability, with the studies that we have found that abnormal in autism already, whether or not you're actually measuring dysfunction in the autonomic nervous system or if you're measuring anxiety, if somebody could sort of address that issue.

Then the second was the use of beta blockers in ASD, which there's been a few small trials and it's been very helpful in terms of social skills, and I'm wondering whether or not that might also be a way to reduce some of the anxiety, and if anyone is looking at that as well, if it is

something that is a physiological abnormality that's driving the anxiety.

Dr. Scahill: To comment on the heart rate variability, a few thoughts. One is I do think that the studies that have been published already didn't necessarily manage the anxiety question very well. There is one recent one that I think does a little bit better job.

Our take on it is that we're going to try to do a better job of defining anxiety and then see how it maps to heart rate variability, not the other way around. If it does, then heart rate variability could serve as an early marker in early drug studies that would be more precise than some of our measures. On the issue of beta blockers, right now I would say we have a challenge to measure the outcome, but it's not a bad idea.

Dr. Dawson: John.

Mr. Robison: Go ahead. You were about to answer.

Dr. Anagnostou: I was just going to make a very brief comment on the beta blockers. I think

that's the question. If the lower-functioning kid who's walking around and pacing and touching and has extreme heart rate and high blood pressure has a different anxiety than the other kid, then the evidence for the SSRI's for the lower-functioning kid would be not very good and we would think about mechanisms of manipulating sympathetic tone to treat that child. So we need to figure out if that child's anxiety is the same as the anxiety of the other child.

Mr. Robison: I just, I'd like to offer a perspective from being an autistic child. You know, my grandfather always said to me: Boy, it's easier being dumb. But at the same time, you know, I know now when I was growing up people said horrible things about me, and they went right over my head. And all this child abuse stuff and all that was in my family, much of it passed me right by, and I think now it's because I was autistic and it protected me from the worst of it.

But at the same time, what I did perceive hurt me terribly. And the idea that he's oblivious to it, so it's not a problem, was absolutely wrong if

my pain is a guide. I want to make clear that we can be autistic and oblivious or we can be dumb and oblivious, we can be whatever you want to say, but that doesn't mean that we can't suffer tremendously. I think that's a really important point when we talk about these kinds of treatments.

It's one thing to say we don't suffer from autism; we are autistic and we are different. But when we talk about depression and anxiety, people absolutely suffer from those things and their end their lives over it. That brings me to the next point I want to make about what you said, which I thought was very significant. It's a good question to ask if the biological foundation of anxiety or depression is the same in autistic people as it is in the rest of the population. But we could just as well ask that question of many other population subgroups with respect to psychiatric disorders, and that's not a reason for inaction.

One thing that really troubles me is that it's very easy to go from raising a perfectly valid research question, and I absolutely agree we

should study it, to saying, well, we're not ready to tell the clinician community that they should be looking out for anxiety and depression in autistic people. Just because we don't know if the foundation's the same does not mean we shouldn't be taking actions. Absolutely time to act in my opinion. Even if I'm dumb, I see that.

Dr. Dawson: We know you're not dumb, John. That's for sure.

Mr. Robison: My grandfather said so, anyway.

Dr. Dawson: Okay, right. And I do want to just emphasize the point that you made, because I think it came up in a number of the speakers' talks, which is the idea of early stress as a risk factor for later anxiety. I think what you're talking about is that. People with autism do experience a lot of stress in lots of different ways and this could contribute to later anxiety.

Mr. Robison: I think that's the thing. People -- it's very easy to laugh at people and say we're just like dogs and we don't know the difference, and you can tell the dog you're going to eat him for dinner and he wags his tail. But at some

level, we soak this stuff up and it hurts, and it really does. And it's followed me all of my life. And everyone who considers that -- I think we should be aware of that, because I think it's crazy to think someone who's less verbal than me is immune to those feelings.

Dr. Dawson: And I do think that is one of the points that a couple of the speakers were making, is the challenge that these internalizing kinds of disorders, whether it's anxiety or depression, often have relied on introspection and self-report, and so because people with autism have trouble talking about their own feelings perhaps we assume that they're not experiencing these, and that is really a misjudgment. I know, Mustafa, you have a point to make.

Dr. Sahin: No.

Dr. Dawson: No? Okay, Bob.

Dr. Naviaux: It seems that what the speakers today are -- we're all struggling with is the concepts of epistemology, how we actually know what is an emergent property or a complication of autism or if it's just an accidental co-occurring

phenomenon. And I'll bring a metaphor of diabetic kidney disease to the table. Patients with diabetic kidney disease, or with diabetes, are at increased risk of having kidney disease. We can treat that kidney disease in a couple ways. We can treat it with a change in the fundamental process that's involved in the pathogenesis of diabetes and change diet and exercise, and that will improve kidney disease. Or we can treat the fibrosis with anti-fibrotics that are directed specifically at the kidney disease. Both have some validity. Both are supported by the scientific evidence. But if we can get at something that's fundamentally involved in increasing the odds ratio of complications of autism, then we're doing something more. We're changing the whole field of things that a child might have to face over the course of their lifetime.

So this idea of construct validity is incredibly important because if we just call it something similar -- if anxiety is just this isolated concept, like kidney fibrosis, then we treat it just like kidney fibrosis, with a drug

developed to do that. But if we think of it in the broader context of the pathogenesis and pathophysiology of autism spectrum disorders, then we do more for our children.

Dr. Dawson: Beth.

Dr. Malow: I wanted to build on that, because I agree that the speakers were fascinating, and it got me thinking, because I'm going to talk in my talk about arousal dis-regulation potentially being a trigger and feeding into -- and I don't know if this is correct or not, but let's say anxiety, GI problems, insomnia. And Dan already brought up the connection between GI and insomnia and what might be driving that. I think you're absolutely right, because if that is true and if we do show that there's potentially an autonomic driver that explains all these different conditions, then we can focus treatment, right, on that driver.

I think that's what you're getting at. So it might be CBT, like we heard about. It may be certain drugs. But really understanding and teasing out what the driver is I think is

extremely important in terms of planning therapies.

Dr. Dawson: Sally.

Dr. Burton-Hoyle: I think the importance of this discussion translates to education, and things must be quantified first in medicine before schools ever pay attention to them. I can't tell you how many times services have been denied to an individual on the spectrum because it was said that they were too low to have anxiety or too low to experience different sorts of constructs that you are working hard to quantify. So keep it up. Thank you.

Dr. Dawson: Anshu.

Dr. Batra: I want to thank the speakers. All of them were wonderful. It sort of demonstrated how complicated this issue is. I wanted to touch on a couple things in terms of the age, even though the age I guess shouldn't matter, but it does, because in my world of pediatrics, as one of the speakers mentioned, we don't diagnose little itty bitty ones with anxiety traditionally. And it's not a surprise to me, seeing Dr. Scahill's

talk, that as the age rises the increased incidence of medication rises, because as these kids get older the demands are more and they demonstrate it behaviorally. One of the key things here is, as he mentioned, really starting to identify a tool to help us figure out and quantify the chief complaint the parents come to us with, which is my child is anxious. And it's very difficult for us to tease apart, what does anxiety mean, as he mentioned. Is it resistance to transition? Is it separating from parents? Or is it not wanting to do something that's novel? So the observable behavior I think is really key here, because that is what we're seeing, whether it's in the school district or whether it's in the doctor's office, and quantifying it. That's number one.

Number two, I just wanted to, more from a philosophical standpoint, but when we talk about drugs I hope we're really using that as a term for interventions, because again in pediatrics and I think across the board most of us would agree that medications may not be the appropriate first step

for treatment for this and that there are some other treatments that can be used, including diet, nutrition, etcetera, etcetera, as well as drugs.

Thank you.

Dr. Dawson: Anjali.

Dr. Jain: I wanted to dwell a little bit on the construct idea. I wonder if we wouldn't get further perhaps by thinking about response to stimulus or just regulatory response to stimulus, in a sense that it's being potentially expressed differently and triggered differently in kids with autism, but it's kind of the same thing in the sense of the biological construct, almost as if it's a language of expression or the kinds of triggers.

I just, I'm not being very articulate, but what came to mind was in Dr. Coury's talk about some of the scales that you're trying to develop in terms of response to noises and crowds and that kind of thing potentially being similar across kids of a certain age group who are getting exposed to these kinds of environments, but then how do they process that and then express it

differently.

Often I find with my daughter, as well as a lot of the kids I've seen in practice, that it's really a matter of degree in terms of how these things get both triggered as well as expressed. I wonder if we might be able to kind of think about what a construct means a little bit differently as a matter of threshold or degree, as opposed to something altogether different.

Dr. Scahill: So, you're raising to me, I think a really central issue. This idea of categories verses dimensions. And to me it would be more useful for understanding the range of these problems in children with ASD, if we thought about it dimensionally. Whether it would really come out that way, I don't know. But there’s a lot of scales that have lots to back them up, but their practicalities runs into because there are multiple factors that bars you from using the total score because the factors collide, and the individual factors are few in number and so they don't work as individual factors. I hope we don't find ourselves painted in that corner, but I'm

interested in dimensions.

Dr. Insel: I would concur. The importance of getting away from these current categories is essential. I was really pleased that each of the speakers talked about anxiety sort of more generically and didn't bother to invoke any of the 9 or 12 or 15 different categories that are in the diagnostic manuals, because it's clear that there's no biological validity to any of those and those have to be redone from the bottom up, letting the biological data tell us where the classifiers would be. But the same thing is probably true for autism. We don't know how many disorders autism will turn out to be. This goes back to Zack's comment earlier about the many autisms. The question I have for the three of you on the panel is: To what extent is the presence of severe anxiety helpful as a classifier? Does it tell us -- does it identify a subgroup in terms of prognosis, in terms of other aspects of the disorder, in terms of treatment response? Are these the kids who respond better or worse to behavioral interventions, to medication? Can you

give us any sense? Or maybe it's not a useful classifier, but it would be helpful to know that.

Dr. Kohane: Jeff has done quite a bit of work on the CBT angle. I'm interested in it because I think that there probably are medications that we should be pursuing for children that are teenagers that are on that upper end of the dimension. So I think it is worth finding out who's low, who's medium, and who's high.

Right now it's a little bit confounded by language, because most of the measures require language and they are biased against children with language disabilities and intellectual disability. So that's why I feel there's a need for a new rating. I'm very interested in medications for it.

Dr. Naviaux: On the CBT side, I think unfortunately the research is too preliminary, because the studies on CBT for anxiety and autism have focused only on the subgroup of those with anxiety and autism and haven't been more broadly distributed across the range of anxiety, which precludes us from really understanding what does anxiety tell us about the potential of treatment

response. Now, there's been some conceptual work that has suggested that anxiety might be a marker of greater treatment responsiveness, if only because children may be more, in some cases with anxiety, responsive to requests to engage in certain types of intervention due to their harm avoidance characteristic and this is a complete conjecture, but in our experience with this subgroup of children with an anxiety disorder and ASD there does tend to be a very similar level of compliance with therapeutic tasks as compared to children with just anxiety and not ASD, which is an important, only a clinical observation, but potentially important.

Dr. Insel: Just as a follow-up, we know in so-called typically developing children -- not a very, very good term, but it's the one we have -- that the presence of anxiety, severe anxiety, at age eight is a very good predictor for depression at age 28. And I was thinking about Lisa's data from earlier this morning, very high rates, actually strikingly high rates, of depression in autism and suicidal events or thoughts. It's

really remarkable if you just look at the odds ratio.

Do we know anything about the link within the autism diagnosis, whether the kids with anxiety are the adults with autism who have depression? Is that actually known or has anybody looked at that? Okay.

Dr. Dawson: I was just going to make one comment about this idea about a subtype, and I'd be curious, Zack, whether you have any evidence of this. But there is some research in the literature that correlates early sensory sensitivities with later anxiety or the development of anxiety, but also correlates it with the development of GI-related conditions. I don't know whether this is specific to abdominal pain, which often does go with anxiety. But I wonder about that cluster of symptoms and whether that might be a type or subtype?

Dr. Kohane: Since the question was directed to me -- unfortunately, I can't give you a positive answer, because you're talking about two different sources of data. One is measures of sensitivity

and I'd have to figure out whether there was evidence in the clinical notes about that in the general pediatrician's notes, and that may or not work, whereas the GI ones seem to jump out. I'll tell you, as I hear all these discussions; it's great that we've sort of raised the game of everybody by looking at these large epidemiological databases. It seems to me that what's missing with all of us, although we can push a little bit further towards it, is longitudinal information, just who are the kids who are going to get better no matter what we do, who are the kids that are going to get better if we do certain things, and who are the kids who stay or get worse regardless of what we do, and so on. I think that's hugely important and I think it will give us even better stratification of subgroups. So I think your question is a subset of that question, of that challenge, and I think it's hard until we get better at sussing at. So just speaking for myself, I am going to try to understand those intermediate measures, but I suspect we'll have good specificity in the sense

of we'll be able to find cases where there's high sensitivity and track those along. We're not going to have good -- high specificity. We're not going to have good sensitivity of the bunch of kids who had sensitivity issues which we won't pick up because no one bothered to actually note it anywhere in any either database or electric medical record.

Dr. Malow: Were you asking if there was such a study, or, because there is one by Micah Mazurek?

Dr. Dawson: No, I was mentioning there is some really nice literature on anxiety and GI and sensory, and I just hadn't really heard the speakers talk about that cluster of symptoms, and also some developmental models about how early sensory sensitivities could lead to later development of anxiety disorders as well as GI-related conditions. Yes?

Ms. Redwood: I just wanted to go back to my comment on the autonomic nervous system again, because that's also very important in controlling GI function as well. So I'm wondering whether or not we're seeing a pattern here with this sort of

abnormal fight or flight response. We're seeing to me abnormalities in the autonomic nervous system that we really haven't fully investigated, and I think that's an area that would be really ripe for research because it can explain some of these later disparate co-morbidities that we're seeing with sort of one underlying mechanism, which should be really nice, if that is the case, to start developing targets for treatment.

So I really hope that we can bring a lot of these abnormalities together using maybe systems biology to try to understand what is the driver. That I think is also going to help us to determine what is causing these abnormalities in our children and what's the actual etiology for this disorder. I can't beg any more to, please, do that as fast as possible.

Dr. Batra: Gerry, you brought up a really interesting point, actually, about the sensory sensitivity as being maybe a subtype within this broader term. I think one of the issues goes back to not having a tool, an outcome measure, that's validated. In that world, we have our sensory

screeners, our profiles, but they are not as -- they're not used in practice or especially to, again, generate -- to assess changes in outcome measures. I think that would be another good thing to look at in terms of developing tools to drive therapy.

Dr. Dawson: Yes?

Dr. Anagnostou: I just want to clarify something, because I don't want to give the wrong impression. I don't think we have any evidence for an autonomic collision. At least with the data we have so far, we don't have evidence for the referral vision. But you can get autonomic dysfunction from sensory vision fairly easily, and most of the time where we get autonomic dysfunction it is not from the autonomic nervous system internal dysfunction per se; it's CNS dysfunction driving autonomic dysfunction. We have some evidence for that.

Going back to the idea of the sub-phenotypes, there was -- the early data had this kind of very mixed finding of what the amygdala is doing in autism. It was up and down and the same, and very,

very messy data. Now the data that I have seen that's coming out of the longitudinal consortia looks like the kids who have the big amygdala are the kids who are developing anxiety. So they look like a distinct group who have a very early overgrowth of amygdala and they look like they are now ultimately the kids who develop the anxiety. So some of that stuff, will ultimately, I don't think it's clean, but I think between CNS measurement, autonomic nervous system measurement, and whatever we manage to do with clinical constructs of anxiety -- I don't think this would be a distinct -- it looks like it may behave as a distinct subgroup.

Also, in our cohort it's a bit too early to make a big statement about whether social motivation predicts anxiety. But we now have so far kids who score low on social reward do not seem to be having high scores on anxiety. So it seems to be another, again, kind of subgroup of kids. The kids who get anxiety seem to be the group of kids who care, and the kids who don't care have lower rates of anxiety, provided that we

know what anxiety is.

Dr. Dawson: Well, that was an excellent session -- we have one more comment.

Dr. Jain: I was just going to say one more thing, that we should also just not forget that the response to anxiety and how it's dealt with is playing a huge role, and with a great deal of variation as well, both in terms of the parents and the family and the schools and the social milieu. So that's another huge variable in the mix.

Dr. Dawson: Excellent. All right, well, we're going to break for lunch until 12:45. Is that right, Tom?

Dr. Insel: Right. We'll need you back here right at 12:45. If you need to, bring your lunch back in with you. I think we're allowed to eat in here. If not, we'll find out when we break the rule. But we do want to start public comment right at 12:45.

(Whereupon, at 12:18 p.m., the workshop took a break for lunch and reconvened at 12:51)

Dr. Insel: We need to reconvene. We're a bit

behind schedule and we want to get into the public comment period.

[Pause]

This is a really critical part of the meeting. For those of you who aren't on the IACC, we're happy to have you sit in. Now is a chance for the public to talk about, in this case, the topic of this symposium, which is on co-occurring disorders. We have a list of five people who have signed up for giving public comment. I want to remind you that you have both a written version of this in your packages as well as a lot of other written comments that came in. I think we have 52 pages or so of written comments for this meeting.

We ask each of the commenters to keep their remarks to as brief as possible. You won't be able to read the entire thing that you sent in because we just won't have the time. But presumably the committee members have already read that. Then we'll have some time for discussion thereafter. The first public commenter is Caroline Gammicchia. You can either use the podium up here or you can come to the table if you'd be more comfortable

with that.

Dr. Daniels: She missed her flight.

Dr. Insel: Missed her flight? Sorry about that. Yes, John?

Mr. Robison: You know, at the last meeting I had read off the names and topics of the written public commenters, and if we might just take a couple of minutes, especially since we lost one of our other folks. Could we read these to recognize the people who have written in to us?

Dr. Insel: Please do. Go ahead.

Mr. Robison: The folks who have written -- pardon me if I get your names wrong here. We have Teresa Arens, who has written in about concerns with life. We have Bhagwan Mirchandani who's written in about his dad on the spectrum. Martin Theiss, about his education. Teresa Rietveld, about the need for us to help autistic people get education, get jobs, something that I have a personal interest in. Marian Dar, talking about the challenges of life as we try and become independent adults. Maria Ferreria, talking about health issues and why we don't do our jobs here.

Beverly Frost, talking about her son, adult son, and life with autism. Ann Bauer, who wants to talk about the public health crisis of non-vaccination. Eileen Simon, who has offered quite a number of written comments and is also here as a public commenter. Teresa Rietveld again on the assistance to a college student. Shannon Rosa has written in to ask that we recognize the capability of autistic people and their need for support. She asks that we stop accommodating pseudo-science and specifically vaccine and mercury causation theory.

Then after that we have Dawn -- boy, I'm embarrassed; I was just talking to her, and if I get her name wrong -- Loughborough. I'm sorry, I got it wrong, but you know who you are. She's here, too. Mike Hoover, Heather Price, Michelle Schneider, Kathleen Levistein, Carol Fruscella, Joyce Herron, Rafael Sepulveda. The principal theme of these comments is the opposite of those of Shannon Rosa, that we are ignoring vaccine causation.

All I guess I can really say is it just shows how hard it is to try and be impartial when we

hear completely opposite things from people, and then we have to just do our best. Kristin Kauffman, Joseph Jackson. I'd like to just say one thing in response to Mr. Jackson's comment. He's talking about the consequences of what we've done to cause autism and that his son, born in 2008, did not have to have autism. I don't profess to know why I am autistic or why my son is autistic, but I have yet to meet an autistic adult who cares a great deal about how we came to be this way. The fact is this is how we are, and I just wish parents would remember that one day the children who are described as diseases things, we will grow up, and we will look at these comments. But at the same time, I would want to say as an autistic adult that I feel your pain and I know how hard it is, but we have our side of the view, too. Katie Harris; Eileen Nicole Simon has written in again; Susan Wald about the autism epidemic; Leslie Phillips about the troubles of her two sons with autism; Chanda Jackson, who writes about our fraud as a director -- and who she is, I don't actually know who she is, but I guess Ms. Jackson knows.

I'm not being cynical. It's not mentioned here. Courtney Reid has written in about the statements from William Thompson, the CD whistleblower thing. Tara McMillan, again writing about her vaccine-injured child. Mike Hoover, Mr. Hoover, is writing about his vaccine-injured child. Christine Marshall, about what we are going to do with autism in schools. Haven Delay on what autism really is and how it is a vaccine problem. Shannon Strayhorn and we have our lack of action and our conspiracy with pharmaceutical companies. And Dave Walsh.

I guess -- and finally, we have Donna Young. You know, I just, I wish I knew what to say to settle this business of vaccine, because it is the most common source of commentary here. As an autistic adult, I would just like to say that I wish that we could move forward to develop therapies to make our lives better, instead of being hung up on how we got that way. But I know that so many people see it differently, and all I can really do is recognize all of you who wrote in and that we respect your opinions and we've read

them and I've named them here.

Dr. Insel: Thank you, John. Let's go ahead with the comments of people who are here. Cassandra Oldham.

Ms. Cassandra Oldham: I just want to thank you for the opportunity to be able to speak today. Before I read what I have written, I just want to say that if my children could articulate so well as this gentleman just did, I'd sleep better at night. I have pretty severely nonverbal children that I'm talking about. I'd like to know the cause because I want to stop it from happening for other parents and children. The numbers of children being diagnosed continues to rise, with little being done to find the cause or the cure. Everyone seems to be moving at such a leisurely pace. We need to call this the epidemic that it is.

My children acquired autism via toxins. We know that based on medical tests, and that these toxins were vaccines. Something needs to be done to prevent other children from such injuries. I know that at least one of my children's doctors has spoken here in the past and has mentioned

medical tests that can be done starting at the pediatrician's office. In case you forgot what these tests are -- and I'm not going to take the time to go into them -- I have brought a couple Journey Guides that put them forward. I'd like to give one to the pediatrician as soon as I'm done.

And if anybody else wants one, I will provide one free of charge. Just let me know, give me your name and number, and I'll get that to you. I've written my name and phone number on the inside cover, so if you have any questions you can call me and I'll go through anything with you. My children have no future. They are extremely affected. They do not talk, and that needs to stop.

It was brought to my attention that some of the studies that this committee uses to base certain opinions were falsified and corruption was taking place. People need to be held accountable because children continue to get harmed. Also, any of the numbers that you read on vaccine injury don't include my boys. Any numbers you read on autism don't include my boys. If they don't

include these boys, how many thousands of children are you leaving out of these numbers? These are people and they deserve a chance.

As these studies have been skewed, we need to question the validity of them by people who have gains and financial ties and conflict of interest. I was personally asked to remove my son from a study at Kennedy-Krieger because my son was negatively affecting the findings. During that time period, a geneticist at Hopkins who studied my boys told me he was not publishing some papers on autism because he was scared of the repercussions. He told me certain key aspects of my sons' medical conditions were going to be omitted from their file, not because they were not accurate, but because he said he didn't know who I was going to show them to. Not only do my children count -- not count, they suffer for the benefit of the "greater good." Some committee members have said that I am a parent grasping for false answers and looking to blame. I wish I had the luxury to go to bed with the peace of mind that my children were born with autism that it was like Down

syndrome.

But I know better. I did not seek a mitochondrial diagnosis. I walked into a hospital with a child who had developed normal, got sick, regressed, developed autism. They told me toxins caused it. Now I know better and I must speak for future generations. You have the power and the authority to move forward on change. Sit and think where your moral compass is. Are you going to be part of the problem or part of the solution? My children suffer daily. One little thing I'd like to suggest for further meetings that is a huge hindrance for my family, is that my children continue to be treated like fifth class citizens. I can't take them out in public. Here are three examples: My nine-year-old lost the tip of his finger while he was doing special needs hockey. When we were in the ER, they said that because he had autism it wasn't worth sewing back on, but normally they'd do a graft. This was at Virginia Hospital Center. My six-year-old when we were traveling walked through TSA. He has a tracker on him given by the sheriff's office. He set off the

alarms and, because he didn't have the verbal understanding -- and I was not allowed to touch him -- to be told to go over to the side, he was treated as hostile and thrown in a box by TSA agents. I wrote a letter of complaint, but TSA investigates TSA complaints and they found they were not at harm.

One more thing before -- I had three therapists tell me that one of the therapists had been abusing my children. I called the CPS and the police and, even though I had three witnesses, no charges were filed because my child couldn't describe what happened and he didn't look traumatized. The abuse and the trampling of basic human rights for these children, these children and others, needs to stop. Please consider talking about that and trying to make change. Thank you.

Dr. Insel: Thank you.

[Applause]

Dr. Insel: Alison Hoffman.

[No response]

Dr. Insel: Not here. Eileen Nicole Simon.

Ms. Eileen Simon: My first two sons suffered

trauma and oxygen insufficiency at birth. Pediatricians reassured us that our children would outgrow their developmental delays. They did mostly, but problems with language and development remained as a serious impediment for cognitive growth.

In my written comments I discussed auditory processing deficits and problems with speech production. I also describe research with monkeys on asphyxia at birth. Damage was most prominent in nuclei of the brain stem auditory pathway. But then, maturation of the cerebral cortex did not proceed normally. Autism is the result of many different causes.

In my written comments, I pointed out some of these and why all are likely to affect subcortical sites. Nuclei in the brain stem auditory pathway are susceptible to damage by all of autism's known causes, during gestation, during birth, and from some neonatal interventions. Please discuss the possibility that co-occurring conditions in autism may all result from injury of brain stem sites and subsequent disruption of maturation. Please

discuss also any evidence that language disabilities and co-occurring conditions might be mere differences on a spectrum of neurodiversity. Thank you.

Dr. Insel: Thank you, and finally, Megan Davenhall.

Ms. Megan Davenhall: Hello. I'm here representing The Thinking Moms' Revolution and I'm reading a statement that was crafted by our organization. What we're here to say is absolutely nothing new, nothing that this committee hasn't heard before from multiple other public commenters over the years.

There's a huge subset of individuals with the label of "autism" that were not born with autism. These children, young adults, and adults were born as typically developing, healthy children and then regressed into autism. This is not the autism that you see in our highly functioning adults, the way that Mr. Robison described himself. This is not what we are talking about. But we don't have another word. We have "autism." So we are talking about high functioning adults, people who love who

they are and should celebrate who they are, and we're talking about kids who are sick. They are two different things, and we call it all autism.

This autism is extremely different. It's a different experience for these individuals. It's pain, it's bowel disease, it's mitochondrial dysfunction. It's seizures. It's immune deficiency. And in many cases it is a silent plea for help through head-banging in self-injurious behaviors and aggression. Parents have been searching for treatment for these co-conditions for years. We pay out of pocket because insurance won't cover the staggering cost of healing the many physical ailments our children suffer from.

Our kids who fall into this model of autism, the ones who were healthy and become urgently ill, need to be treated with respect and like human beings who are sick. Their physical symptoms need to be addressed by medical professionals in the same ways that they would be handled in a person without autism. Never again should a parent have to hear from a doctor or a psychiatrist that a physical problem such as diarrhea or constipation,

as we've discussed earlier, that it's just part of their autism. But it still happens. That is what parents are hearing. When you go to the pediatrician, they hear: Well, kids on the spectrum have diarrhea, they have constipation as part of autism. I talked about my son's regression at the pediatrician, a regression. A typically developing child regressed into autism. And I was told: Well, that's the very definition of autism. We need to rework how we're talking about these things in pediatricians' offices across the country, and you need to be the change for that happening. Parents have been telling you for years that there was some trigger that sent their healthy child into a physical and developmental tailspin. They watched this happen to their kids and were ignored. You ignore our first-hand eyewitness accounts of damage to our children. You hold these meetings that accomplish nothing and give us the mike a few times a year. And we tell you: Autism is medical, this version of autism that the parents come here and talk to you about. Let me be clear on that. Our children get better

when we treat the medical problems they have. Their behaviors that land them on the spectrum in the first place improve when they get healthier. And you don't hear us. You give us 15 minutes of your day and interrupt parents who travel on their own dime to come here and speak to you. If they go over their allotted three minutes, they get interrupted, as long as we end the meeting by 5:00. I want to thank Dr. Coury for recognizing one thing I haven't heard here in all the time I've been listening, watching, and coming to these meetings. I heard the phrase "The parents are the experts on their children." I heard it from other people in the room today, too. The bottom line is we are. We are the experts on our children. We see what they are living with day in and day out, the medical conditions that we are trying so desperately to find answers for. But we receive none. I hope today that you hear this well. Treating the co-occurring conditions is critical, but it is absolutely not enough. This committee needs to start getting serious about prevention. You need to start investigating the dangers of

vaccines, of pesticide exposure, of antibiotic overuse, chemicals that are in our food supply that we know cause neurological dysfunction.

We've a medical system that is run by pharmaceutical companies who don't care one bit if our kids are healthy or not. This committee needs to start working with our government to lessen the toxic burden our children are exposed to. We parents are watching. We don't see this committee doing much of anything. The autism numbers continue to climb, with no end in sight, and we have been screaming into the abyss. We have been telling you what is happening. We're giving you clues to study. But you ignore us. Are you afraid of what you will find, afraid of doing the right thing until it's too late? It's quickly becoming too late. How many more kids will die in ponds or in pools because they wandered off and drowned? How many more diagnosed will it take for you to act?

This epidemic and the U.S. government's inaction is creating a vocal, intelligent, passionate army of loved ones that has reached a

critical mass in number and will not back down. We'll be at every one of your meetings. We want to hear what you're going to do about these co-occurring conditions and we want to know what you're going to do to prevent this rise in autism. It can't be ignored any longer. We have been telling you these things for well over ten years. What I want to know today is who in this room is going to be a champion for this? Who will stand up and force the independent study looking at causation, or spearhead individualized effective treatment for our sick children? If that person is in this room, now is the time to stand up. Thank you for your time. And on a separate note, I really would like to thank Lyn Redwood for always being a voice for the families that have been screaming this. She asks the hard questions. She's not given up on that job. So thank you.

[Applause]

Dr. Insel: We can take a few minutes for discussion. John.

Mr. Robison: You know, I just see so much, so much anger and frustration that we have not

delivered value to our community. I have said this so many times. No matter where you think this autism comes from, we have a duty to deliver tools to make our lives better. I'd say to the person who just suggested how much worse her own child was than me, the sad truth is that my end of the spectrum is where most autistic people kill themselves. I have lived with enough complications myself that I know the pain of this is very real everywhere on the autism spectrum. I think frankly all of us are equally deserving of respect and recognition that our problems as autistic people are legitimate and real. And all of us should be pulling together to help, not fighting.

One thing I guess I have to say, Tom, about this vaccine business and this causation business is that I wonder if we need to do some kind of exploration of what these views are that people are bringing to us, because consistently I come here to the IACC and half the commentary I see is accusations that we are not doing our job, we're not addressing these vaccine and causation questions. I have to ask myself, is this an

incredibly vocal minority and I'm in left field, or is this truly an opinion that is held by a great many families in the autism community? And if it's true that that opinion is held by a great many families in the community, then whether I personally agree with that or not, I guess I would have to say as a member of a public committee if that's a view of a significant percentage of the constituency we serve we have a duty to them. I wish I knew the answer to that question.

But I'm hearing it so, so much that I guess I have to ask that maybe we should quantify how widespread the view is and consider what we're going to do. But I also think that if we deliver value to make lives better, which I think we could focus on in a redirection of our efforts, we would do a great deal to ameliorate the criticism of our committee. Increasingly, I see this. It's founded in a lack of deliverables.

Dr. Insel: Other? Lyn?

Ms. Redwood: I just wanted to follow up on John's statement. As you know, I have a son who's almost 21 years old, and when I first, when my son

was first diagnosed and there were concerns about vaccine voiced I thought at the time: I'm a nurse practitioner by my profession, I've administered vaccines, I sit on the board of health for our county. Vaccines are our biggest program. And it wasn't until I actually started looking at the science that I realized that this is biologically plausible. So I've been listening to these arguments for 20 years now, Tom. The comments that we've received this meeting refer to a gentleman who's a research scientist at CDC, William Thompson, who, as you may or may not have heard, has recently come forth as a whistleblower and in a statement that was released by his attorneys acknowledges, quote, that he "omitted statistically significant information linking the MMR vaccine to an increased risk of autism" in a 2004 study. He said decisions, again quote, "were made regarding which findings to report after the data was collected." This I feel is the tip of the iceberg. Back in early 2000 my organization filed FOIA requests and received thousands of pages of documents. We looked at different CDC studies. One

in particular authored by Dr. Verstraeten which was looking at thimerosal exposure and adverse neurodevelopmental outcomes, in their first run of that data, that was again never reported, that we received by FOIA, they found that in children who received high levels of exposure compared to no exposure an increased risk of autism that was 7.6 to 11.4 times that of the children, who have not received any exposure. They altered the entrance criteria by making it mandatory to be in the study that you had to receive two polio vaccines, so the next run of the data they had no control group, they had no zero exposure levels. So it was just a comparison between -- an analogy would be a two-pack a day smoker versus a four-pack a day smoker in lung cancer. These are the reasons why the parents have concerns. That particular data was altered four more times before it was published. So other associations that still stood were speech and language delays, neurodevelopmental delays in general, ADD, ADHD, speech and language delays, tic disorders, misery disorders. Those were the findings in that particular set of data. So these

problems have been going on for years now. I can cite three other studies, two of them authored by Dr. Thorsen, who is now on the most wanted list by the inspector general's office for fraud and money-laundering, who authored two studies, and these studies were used by the Institute of Medicine to say that there was no association between vaccines and autism. So I think that this committee should ask the Secretary. One of the things that we're charged to do is to report things to the Secretary that are concerning. I think this should be reported to the Secretary and ask for a special counsel to investigate these allegations, because they directly affect what we do here as a committee. So that would be my recommendation, John, in terms of having this investigated to try to get truth for these families. In terms of the comments about co-morbidities, I hope that this workshop today will continue and that this work group will continue and that this will progress rapidly. It's been far too long in coming.

Mr. Robison: What I want most of all, I want

to respect the views of the people who had gone to the trouble to come here, even though sometimes I disagree. But I just hope we can all pull together and we can take an opportunity like this to recognize that we need to make our mission the delivery of tools to help with this co-morbidities. What we really need, no matter how we became autistic, is tools to have a better quality of life at all levels.

Dr. Insel: Anshu.

Dr. Batra: I'd like to piggyback on what John said. But before that, I'd like to thank --

Dr. Insel: Would you talk into your microphone? You're hard to hear.

Dr. Batra: I'd like to thank our public speakers, as well as the written speakers, to take the time and have the courage to come up and speak. It's not new. It's repeated. It's agonizing as a parent to do it. And time is always of the essence when you're dealing with your child, and it's never enough. I have to see this conference -- I see this conference as a lovely step forward to hopefully start phenotyping the autisms, and I

loved every single speaker so far has said "autisms" and has referred to the fact that there are several different types. Once we do that, then we can develop the therapeutic modalities to individualize and personalize the therapies. That's what I -- I hope that that's at least a shining -- a small ray of hope as we move forward. Thank you.

Dr. Insel: Other comments or responses? Matt.

Dr. Carey: I was going to bring up one of the written comments. Full disclosure: I'm actually a friend of Shannon Rosa. She lives very near me. One of her statements -- she's got a number here that are good, but one is very direct to what we're doing here. It says: "Focus on research that helps autistic people who are already here. We need to know more about autism and sensory issues, autism and anxiety, autism and co-occurring medical issues, and so on." She goes on to say: "This should be a higher priority than research into causation."

If we can focus on the first part, one reason I bring up Shannon, her statement, not only just

to highlight that, but because I think most of that message is already -- the idea to focus on co-occurring medical conditions is obviously what we're already doing. But Shannon and I actually, we live about 30, 40 miles apart. Shannon's son is put on a bus, drives to my city, goes to school. My son gets driven -- we drive him, actually -- up to her city. We always joke that our kids are passing on the freeway every day. If you stratify kids by high-functioning, low-functioning, terms I actually really don't like, but if you start doing that, you would say these two kids are the same. But there's a big reason why one kid goes 30 miles one way, one kid goes 30 miles another way. There's a big reason why both kids are going 30 miles. They're very unique, even though you might stratify them together. Even medical, anxiety, everything else -- we start talking -- we tend to always kind of group by intellectual level. I know it's important when we're starting to do the epidemiology and everything else to look for these groups and try to figure out who's got more problems and more issues and what communities are

going to have them. But even within these groups, they're very diverse, and we need to keep the focus on that. Thanks.

Dr. Insel: Any other comments?

Dr. Jain: I'd just follow up with that for a minute. I think we should take a lesson from applied behavioral analysis and think about part of the reason it's so effective is that it's highly, highly customized, and it's focused on actual behaviors that are causing issues. So it's kind of a downstream impact of something that affects the underlying condition. So if we can begin to think about treatments more in that way, in a really individual way, but deal with what is bothering the patient and the family, I think we could also make some headway.

Dr. Kohane: Could I make a quick comment?

Dr. Insel: Zack.

Dr. Kohane: First of all, I would like to recognize John for having created the rockets in the guitar that came out of the Kiss rock band members.

[Applause]

Dr. Kohane: Very impressive. Second, I think what I hear here is something that as a biomedical statistician I see very broadly, which is it's very hard not just in autism, but many diseases, to talk rationally about therapy or prognosis when we don't even know the beginnings of what are the components of it. It's truly heart-wrenching to hear a mother say: I have a kid with a very different kind of autism. And the fact is I don't think we know what are the natural trajectories of these diseases and how they relate to functioning, which 30 miles they're going to have to go along. And so I think what's very inspiring about this meeting is the recognition by Tom and this committee that the co-morbidities is just another dimension in which we're going to be able to understand better what these individuals have that we're all lumping together. My only fear as I was listening to this is, even if these end up, as is likely to be the case, very different diseases, they still should get the broad support of having a nice, large community that is labeled, perhaps incorrectly, by the same label today, currently

provides. So I just think if we keep on in the direction that this workshop is going, there's a reason for optimism.

Dr. Insel: Maybe I can use that to sum up a little bit, because we will need to go on with the rest of the agenda. And I also want to thank the people who both made oral comments and those who sent in written comments. Clearly, as John said, the frustration and anger, especially at the committee, but the frustration more generally at the state of care is profound. There's no question about that. Zack, I think your comment is to the point that we're at a very, very early stage here. It's as if autism, if you wanted an analogy, was like fever and everybody's trying to figure out what causes fever. And some kids have Ebola and some kids of strep throat and some kids have something very different. The only thing they share is the elevated temperature, and even that ranges from 101 to 105. I think we've got a real problem at this very early stage of this field, and it is early. This is a field that's been deeply invested in biomedical research for only a

couple of decades, and there are very few parts of the NIH that are that young in terms of how far they have been expected to go. I can't help but say, though, that part of I think the frustration in the committee is a continued misunderstanding of what we can do, what our authority is, what our resources are. We have no money. We have no ability to fund anybody to do anything. We are a bully pulpit and the best we can do is to try to inspire some of the funders around the room, the NIH, CDC, Autism Speaks, the Science Foundation, and others, Autism Science Foundation, to make appropriate investments in the issues that are in the strategic plan. But there's no real mandate to do that, either. We can't -- we have no recourse if someone doesn't. So I think, as I think the committee understands, but I'm not sure that the public fully understands -- and I can tell from some of the written comments that there's a clear misunderstanding about what our actual authority is in terms of what we can accomplish -- we can have these very honest exchange of views. I think it is useful to try to find a way to align the

community, which is now very polarized -- and John, I think your comments actually help in some ways to sort of put it all out on the table and to say; at least we can begin to listen more carefully. I realize that this is a multifaceted problem, with people having very different experiences. Go ahead, and then we'll have to move on.

Ms. Jan Crandy: Dr. Insel, this is Jan Crandy on the line.

Dr. Insel: Hi, Jan. Thanks for joining us.

Ms. Crandy: Is it possible, I would like to make a short comment.

Dr. Insel: Please do.

Ms. Crandy: I wish that our committee would at least acknowledge, how John stated the whistleblower thing, because what's happening in our communities is parents are opting out of vaccines. In California the data shows --

Dr. Insel: Let me just -- I'm sorry to interrupt you, but this isn't an IACC meeting.

Ms. Crandy: Right.

Dr. Insel: And that's a topic that you would

want to take at that meeting. But this work group is not the place to decide what to do about that, if anything.

Ms. Crandy: Well, I'm not asking us to do something. I'm saying I don't think as a committee, though, when we're hearing public comment today, that it should just be stated, the whistleblower thing. I think that I would appreciate if you made a comment just to address the public and the public comments on this issue, because it is polarizing our community and families are choosing not to vaccinate their children. California data shows in the last seven years it doubled, opting out of vaccines. That's a problem, too, for our community, because if we can't trust the CDC -- how are we going to change that to make parents trust and vaccinate their children?

Dr. Insel: Jan, I'm happy to respond to the question about that particular issue. But again, this is not the place for the IACC, since the committee isn't here in full and this is not a meeting, to decide on anything we want to do with

respect to policy. I wish I knew more about that particular instance. I don't. I can tell you that the 2004 Pediatrics paper was one of about 14 papers that the IOM reviewed, and then there have been another multiple papers since then that have weighed in on this, all of which the IOM said in 2011 were consistent in not finding a relationship between vaccination and autism. What the IOM doesn't say and what nobody has said, at least in a way that I find compelling, is that there could still be rare cases in which that could occur. What we need to think about is how one would investigate that if that were the case. So that's another topic. But again, I don't think that's a co-occurring question. So I'd want to really make sure that we use the day for what we had set out for, which is to define the co-occurring issues. John, you get the last word.

Mr. Robison: I just would say that, with respect to what we should do in this committee and in this workshop, I think that we would be wise in responding to our constituents' dissatisfaction to ask if the purview of our committee might be

expanded, to move more into recommendations for services and treatments, because it seems like the IACC was originally chartered to offer guidance in the direction of research. And what we hear almost exclusively from our community is that they want us to offer guidance and action in deliverables and services, which is rather different from what we were chartered to do.

Dr. Insel: That's actually going to come out in the CARES Act, and that will be in the next version of the committee. There's very clear language about the mandate for this committee when it's re-formed to focus on services as well as research. It's a little complicated because obviously services are done at the state level, research is done at the federal level. So it's a lot easier, to the extent that we can do anything, to at least bring the people around the table who can have some impact on research. The 50 different systems that are supporting services aren't in the room and that becomes more complicated for us to have an impact there, except through CMS or something like that. But we're going to need to go

on. I want to turn this over to Gerry to start the afternoon session, which is on sleep and neurological disorders.

Dr. Dawson: Okay. Right, so we're going to begin with Beth Malow, and she is a Professor of Neurology and Pediatrics at the School of Medicine at Vanderbilt University, and a well-known researcher in the area of sleep.

Dr. Malow: Thank you. I wanted to thank the IACC committee and Gerry Dawson and Tom Insel for having me today, and also for recognizing the importance of co-occurring conditions in autism. I also wanted to thank Autism Speaks and NICHD for the funding support they've provided me. I wanted to give you a little bit of background. I'm a sleep specialist and when my children were born and diagnosed with autism I was encouraged to move into the field of sleep and autism, and I'm very excited to be part of this vibrant community.

I wanted to start out with a case, just to paint a picture of how disruptive sleep disturbance can be for children and their families. Alex is a six-year-old boy with autism

spectrum disorder. He takes hours to fall asleep. His parents say he can't shut his brain down. He drinks Mountain Dew with dinner he plays video games after dinner. He can't settle down to go to sleep, and he leaves his room repeatedly to find his parents.

Once asleep, he wakes multiple times during the night. Sometimes he awakens his parents. Other times he wanders around the house, goes to the kitchen to eat, and falls asleep in a different room. It's nearly impossible to awaken Alex in the morning for school. His parents are exhausted, overwhelmed. His teacher describes him as being hyperactive and disruptive in class. Even after taking away video games and Mountain Dew, kids like Alex may still not fall asleep.

So we were asked to come up with framing questions for our presentations today. I'm going to talk about what we know about sleep and autism, the evidence linking biological causes of sleep disturbance with features of ASD, which may be a window for biomarkers we can develop, what we need to learn in order to treat sleep disturbance and

ASD. And I'll try to listen to the comments that were made and be practical here as well research-oriented, talk about the gaps, talk about the opportunities, and talk about the autism-specific features, which can affect diagnosis and treatment and get in the way.

I wanted to bring your attention -- I put together a bibliography with citations. So if you see a reference that intrigues you, you can look it up on the sheet. This should be in your packets.

What have we learned? There is a high prevalence of parent-reported sleep concerns in ASD across cognitive levels. These are some of the studies that have compared ASD with typically developing and DD populations. The Krakowiak story was from the CHARGE study and Lisa Croen who spoke earlier, was an author on that. Sleep disturbance is also associated with child behavior and family functioning. This may be bidirectional. But we do know that many aspects of child behavior, including repetitive behavior, including inattention, hyperactivity, including parenting

stress, are associated with poor sleep. Insomnia appears to be the most prevalent sleep disturbance. It may take the form of prolonged time to fall asleep, preference for delayed bedtime, bedtime resistance, increased arousals and awakenings, and decreased sleep duration.

We've also learned that there are multiple causes of insomnia and many are treatable. And this is where we can get at some of the practical aspects. We really want to be vigilant about hunting for medical causes, such as GI causes, or neurologic causes, such as epilepsy. We've already heard a lot about the psychiatric causes today. They can affect sleep. Medications that we use to treat medical and psychiatric causes can affect sleep. Then other sleep disorders can also play a role in resulting in insomnia. The behavioral category is very important as well. We oftentimes think about poor sleep habits like the Mountain Dew, like the video games, but features that are related to ASD, such as difficulty with transitions, sensory sensitivities, can also contribute to the behavioral issues with sleep,

and exhausted parents may think poor sleep is part of autism -- we heard that a lot today -- and be unaware that behavioral approaches can help.

Then other causes related to ASD, neurotransmitter abnormalities, including the melatonin pathways, possibly GABA and serotonin, can play a role as well. And if you're going to look at these biological causes and do genetic studies and other studies, it's important to keep the whole list in mind, because you may have the gene that causes sleep disturbance in autism, but if the child is involved with video games or getting caffeine or other environmental or medical issues are going on, that may confound your results.

So I'd like to now take a moment and discuss the evidence linking biological causes of sleep disturbance with features of ASD. I'd like to discuss emotional regulation for a moment. We all know what it's like to not sleep well and feel crabby and cranky the next day. There's actually a biology underlying this and it links sleep and ASD. We know that sleep deprivation affects the

neuronal circuitry underlying the emotional regulation, including how the amygdala and the prefrontal cortex are connected. The amygdala is involved in fear processing. The prefrontal cortex is involved in reasoning and in processing the fear from the amygdala in such a way that is healthy, that is that it is under control. And we know that when this goes awry we can have emotional regulation problems, behavioral disturbance.

This abnormality, this abnormal connectivity, also exists in ASD. So you can think of it, if you already have abnormal connectivity between the amygdala and the prefrontal cortex in ASD and then you're sleep deprived, you add sleep problems on top of it that can really make the brain go awry. Just one example is from a functional fMRI study, in which sleep-deprived, healthy adult participants were compared to those who had slept. Those who were sleep deprived showed increase signal in the amygdala, they showed increased peak amygdala signal and extensive amygdala activated when they were viewing images that were

emotionally aversive. Then the functional connectivity was stronger in the sleep control group, those who had slept. The medial prefrontal cortex and the amygdala were communicating normally, and that's a good thing, that's a healthy thing. In the sleep-deprived group, the amygdala was actually communicating with autonomic brain stem regions. This could be viewed as a more primal or more primitive reaction. So the bottom line here is autism may already be vulnerable to emotional regulation and sleep deprivation can make it that much worse.

We heard earlier about arousal dysregulation. This is really interesting to me because I wonder if one theory is that hyper-arousal or arousal dysregulation may tie together several features of ASD, including anxiety, sensory over-responsivity, and functional GI problems. These features were found to be highly associated in a study of almost 3,000 children enrolled in the Autism Treatment Network. In addition, I think you can put insomnia in the mix. So you can look at some work that's been done with the HPA axis, the hypothalamic-

pituitary-adrenal axis, and dysregulation occurs both in insomnia and in ASD in association with daytime stressors. So you can postulate a model where you have stressors during the day, they lead to insomnia at night. What happens is normally our cortisol levels fall at night and then we can go to sleep. But in HPA axis dysregulation and the accumulation of these stressors, you have elevated levels of cortisol, which can then result in insomnia, and then you're not sleeping well at night, so you have more hyper-arousal and more dysregulation, and then you have behavioral challenges during the day, and it's a vicious cycle.

Then we already heard from Evdokia about these autonomic function studies, including elevated baseline heart rate, and also electrodermal activity, which certainly require more study, but are very provocative. The argument I would make -- we've been hearing today we need to do something now, we also need to understand these biomarkers better -- is I would say why not we design some insomnia treatment studies either with medications

or with behavioral techniques and behavioral strategies to try to target hyper-arousal and, while we're at it, measure biological markers of autonomic and HPA dysfunction, including heart rate, heart rate variability, electrodermal activity, and cortisol.

One other area that links sleep disturbance and ASD is melatonin. Endogenous melatonin is produced by the pineal gland. It promotes sleep; it stabilizes rhythms through actions on the receptors of the suprachaismatic nucleus. Apart from hypnotic and circadian properties, melatonin inhibits ACTH responses in the human adrenal gland, so it may be mitigating hyper-arousal. Melatonin processing appears to be altered in ASD, so again it's acting in sleep, it's acting in autism. It's a little complicated, but I think it's worth reviewing the pathway. N-acetylserotonin is converted to melatonin through ASMT, this enzyme, and then CYP1A2 is involved in the breakdown of melatonin to its major urinary metabolite, inactive metabolite, 6-sulfoxymelatonin. Several studies have looked at

the melatonin pathway. Melke and colleagues showed that in ASD melatonin levels were lower than in controls and then the ASMT activity was lower in ASD, and they postulated that this is an enzymatic block, so to speak, that's limiting the production of melatonin. Their study was limited in that they did melatonin levels in the morning in blood and melatonin peaks at night.

We recently found that melatonin levels were normal -- that we documented normal profiles of endogenous melatonin in terms of rise time, peak, and relationship to sleep onset, shown here in blue, in a sample of children with autism and sleep onset delay participating in our NICHD trial of supplemental melatonin. This is one such participant shown here. Then to add to the mix, Tordjman showed that 6-sulfoxymelatonin in urine is actually lower in autism than controls, adjusting for pubertal status. So how do you put all of this together? How do you reconcile the normal melatonin levels that we found with the ASMT levels that are abnormal in Melke's work and the low 6SM? I think approaches that examine

melatonin synthesis and degradation pathways together with both biochemical and molecular approaches may be very enlightening.

Olivia Veatch in our lab recently showed in a genetic study, in a sample of children responsive to supplemental melatonin, that dysfunctional genotypes that were responsible for both decreased melatonin production and decreased CYP1A2, as shown here, looking at both ASMT and CYP1A2, may appear to be correlated. So this is allowing us to generate a hypothesis that children may have normal levels of endogenous melatonin because CYP-1A2 is less actively degrading the melatonin they have available. This would bring together Melke's work with the ASMT and Tordjman's work with the 6SM with our recent findings. We need to do more studies. This is important and relevant because if we can identify some biomarkers for which children have abnormalities in their melatonin pathways and enzymes it might help us identify which children may be more responsive to behavioral therapies versus melatonin versus need more potent medications.

That's a segue way into what I want to do in the last minute or two with the gaps and the opportunities. I wanted to bring up the supplement that Dan Coury mentioned earlier in the practice pathway in pediatrics. Take-home message is clinicians need to ask about sleep. We oftentimes forget to ask. Everything else eclipses that. We need to look at these medical co-occurring conditions, identify them, and treat them. Behavioral sleep education does work. Working with the families on implementing bedtime routines, taking away the electronics close to bedtime really do work, and they do improve child behavior and family functioning.

We need to understand sleep medications better. I wanted to mention that immediate release melatonin has its limitations. It only works for about an hour. But there are longer agents that are being -- prolonged agents and agonists that are being studied. Then we also need to look at measurements of baseline sleep status, treatment, response, including actigraphy, which may be an alternative to polysomnography, which isn't always

as well tolerated in kids. We have toolkits, thanks to the Autism Treatment Network, that can be very practically used.

To, to sum up, we know that sleep disturbance is common. Sleep disturbance can be associated with child behavior and family functioning. There's many treatable causes. We think we know that improving sleep impacts favorably, but we need to do more research. And these are the things that I think we still need to know. I appreciate your attention. Thank you.

[Applause]

Dr. Dawson: Thank you very much.

Our next speaker is Ashura Buckley and she is a Clinical Investigator at National Institutes of Mental Health.

Dr. Buckley: Good afternoon. Thanks for the invitation. I'm going to be discussing epilepsy and ASD in the next 15 minutes, so maybe I'll go a little quickly, but bear with me, and I'm happy to answer any questions I can afterwards.

So the objectives for this talk. We're going to define who we're talking about in this co-

occurring --can you guys hear me?-- condition. What are the clinical and biological relationships between ASD and epilepsy that we know about, and where do we go from here?

I want to first start by saying that the framework for this talk really comes from a wonderful workshop that was put together by NINDS, M-I-N-D-S, two years ago, and Dr. Deborah Hirtz and Dr. Roberto Tuchman, with help from Laura Mamounas, put together a really fabulous workshop bringing leaders in the field really just to discuss this, co-occurrence, ASD and epilepsy. I know many of you in the room were there and it was great. It was also sponsored by NICHD, Autism Speaks, Citizens United for Research in Epilepsy. The three objectives that we're going to talk about really come from wonderful discussions from that workshop, and there are more. There were four or five or six or seven different directions people wanted to go. The proceedings from that workshop were published last fall in Neurology 2013 if people want to reference them further.

Who are we talking about? I think first we

need to start by acknowledging that definition really matters and where you look for data really matters. So how you define epilepsy is going to really impact where you find your prevalence rates or what they look like. The International League Against Epilepsy defines it as "a chronic neurologic condition characterized by recurrent spontaneous seizures." Other folks may use sort of less stringent definitions. There are some papers that I've looked at that really include in the epilepsy group people who have evidence on their EEG, but maybe not frank seizures or loss of consciousness. You really need to know what you're looking at.

What I decided to do is sort of pull two meta-analyses just to get a good idea about what the prevalence rate might actually be. The first one was published in 2008 and it was really only looking at cross-sectional studies that looked at the prevalence of epilepsy and ASD, if they could also link it to the prevalence of intellectual disability. What they found -- and this was very -- four decades of work that they looked at, and

they chose really good studies. They found something really interesting, which is that if intellectual disability was present then we had a much higher rate of epilepsy than if we had what we call a normal IQ, so IQ over 70. So that's about a third.

The next meta-analysis I looked at was one from 2012, and there was very little overlap. I think it's only one study here. This was from 1984 to 2010; I think was the last paper that they looked at. They found pretty much the same thing, and they also had a very interesting sort of dichotomy that was age-related. So the lowest prevalence rate was for children less than 12 who did not have intellectual disability, and that rate was 2 percent, and the highest was for people that were looked at after adolescence and into adulthood who did have an intellectual disability, and that was 25 percent. So pretty similar - these numbers are pretty similar. The highest risk was in people with ID. It's true also when you look at prevalence of ASD in epilepsy, the highest risk was in people with intellectual disability.

These were interesting papers as well and I put the references here for you to look at. This was two large prospective studies in pediatric populations. The rate was 4 to 5 percent of ASD in epilepsy. This was a large cohort study out of England looking at just adults or people 16 years or older, 16 years or older, which found a sevenfold increase in the odds of having ASD if you have epilepsy. The other thing to note here is that this doesn't pull people apart. None of these studies say, well, we're going to exclude people who have a syndrome, or we're only going to look at people who have what we think and what we call is idiopathic autism. These are all comers, but just to give you an idea of who we might be talking about.

What causes them to occur together? That's really what we want to know. It's a great deal of people that we're talking about here. So early neural development is this time of really increased excitation, and that's a good thing. We need that because excitation really is what the neurons need to get going, and there's all these

activity-dependent processes that have to occur. So that's great. We have the highest rates of synaptogenesis early in life, in the first two years. We have this rapid maturation of synaptic plasticity mechanisms. These overlap. So we're primed for activity-dependent processes to happen.

But what happens because of that is that we are also uniquely vulnerable for any kind of insult during that very excitable time to have deleterious effects that maybe cascade and continue to cause neural disruption for time periods, you know months, years down the line. So the thinking from this workshop was that there are a couple different pathways that this could take. When we have ASD and epilepsy plus intellectual disability in the same person, this may represent a primary disruption in synaptogenesis. This could be a genetic abnormality, a mutation. This could be an early insult, like HIE in the neonate, where you're getting -- the primary insult is causing both your ASD and your seizure. You could have some genetic predisposition to have a seizure or it could not be genetic at all, like we talked

about with an HIE. I think we heard from one of the public speakers about that in her sons. And that's the primary disruption and that results in both cognitive impairment and ASD. You could have some kind of predisposition genetically programmed to have cognitive impairment and ASD and then the seizures further exacerbate that condition. So there's a lot of different models and they're probably all related, and we really are beginning to make strides in piecing out which is what.

This is to drive home that point. The association between epilepsy and autism spectrum disorders is really well recognized. It's just beginning to be well understood, better understood. And that's exciting.

So enhanced excitability in the developing brain. We can go this way. This is just to drive this home. Disrupted plasticity. This could be abnormalities in the receptors, in the molecules, in the neurotrophins, anything that's sort of building part of that scaffolding, part of that picture, and that leads to epilepsy. Then these ongoing seizures are really what's driving the

cognitive deficits and the autism. So that's one pathway. You could have people who have a disruption here, similar molecule, similar disruptions, and you just get the cognitive deficits and the autism and maybe you don't see the epilepsy.

This is from Amy Brooks-Kayal, and this is a cartoon just to sort of underline the fact that the initial insult could be here (indicating), anywhere in here, but once you start generating the seizures the seizures' ongoing effects, because when you have a seizure there are sort of immediate responses in the brain -- early genes get turned on, all sorts of things -- but then there's a delayed effect, and then there's an even longer effect down the line that maybe is characterized by inflammation, gliosis, and ultimately neural reorganization.

So what this is showing is that here is the initial effect that maybe hits one or two or three of these processes, and then you have ongoing seizures, and you're actually disrupting maybe pruning later on in life, maybe dendritic and

axonal refinement, and receptor and ion channel maturational changes. So these are ongoing and chronic disorders. Where do we go from there, and what's the way to sort of get into that and start unpacking it? We're really lucky that we're going to hear from Mustafa Sahin really shortly -- I have seven minutes or something left -- about TSC. What we do is maybe one approach, the workshop decided, was to look at single gene disorders that have a high occurrence of ASD and epilepsy and also in fact of intellectual disability. The three that sort of stood out were tuberous sclerosis complex, Fragile X, and Retts. Right? These are disorders that have all three of those things. In TSC I think it's 50 percent of the kids may have ASD. 80 to 90 percent of them will then generate seizures; will have epilepsy, and Dr. Sahin can speak to that in depth in a minute. Fragile X, the same. 30 percent of these boys will have ASD and 10 to 15 or 25 percent of them will then develop seizures. Retts, while it's not exactly autism, there's a lot of phenotypic overlap here. The interesting thing about the seizure generation in

Retts disorder is that the seizure type character in these girls is very developmentally mediated. So if you're a girl and you're five, your seizure disorder looks really different than it does when you're an adolescent, and looks even more different when you're an older person, and the prevalence rates are different. So those may all be clues.

The other really interesting thing about monogenetic disorders and these three in particular is that the gene is known, so the gene product is known, and more and more we can try to dig down and figure out what that gene product is doing in terms of its role in synaptic plasticity, and what is the gene product doing in its role in this imbalancing of excitatory and inhibitory brain circuits that we think is happening? We're getting closer and closer to figuring out that there are overlaps here between these gene products and those processes, and that's really exciting.

In summary, what we know. Both ASD and epilepsy are spectrum disorders. I think people in

this venue are really comfortable with talking about ASD as a spectrum disorder, but, you know, epilepsy is as well. More and more people in the field are beginning to say that. People who have epilepsy have incredible overlap with other neuropsychiatric disorders and other abnormalities. So epilepsy is a spectrum disorder as well. Both of these can be conceptualized as disorders of neural connectivity, resulting maybe from this primary dysregulation of synaptic plasticity. This is really important. If you have one and you also have ID, your risk is greatly increased of having the other.

What do we want to know more about? We really haven't talked much about this at all, but we really should be thinking more about better characterizing the seizure patterns. Like the children who have Retts, what is that telling us about people who have ASD and seizure? These are probably all really different and there may be knowledge here that we're not gleaning. What is the role of an epileptiform EEG in that child who's never had a frank seizure? We think of

seizures as motoric disruption and loss of consciousness, but what about the kid who has a really, really ugly EEG? We don't know what that means, and they have behavioral abnormalities. So we're not really sure what that means. We need to characterize better. What's the role of ID in outcomes in these ASD-epilepsy phenotypes? We don't have a good handle on that yet. Something that's near and dear to my heart, which is, is there a critical window for intervention that can arrest or reverse a dysfunction that we think is going on in neural circuitry? How do we do that?

I'm going to start what we need or next steps from the bottom up. We really need models that better identify these neural dysfunctions in order to be able to intervene and correct them in populations that have both ASD and epilepsy and also include people with ID. A very interesting paper -- actually, at the end of this workshop one of the things that people talked about would be a great model would be sort of this model of West syndrome.

West syndrome is an epileptic encephalopathy

in little kids. It's sort of very developmentally mediated. It usually comes on at a certain time point and then it ends at a certain time point. It's clinically characterized by infantile spasms and by EEG, by hypsarrhythmia. I see people nodding around the room. They're very comfortable with that.

There's a really interesting paper just this month in Seizure by Gregg Holmes, who's at UVM now, and Scott Brose, who's at Dartmouth, where they looked at sleep incoherence patterns, so really using coherence as a way to look at neural connectivity in different groups of kids, about 12 kids who had West syndrome and matched to their typically developing controls. What they found is that the coherence patterns in these children were really, really different for the ones who had West syndrome, and this is at sleep so this is a default state, than the typically developing kids, which was really interesting. And they were different in ways that they hadn't anticipated. A little bit of a teaser in this paper -- and it's a brief communication and you all should just read

it; it'll take you like ten minutes -- was that when they did a follow-up a year later the kids who now didn't have hypsarrhythmia anymore, but they did have ugly EEG's, those kids were still developmentally delayed. And the child -- it was one child, but still exciting -- whose behavior had normalized and was developing normally, that child did not have abnormalities in the neural circuitry. So these are things that we need, that's the kind of modeling and innovative thinking that we need to be doing to try to identify where those windows are and how do we measure that. We really need this, and that starts with all using the same definitions or people really talking. Better animal models and you can read that one on the top. That's it. Thanks.

[Applause]

Dr. Dawson: Thank you. The last speaker in this session is Mustafa Sahin, who is the Director of the Translational Neuroscience Center at Boston Children's Hospital and an Associate Professor of Neurology at Harvard Medical School.

Dr. Sahin: Thank you very much for having me.

I have learned a ton today in this workshop. I think one of the themes that's come up a lot during the discussion as well as the talks is how heterogeneous autism spectrum disorder can be, both in terms of the etiology and also how it presents. There are different approaches to this obstacle that autism spectrum disorder presents to us. One is to start with a heterogeneous group of individuals, like Zack is doing and others are doing, and try to identify potential overlaps, potential biological signatures that allow us to subdivide that disorder, to be able to treat it better. An alternative and I think a complementary approach is to start with a defined biological entity, potentially a genetic disorder, that there's a high incidence of autism spectrum disorder and use that as a model to understand autism spectrum disorder and its neural circuitry better. What I'd like to do today is to present to you some of the work that's been going on, not just in my lab, but also with my collaborators around the country, using tuberous sclerosis as a model.

I'll start with a story of a patient I saw 12 years ago. He was actually diagnosed in utero at 20 weeks. An ultrasound, a fetal ultrasound, showed that there were tumors growing in his heart, and then he had a fetal MRI that showed that there were tumors in his brain. So the combination of those two findings made the diagnosis of tuberous sclerosis.

He was born at full term, an uncomplicated delivery. I saw him soon after birth when I counseled the parents that he may have a high incidence of seizures, especially infantile spasms, which might be difficult to identify at that age. As Ashura mentioned, this presents as what used to be called West syndrome.

He started having these infantile spasms around three months of age. Luckily, the parents called us in the first couple of days of presentation of these spasms. We started him on a medication called Vigabatrin. The seizures stopped after two or three days and he has not had any seizures since then.

However, he has had multiple issues. He is

followed by our multidisciplinary tuberous sclerosis program at Children's Hospital. He's seen by a nephrologist, by a cardiologist, by an ophthalmologist. His seizures have been under very good control, but he does have significant sleep problems, as Beth mentioned earlier.

Tuberous sclerosis patients also have sleep issues. This child's [name redacted] main problem seems to be sort of a circadian rhythm abnormality. He wakes up at 2:00 in the morning, wakes up his parents, and acts like it's the middle of the day. It's quite disruptive to his schedule and to his parents, as you can imagine.

Importantly, he was diagnosed with autism spectrum disorder. At the age of 12 now, he is nonverbal. He has self-injurious behaviors and he has only one single toy that he plays with. His parents have bought 50 copies of the same toy so they don't lose it. So, tuberous sclerosis has a high incidence of autism spectrum disorders. I'd like to argue that we can use tuberous sclerosis as a good model to study ASD.

Here are some of the reasons that make

tuberous sclerosis a good model. First, about half of the patients with TSC are affected with autism spectrum disorder. Importantly, many of the patients, like [this child], can be diagnosed either at birth or before birth. Due to work ongoing in various laboratories around the world, cellular mechanisms aberrant in TSC are beginning to be understood. And very fortunately, there are some FDA-approved specific inhibitors of these cellular mechanisms that allow us to repurpose those inhibitors for clinical trials relatively rapidly.

So the combination of these four factors I think makes TSC, tuberous sclerosis, a good model to study for autism. Just very briefly, what is tuberous sclerosis? It's a multi-system disease. Just like autism is, it's a multi-system disease. It affects the brain, obviously, but it also affects the eyes, the skin, kidneys, and the heart. In all these organs, it causes benign tumors.

TSC patients present to child neurologists like myself because 90 percent of them will have

seizures some time in their life. About half of them have intellectual disability and half of them have autism. The incidence of the disease is about one in 6,000, so we think there are about 50,000 people in this country and about a million people worldwide affected with TSC. The genes have been known since the 1990s, TSC1 and TSC2. What these genes do is to control cell size.

Here's an example from the brain of a patient with tuberous sclerosis. The tissue was taken at the time of epilepsy surgery. What the brain shows is the presence of these giant cells, which are about ten times the size of a normal neuron. In every organism in which TSC genes are missing, you see enlargement of the cells and the organs.

This is from the fruit fly. The TSC-missing fruit fly eye is bigger, the hair cells are bigger compared to control hair cells. Basically, why does this happen? It turns out there's a pathway in cells, and this seems to be extremely well conserved throughout evolution, that controls protein synthesis. The more protein you make, the bigger the cell gets. And that's under the control

of an enzyme called mTOR, or mammalian target of rapamycin.

What TSC genes do is very closely related to mTOR. They put a brake on mTOR. As you can imagine, if TSC1 or TSC2 is not present, then mTOR becomes, without a break, becomes overactive. It makes too much protein synthesis and the cell grows.

The advantage of this connection between TSC seizures and mTOR was made by five different labs around the world in 2002, and it really has changed the landscape of tuberous sclerosis research and care since then. We have very specific inhibitors of this enzyme. They are in the family of proteins called rapamycin and rapalogs, and those are being used in both research and, more recently, in the clinical setting.

In the past, before a closer understanding of the role of TSC genes in the brain, most of the research has really focused on these benign tumors that patients with tuberous sclerosis develop in the brain, and there were some studies suggesting

that these benign tumors, called cortical tubers, especially in the temporal lobes, were necessary for developing autism. But several other studies have contradicted this evidence and some have suggested the frontal lobes, others have suggested the cerebellum as a cause of autism.

My lab and several others have recently turned to an alternative hypothesis that miswiring of neural connectivity may contribute to the pathogenesis of TSC. We've done a lot of work looking especially in the axons and the dendrites of nerve cells and shown that TSC-missing, TSC-deficient, nerve cells have abnormalities with both the axonal connections and the dendritic connections.

I don't have time to go into those. I just want to briefly describe one project we did looking at the neural circuitry of autism. We wanted to choose parts of the brain which we thought would be particularly important in the circuitry underlying autistic-like behavior and use the mouse model as a way to test this hypothesis.

As you know, the cerebellum, the part of the brain that has been implicated in motor coordination, but more recently in working memory and language, has also been implicated in autism. In fact, the most consistent finding on brain pathology in ASD patients is a reduction in a particular cell type in the cerebellum, Purkinje cells.

Then more recently, Katherine Limperopoulos and colleagues at Children's Hospital in Boston showed that if you have a newborn with an isolated hemorrhage, bleeding in the cerebellum, you have a 37 percent chance of developing autism spectrum disorder. So these type of findings suggest that the cerebellum is particularly important for developing, potentially developing autism in the future. There were some studies prior to our work in the work of Harry Chugani and his colleagues. They looked at PET scans of individuals with tuberous sclerosis, and what they showed was they showed that deep cerebellar nuclei in the brain stem of individuals with tuberous sclerosis and autism showed hypermetabolism.

This is a little complicated, but basically the cerebellum inhibits the deep cerebellar nuclei, so hypermetabolism in deep cerebellar nuclei suggests that the cerebellum is hypofunctioning, is functioning less. Based on this preliminary observation, we decided to test whether deleting the TSC gene just in one particular cell type in the mouse, the Purkinje cells, would result in a social phenotype.

We used a three-chamber apparatus developed by Jackie Crawley here at NIMH, and here what you are doing is to put the mouse into this middle chamber, allowing it to explore another mouse, a live mouse, versus an object. Typically developing mouse models usually spend more time exploring the live mouse versus the object. And that's exactly what we saw in our control group, more exploration of the mouse versus the object. Our mutants of TSC in just this one particular cell type in the cerebellum actually made no difference.

They showed no preference to the mouse versus the object. So we then asked the question, if we treat these mice from early on in life with

rapamycin could we prevent this autistic-like behavior in the mouse model? The answer seems to be yes. So we treated these mice with rapamycin, and this is control mice treated with rapamycin and this is the mutant mice treated with rapamycin. They spend more time with the live mouse than with the object.

Now we're starting to ask if we can treat these mice after they start showing autistic-like features, whether we can actually treat these, and we are getting to those experiments right now. I don't have enough data to talk about that yet.

Everything I've told you so far in this experiment has to do with mouse models, but I think it provides us with proof of principle to be able to test the same hypotheses in our patients. As you know, one of the leading theories in the autism spectrum field is that autism spectrum represents a developmental disconnection syndrome. If this is the case, then our work on tuberous sclerosis is congruent with this hypothesis, and in fact we have one particular advantage studying patients with tuberous sclerosis compared to other

types of autism. That advantage is that many of the patients with tuberous sclerosis will be diagnosed either before birth or at the time of birth.

One of my colleagues at Children's Hospital Boston has shown that among fetuses and newborns born with cardiac tumors, the chance of having tuberous sclerosis is 95 percent. So there's a beautiful biomarker that tells you that a fetus or a newborn is likely to develop tuberous sclerosis. If we combine that fact with the fact that a child with tuberous sclerosis has a 50 percent chance of developing autism, we ask whether we could use that to answer a simple question: Can we detect which infants born with substantially will go on to develop autism?

This is a study we started at our single center at Boston Children's using neurocognitive assessment, diffusion tensor imaging, and neurophysiological assessment, phase processing, and other social paradigms. Now we have some preliminary data from that study that we published a few years ago. Here's diffusion tensor imaging,

which is an advanced form of MRI imaging, in three groups of patients: either typically developing controls without tuberous sclerosis; tuberous sclerosis patients with no signs of autism; and tuberous sclerosis patients on the spectrum.

What we are looking at here are the connections in the main connectivity between the two hemispheres of the corpus callosum. As you can see, there's no significant difference by eye between these two groups, and in fact by quantification we don't see a significant difference between these two groups.

However, TSC patients on the spectrum have much less connectivity between the two hemispheres. This is actually a finding that's been shown in the non-TSC autism population in the past as well. So this allows us for the first time to take a genetically defined group of patients and be able to differentiate them as to whether they have autism or not have autism based on diffusion tensor MRI.

So this was a single scientist study for about 40 patients. We were lucky enough to get funding

from the NIH to ask this question prospectively at a larger group of centers. So we now have a consortium, the Autism Center of Excellence Network, of five centers that are geographically distributed around the country, that are analyzing patients born with tuberous sclerosis exactly the same way, using EEG, MRI, and neurocognitive testing. This study is about halfway done. We've enrolled 75 out of 100 patients and we'll hopefully have the results in the next couple of years.

At the same time, a parallel study funded by the NINDS was looking at the predictive value of EEG to predict epilepsy in children with tuberous sclerosis, and that study is almost completed. One of the things, of course -- we want to predict who's likely to have autism and who's not likely to have autism. But really the basic question is can we intervene in some way? Is there some intervention that would change the course of these autism deficits in children with tuberous sclerosis? In the mouse models, the group of drugs called rapalogs or rapamycin-like drugs look very

promising. They can improve connectivity in terms of myelination. They can prevent seizures. They can improve learning. And, as I've shown you before, they can prevent autistic-like features in the mouse models.

As a result of that, we started a phase two trial in patients with tuberous sclerosis between the ages of 6 and 21. We're looking at neurocognitive features as a primary end point, but we're also looking at autism seizures and sleep as secondary end points. We have enrolled 50 patients from two sites and the last patients are going to be done with the trial at the end of December, so I hope to have some results by early next year. We'll be able to compare neurocognitive testing at baseline, at three months, and six months of treatment versus -- treatment with the active drug versus placebo in this group of patients.

I think everything we've done with tuberous sclerosis begs the question: How many of the findings that we have in tuberous sclerosis are specific to tuberous sclerosis, how many of them

are potentially generalizable to a larger population of patients with tuberous sclerosis? To be able to answer that question, we recently formed a consortium, a Rare Disease Research Network consortium that just got funding by a combined effort of four institutes at NIH.

That consortium will look at not just tuberous sclerosis patients in a longitudinal way, but also Shank3 mutations in the Phelan-McDermid population and P10 mutations as well, known causes of autism and intellectual disability, and to see what are the similarities and the differences between the three different syndromes. We'll also ask the question whether patients with P10 could also be treated with inhibitors to see if we can improve cognition in those groups of patients as well.

I think that a comparative analysis of the single gene defects that lead to intellectual disability and autism will tell us a lot about the overlaps and the convergent biology in autism spectrum disorders. I'd like to stop here and thank our collaborators and funding sources. Thank you very much.

[Applause]

Dr. Dawson: Well, thank you, Mustafa. Do you mind if I start with a question. No, I'll let you take over if you want? I'm trying to understand, Mustafa. You know, I love your findings using diffusion tensor imaging to show the difference in fiber tracks between children with TSC with and without autism. So I'm just wondering, when you do the studies with rapamycin where you're affecting the mTor pathway and your mouse model it's affecting the autism outcome, right? But yet, my understanding is it also affects the tubers, right? Doesn't it affect tuber growth when you give rap in the mouse model?

Dr. Sahin: Ahh --

Dr. Dawson: So I guess I'm wondering whether you think that -- is the medication influencing the autism or the tuberous sclerosis or both? How do you think about that?

Dr. Sahin: I guess as a child neurologist I think of them as a convergent disorder. I believe that the behavioral deficits that we see in individuals affected with TSC, whether they may be

anxiety or ASD or ADHD, are probably coming from the same abnormality in the mTOR pathway. And they may have different neural circuits that underlie the deficits, so some of them may occur because there are abnormalities in the hippocampus, others may occur because there might be abnormalities in the VTA.

Different synapses and different circuits might be affected. But the underlying cell biological defect would be the mTOR hyperactivation. So potentially we'd be affecting all of those symptoms at the same time. In a sense, TSC is compilation of symptoms. Similar to the example Tom was giving about fever, if the fever was caused by sepsis, let's say, an infection in the lung and in the brain in a patient with sepsis, then we would use an antibiotic that would attack the bacteria I all of those organs, all of those pathways.

I think rapamycin, I see that as sort of a transformative therapy that would attack the underlying cellular abnormality in all of those circuits. I think there is some evidence just from

the mouse model that that is true. We have mouse models, for instance, with epilepsy, TSC deficiency that causes epilepsy, and we see abnormalities in the myelin deposition in those mice. And when we treat them with rapamycin both the seizures improve and the myelination improves. I don't think the seizures are due to the myelination defect, but both of the symptoms improve. Does that answer your question?

Dr. Dawson: Yes.

Dr. Insel: Kind of on that same track, for both Ashura and you, Mustafa: Can you use this approach to get any kind of a localization? So if you compare kids with TSC with and without autism, besides the -- you showed the one, the white matter track. But for instance, are the tubers most likely to be in one particular part of the brain? Are they most likely -- granted the molecular deficit is everywhere, but is there something about one area that seems to be affected that will truly increase the risk for ASD in this population? The same thing, Ashura; when you look at seizures, where's the focus that matters most

for having ASD with epilepsy?

Dr. Sahin: I'll take the TSC question because I think it's easier. Several groups have looked at that question, because tubers are relatively easy to identify and people have done it since they have been able to do CAT scans, essentially, looked at where the tubers are. There doesn't seem to be a very good correlation between tuber size, tuber location, or tuber load overall, the way we calculate it, with autism spectrum disorder.

So that's why we've been trying to do more advanced imaging that doesn't just look at the tubers, which are pretty obvious on a conventional MRI, but use things like diffusion tensor imaging to look at the connectivity. Along those lines, we looked at, for instance -- you would think a language pathway might be affected in patients with autism. And we do see that, similar to what I showed with corpus callosum, is more disorganized in ASD patients with TSC than TSC patients without.

Dr. Insel: And what about any functional measures, like just looking at resting state or

something like that?

Dr. Sahin: Those are difficult to do in our population of patients. MRI's are done under sedation due to their cardiac complications, etcetera. So we don't really have good functional MRI's. We're trying to do functional MRI's in young kids that don't need the sedation under sleep, for instance. But we don't really have good resting state.

Dr. Insel: Do you do lumbar punctures on all your kids?

Dr. Sahin: Very rarely. If they seize, we think we know the reason why they seize, so we really get LP's on these children.

Dr. Insel: Ashura, on the epilepsy and seizure focus?

Dr. Buckley: I think part of why I like looking at the sleeping brain is because you can sort of recreate a lot of those coherences or the functional associations between groups of neurons, what that looks like in different populations, without really having to worry about sort of external stimulation, where the child's attention

is, etcetera, or if they're holding still. That's sort of the approach that Greg Holmes and colleagues have taken as well in the example that I sort of briefly outlined looking at kids with infantile spasms.

So you can recreate -- what I didn't mention in that study is that the particular type of abnormality and coherence when compared to typical kids was the sort of very intense what we call long-distance coherences, or very highly -- very high correlation between posterior parts of the brain and anterior parts of the brain, which was surprising for them to find. It wasn't what they expected. The authors interpreted that to mean sort of failure of group differentiation that you would see in a typically developing brain, that this was sort of like an inflexible state.

What was interesting in that study is that a paper published by Duffy et al. two years prior found very similar coherence long distance that they're interpreting as failure of differentiation of different neural circuits in the brain, in populations of people who were awake who had ASD.

So you can also look at temporal organization and short-distance electrodes. You can get closer to areas where you might find functional abnormalities, maybe not pinpoint as well as you could with something like fMRI, but you're not really looking for really localized abnormalities. You're looking for neural circuits and things like the arcuate fasciculus and pathways. So I like that approach better.

Dr. Insel: Lyn.

Ms. Redwood: I have two questions. The first is, from the presentations there were something like 21.5 percent incidence of seizure activity in intellectual disability children. So my first question is whether or not we should be screening those children early on. I hear parents tell me from time to time that their child was having what they called silent seizures, and then once they were started on seizure medications there was sort of a boost in cognition. So whether we should do a better job at identifying that. Number two -- and this sort of segues to the immune presentation later on -- I was reading that microglia cells can

also activate seizure activity, and that when they move into an area of the brain that's been injured and they release cytokines, that those cytokines can activate the neurons and actually trigger seizures.

This is something that is relatively new. So one of the interesting things about that, and they see it in posttraumatic head injury and sometimes after infection, is that you can give drugs that can block that immune response in the brain and actually prevent seizures. So since we know -- Carlos, I'm sure you'll address this when you speak -- that there is some microglial activation going on in the brain, could that potentially later on be a target for treatment, especially in those children that have refractory seizures that are not responding to your typical anti-seizure medications? Those are my two.

Dr. Buckley: And they're both for me. I am going to punt to Carlos the second question because I think he's the better person to answer that, because it's a really intricate question. I think there are a lot of layers there, and we can

discuss it again after his talk.

But I will address the first question, which is that, yes, that's something that we hear all the time and I alluded to it a little bit in my very brief talk about what does that look like? Are there behavioral manifestations that are part of the epilepsy spectrum that may share a shared origin with the ASD spectrum that manifests as something other than what we're used to calling seizure activity?

That's something that people in the field have really been thinking about. It came up at the workshop. It's something that I know colleagues of mine are working on, Sarah Spence and Greg Barnes at the Simons Foundation. They are actually doing that. They are trying to better characterize what, if any, are the behavioral manifestations of these silent seizures that you're mentioning.

So in order to do that, you need to sort of get a good, well described cohort of kids and do the EEG's both during awake and during sleep, which we know lowers seizure threshold, and do the intervention and see if you have behavioral

outcomes. So that is being looked at.

Ms. Redwood: Shouldn't there be a guideline in place that if a child has autism and intellectual disability that they automatically get an EEG, both awake and sleep? That's sort of my question?

Dr. Buckley: Should there be a guideline? I think we're collecting evidence about the prevalence of those things. I think usually it has been left up to the practitioner, what is their best -- that's really your criticism; it's usually left up to an individual practitioner, what is their best guess about when the child should have the EEG?

And should you, if you have intellectual disability, just get an EEG looking for the seizures?

Dr. Malow: I may be able to speak to that. The ATN through the ARP mechanism has come up with or is in the process of coming up with guidelines related to different co-morbidities. EEG in epilepsy came up. Dan, did you want to speak to our current guideline in that area?

Dr. Coury: Yes. It is something that we've

been trying to develop, partly because across the country a lot of EEG's are ordered by primary care providers before they get to neurologists, and we've found that it varies in terms of access for them to order that, but, especially because a lot of primary care providers don't have the level of suspicion regarding some of these behavioral manifestations and so they're not aware that what I just saw might be a seizure and so they aren't ordering it as frequently as they probably should be. So we are working on trying to broaden that.

Dr. Buckley: But before we make a guideline we need to have the evidence that that's what's actually happening. That's why I think I hedged a little bit on your answer, and that's part of what the ongoing study with Dr. Spence and Dr. Barnes is trying to do.

Dr. Insel: That's a really good issue for this afternoon, though. If this is in fact an undetected co-occurring syndrome, which is the -- whether to call them silent seizures or not, I don't know. But in terms of number two up there, getting a lot more information about what those

actually look like and how to manage them would be incredibly important. Carlos, go ahead.

Dr. Pardo-Villamizar: Just a brief comment. The comment is coming from a neuropathology point of view. In the brain of patients without these, you are going to see a lot of cortical disarrangement, malposition of neurons, and a lot of abnormalities in connectivity. That is going to translate physiologically in abnormal electrical signals that are going to be detected by EEG.

So I guarantee that if you are going to use the EEG as a tool for detecting electrical abnormalities, you are going to have a lot of abnormalities in those kids. Then the clinician needs to decide what is going to be the approach, to treat a clinical syndrome, clinical seizures, or to treat the EEG. So I think that, unfortunately, I believe at this moment we are still quite behind in understanding the value of the EEG for the assessment of those patients. I wonder that that because you are not going to use a lot of anti-seizure medications in patients that already have some neurological deficits. So that's

my note of caution.

Dr. Sahin: I think the use of an EEG in a patient that is seizure-wise asymptomatic I think is a controversial one. At this point, I think overall child neurologists in this country would not be doing that, because the yield is low and the information is not there. And we are all concerned about getting results from the EEG that we don't know what to do with at this point.

So what we are trying to do, at least in the TSC community, is to do a prospective study to see how predictive is the EEG and what EEG pattern is really correlated with, first of all, epilepsy, and second of all autism spectrum disorder. And since the patients with tuberous sclerosis are the high-risk group, kind of like the sibs of individuals with ASD, we're trying to use that group as a way to test a hypothesis. I think in terms of epilepsy the results look very promising, that we have some patterns that predict epilepsy. But that's still the first piece of evidence in the TSC population. The results for autism, we just don't have those yet.

Dr. Anagnostou: I guess it is a little bit of a supplemental discussion. Actually, this has been a very hot topic in child neurology meetings and people are yelling at each other across the corridor sometimes. So don't feel bad. Yes, so the critical question is whether the only clinical outcome of a blip from an EEG is a seizure and whether other clinical outcomes are there and they should be treated. But the critical test is if you suppress spike activity do you improve outcomes? And that test has not been done. Part of Sarah Spence's and Greg Barnes' study is trying to do that. But that's the test: If you suppress spike activity, do you get improved outcomes?

And we don't know that. So it's hard to make a recommendation without having answered that test.

Dr. Dawson: Bob.

Dr. Naviaux: This is a cell biological question for Mustafa. Because of the role of mTOR in innate immunity and particularly in gram positive and fungal immunity, have you encountered any dose-limiting immunosuppression effects in the children treated with rapamycin?

Dr. Sahin: It turns out the rapalogs are relatively mildly immunosuppressants by themselves. They are most commonly used with other chemotherapy agents and that's why they seem to have more of an immunosuppressive response. We actually have been using in TSC patients rapalogs for a while for treating renal tumors, and…with no PCP prophylaxis, for instance, and have not seen any adverse reactions. In phase 2 and phase 3 trials where they were placebo-controlled, there was not a striking increase in infections in children in the active drug group versus the placebo group. There was not.

Dr. Naviaux: There was not.

Dr. Sahin: It doesn't seem to be a major problem in terms of that.

Dr. Dawson: Matt.

Dr. Carey: First off, I'd just like to thank whoever put all this together, which had some input from me. But bringing in all this stuff on epilepsy, on day one when I came into the IACC one of the three things I wanted brought up was epilepsy and autism. One of the questions I had

then and I still have now is -- we talk about kind of the overlap of epilepsy and autism and similarities. One thing that's struck me since the beginning is -- is there a difference in the epilepsy in autism and how can we bring that back for treatment? Do the same medications have the same effect in autism and do they have the same adverse effects, or are they worse? This is very much prompted -- I'll put a personal anecdote out. When my son developed epilepsy, I got sort of two approaches from two different neurologists. One was: We don't like Keppra; Keppra with autistics can create behavior problems in our experience. And another neurologist who says: I like Keppra; Keppra has never killed anybody, because the medicine you're being prescribed has had an allergic reaction in some patients and actually, not in a long time, but has actually done that.

So when you're faced with that as a parent, you'd really like to have data, rather than "I like this, I like that." You'd like to have somebody say, you know why, with a kid like yours most often -- we know it's not going to be

specific, but most often this one would probably be better.

And obviously these guys are going by the best data they have, their own experience. But I'd like to be able to see that. I'd like to be able to see in autism, is it different? Maybe I don't even look through the databases of prescription drugs and see, where do kids land after a long time? Do they land -- do more kids land on Keppra if they're in autism and more kids land on…or some other drug if they're not? Maybe we can play back from that and get an idea. Anyway, thank you guys for the work you're doing here. I really appreciate it.

Dr. Insel: Gerry's going to ask the last question and then we'll break. Go ahead.

Dr. Dawson: I'm wondering what we know about the longitudinal course of epilepsy in autism. I know I saw the increase in adolescents, I think in the first presentation. But what do we know about moving into adulthood and whether seizures tend to get worse with time? What do we know about the longitudinal course?

Dr. Buckley: I think I remember putting that on the "Need To Know" slide.”

[Laughter]

Dr. Buckley: Yes, we definitely do need better data. I think what complicates that question a little bit is that people get prescribed all sorts of medications for other co-occurring neuropsychiatric conditions in particular, so they're getting a lot of different medications. So what happens in the natural history part of the epilepsy in an adult patient with ASD is something you don't know much about. But I will just take this extra second to make a plug for thinking about the fact that ID, intellectual disability, in ASD may be a different animal, and that we need to think about including people with intellectual disability more often in studies when we're studying ASD and epilepsy, and we haven't done a good job of that.

Dr. Croen: We actually looked into this question a little bit in our study, and it was mostly anecdotal, but people seemed to think that there might be a bimodal distribution in terms of

seizures either early on or really in adolescence. That's the best we could gather.

Dr. Insel: Lisa, I was looking at your data from this morning. It looks like a sixteen fold -- you had an odds ratio of 16 for epilepsy. Does that look anything like the 21 percent or 8 percent?

Dr. Croen: Yes, I was just looking. I didn't show the rate of co-occurring conditions by intellectual disability, but I happen to have it here. In fact, it's right on exactly what you're saying. In the adult population, the rate of epilepsy or recurrent seizure was 27, 28 percent in the autistic group and about 8 percent in the non-autistic group. So it's just exactly what you were reporting.

And yes, there's this huge -- I don't know what type of seizure. We probably could look at that in our database, not so much in a longitudinal, but in a big group of kids and a big group of adults and seeing if the seizure types are different. That is something that are on my notes.

Dr. Insel: It's helpful to know. It's incredible that all the information is around the table. That's great.

Dr. Scahill: Just a quick clarification. Your division was by intellectual disability, not autism?

Dr. Croen: That's right.

Dr. Scahill: Okay.

Ms. Crandy: Dr. Insel.

Dr. Insel: Yes?

Ms. Crandy: This is Jan Crandy. Can I ask a question?

Dr. Insel: Please do.

Ms. Crandy: I don't mean to be the controversial one, but Nevada recently passed medical marijuana and I'm wondering, because there are parents here that are wanting to address seizure activity utilizing that, is there studies, or is that too young now?

Dr. Insel: Anybody here who can field that? Mustafa?

Dr. Sahin: There is not enough information -- and I think the American Epilepsy Society made

this statement, that we don't have enough information in the clinical population of patients with epilepsy that medical marijuana is going to be effective or safe. In the smaller group of patients with tuberous sclerosis, we have even less data. So we feel like it's a really important area of priority and we're trying to study that in mouse models, first of all, where we know that the mouse models replicate the epilepsy for TSC quite well, to see which, if any, of the combination of treatments, ratio treatments, would be effective in TSC mouse models.

Dr. Insel: Go ahead.

Dr. Anagnostou: Health Canada and the Division of Neurology at SickKids I think just got approval for medical marijuana for a clinical trial in West syndrome. So they should have some data within a couple of years. The only caution I would put from the animal model point of view is that the endocrine system seems to be of interest to us for autism, but it looks like bidirectional deviation, like many other things in autism, it would lead to very similar abnormalities. So whether some kids

would need cannabinoid agonists or antagonists remains to be seen, and so we have to be careful when we put those things in place.

Dr. Insel: Jan, it sounds like the jury's out on that one, but it's another question to be studied. Lyn.

Ms. Redwood: I heard recently that in Colorado, where they've also passed a law legalizing marijuana that a certain percent of the proceeds from the sales will need to go into medical research. So if there's researchers here around the table that want to look at that, I know that a lot of parent report, especially with the CDP type strain, that it's been very, very beneficial. So it's something that would be great if someone would apply for some funding to look at it.

Dr. Insel: Tiffany.

Dr. Farchione: I was just going to say that as long as marijuana remains Schedule 1 according to the DEA it's going to be really difficult to do those clinical trials, because -- and we haven't figured out yet how we can even review them as

long as they're still schedule 1. So even though it's legal in certain states, on a federal level we still have problems.

It's something that we are looking into and working on, though, so that that way those trials, somebody can do them at some point.

Dr. Insel: It sounds like it would have to be Autism Speaks that funds it and not the federal government.

Dr. Farchione: It's not even so much the funding issue as much as it is getting an IND in order to study a new indication for that product, because it would be a medical use, treatment.

Dr. Insel: Right. Pre-IND it could still be --

Dr. Farchione: Animal studies, sure. But humans, it's going to get more difficult.

Dr. Insel: On that note, we've earned a break. Let's make it brief because we're pretty far behind schedule. So let's take ten minutes and reconvene by 3:00.

(Whereupon, the workshop took a brief break starting at 2:55p.m. and reconvened at 3:11p.m.)

Dr. Insel: All right, we'll reconvene. We're running pretty far behind on the schedule. We do have some discussion time at the end that we can absorb. We're going to move into the final session for panels. This is Panel 4: Metabolic and Immune Disorders. We're going to do something a little unusual, which is we'll do a tandem presentation between Carlos Pardo and Judy Van de Water, who are going to -- they have found a way, in the spirit of a coordinating committee, to coordinate their presentations and do them together. Carlos, you'll be starting?

Dr. Pardo-Villamizar: Yes.

Dr. Insel: Welcome. We're all looking forward to it.

Dr. Pardo-Villamizar: Thanks so much. My main responsibility is to keep you awake, so you are going to see two people trying to keep you awake and a lot of slides with colors. But the main message that we have for you is to understand "What is the role of the immune system in autism?"

This is a very interesting challenge and both Judy and myself are very committed to work in the

lab with patients trying to understand the role of the immune system in the pathogenesis of autism. I need to mention part of the background that the central nervous system, the brain, is in constant communication with the immune system. The main reason of this communication is this important part of the human beings is to maintain equilibrium. Basically, the immune system is a very important system for maintaining homeostasis in the human body. So many of the concepts that we learned in the 20th century for the immune system are still valid, but there is a large percentage of dogmas and other concepts that have been changing dramatically in the past ten years. And what I'd like to give you is an update about what we understand the role of the immune system is in brain disorders in particular in the function of the central nervous system.

The main question that we have for this meeting is where we stand with autism in direct equilibrium between the systemic function of the immune system as well as the central nervous system. Everything actually starts from the

beginning, because the maternal environment is providing a very important immunological milieu for the developing brain, and that environment is going to be translated in the future in what is going to be the outcome is the brain, developing brain, that is going to be susceptible not only to genetic factors, but also to the environment, and that is exactly where the immune system is going to play a significant role.

In other words, this system is going to keep that equilibrium that is started at the beginning during pregnancy and at the end when the child is born and is growing and growing. So, following the guidelines for this meeting, one thing that we'd like to discuss is what is the evidence that we have about the role of the immune system in the pathogenesis of autism, and in the future is how we are going to apply these eventually for diagnosis and treatment.

As part of background, I'd like to introduce some important topics about the role of the immune system for maintaining homeostasis. This is important because we believe that understanding

the role of the immune system will allow us to understand how the brain is working and how the brain in patients with autism is working.

The immune system is basically there for maintaining this homeostasis, and this homeostasis is going to be affected by different factors, genetic factors. Any event that happens in the environment, any trauma, any infection, any malignancy, any metabolic disturbance is eventually going to affect this homeostasis.

That is where the immune system is going to play an important role, with two major branches: a branch that is a rapid response part of the immune system that is the innate immunity. That doesn't have any major degree of specificity. This is the first line of cellular and immunological responses that characterize inflammation. But there is another branch that is the adaptive immune system in which there is a very selective production of cells and very selective production of antibodies that is going to maintain and control some of these factors that eventually are damaging the homeostasis in the body.

So these processes actually involve many cell types and involve many chemical mediators, that including cytokines, chemokines, T-cells, B-cells that eventually are going to be part of that systemic reaction when all of these factors are affecting the homeostasis. The interesting part of the brain and the central nervous system is the actors of the immune system are different in the brain. In other words, the central nervous system contains and is comprised by a complex network of cells that are not necessarily T-cells or B-cells, but part of the neuroglial cell networks, that are in constant contact and interaction and facilitate that communication that eventually is part of the immune system.

Among the main actors are the microglial cell population, the astroglial cell population, and particularly endothelial cells that are part of the blood-brain barrier. These are very important for neuronal function because, again, these are the major cell populations that are going to keep this critical element of the central nervous system in a normal function.

The immune system in the brain basically is comprised, again, by two major branches: an innate immunity that is comprised by microglia and astroglia that is in the portion of the glial cell compartment, as well as the adaptive immunity, that is basically the response that the immune system has and is comprised mostly by specific T-cell populations that are trafficking in the central nervous system and eventually when there is a challenge by production of antibodies. And again this interaction is maintained in the equilibrium, but this element that is the blood-brain barrier, this blood-brain barrier is basically the open -- the door that is opening and closing all the time to different elements of the immune system for maintaining the normal communication between systemic events and the central nervous system.

It's very interesting because many of the mediators of that communication, particularly the neurotransmitters, are shared by the neuronal cell population, neuroglia, and eventually is going to be expressed also in different types of cells in

the immune system. So in the past ten years, for example, we have learned that glutamate receptors and other types of neurotransmitter receptors are also expressed in cells of the immune system like T-cells or monocytes, and that's a very important concept because we are going to see a lot of shared communication between the two systems.

Now, the major issue for us is what is going to happen with those immunological reactions and what is the role of the immune system in the process of brain development and later in the process of adaptive synaptogenesis or the process of learning and active brain function. This is one of the issues that we need to solve, is what is the role, if there is a significant component of adaptive immunity or most of the responses that we see in brain development is part of the innate immunity.

Now, what we have in the past 20 years or more is that there is growing evidence that there is a very close interaction between the central nervous system and the immune system in patients with autism. This is derived from studies that link

immunogenetic studies. This is derived from many of the studies on way in the role of the brain. This is coming from the studies of the systemic immunological response in which assessment of cell and antibody cell populations are being screened, and also a lot of information coming from animal models that evaluate interaction of those two systems. What I'd like to explain in the next couple of slides is the process of brain development, this process that includes several steps in terms of neuronal migration, synaptogenesis, glial proliferation, and myelination, involves several elements of the immune system. This is the period in which we understand that all of the processes dealing with synaptic plasticity occur, and this developmental period is basically the period of critical events for pathogenesis in autism.

So what we believe and we understand is that the genetic factors that involve the process of synaptogenesis and brain organization are basically associated with a concert of immunological phenomenology that is going to

affect this process, and eventually this is part of this pathogenic period in brain development. Later, once the brain is partially developed, there is a continuum of activity that is leading to synaptic formation and synaptic elimination that is basically the process of adaptive synaptic plasticity and part of the learning process.

Maternal environment is critical. Maternal environment is critical because the brain is exposed not only to maternal infection, but may be exposed eventually to other potential risks, like autoimmunity, and this is one of the processes that we are trying to understand in autism. As I mentioned before, this critical period of pathogenesis involve many elements of the neuroglia and involve many elements of the immune system. Let me give you a few examples. Microglia and neuroglia are present in the brain during brain development to facilitate this important role. It's the molding of the cerebral cortex and different structures of the central nervous system.

Along this neuroglia role there are several

elements of these immunological mediators like chemokines and cytokines and receptors that are chemicals mediators that we recognize very well in the immune system, but in the brain play different roles and perhaps a very critical role for producing this beautiful process of brain development. And this is closely associated with this developmental synaptic plasticity, that eventually is going to define the neurobiological trajectories of neuronal migration, cortical organization, and going to have the nice outcome of the different behavioral trajectories, including language, communication, and sociability.

On the other hand, during adulthood there is this process of adaptation in which different immune factors are going to play also a critical role and again the same actors that were present here during brain development are going to continue to playing an important role in the process of adaptive and synaptic plasticity. So these processes, these two periods, are going to be affected by different factors, particularly

presence of neurotoxins, presence of maternal immunity, presence of maternal infection, and eventually these factors are going to disrupt this brain organization and obviously is going to produce disruption of these trajectories, both neurobiological and neurobehavioral.

I will pass the torch now to Judy, who is going to explain some of the important antibody work in maternal immunity that she is doing.

[Applause]

Dr. Van de Water: He's going to be back. Don't worry - guys. We're going to be up and down, so just make sure you're awake. So thank you. We thought we'd at least try to get everybody on the same playing field for just a lot of the terminology that we use. I'm just going to give one example of some work that we're doing in how the maternal immune environment can affect neurodevelopment, and I'm going to talk specifically about the autoantibodies that we find present in the selective percentage of mothers that have children with autism, that we don't see in mothers of typically developing children.

There's been a lot of work that has gone into this. We started this -- I think our first paper came out in 2007 on this. This is what -- it all began with defining these two -- this particular band pattern that we saw when we put fetal brain into the Western blot and we took patients. As a matter of fact, all of our studies had developmental delay controls in them as well. So we have mothers of children with autism, mothers of typically developing children, and mothers of children with developmental delay without autism.

In most of the work that we see, the developmental delay population looks every bit the same as the typically developing population immunologically, which I think is interesting. They definitely are distinguished from the autism population at the immune level in both the mothers and the kids. But we have -- these antibodies have been associated with changes in behavior, including regression, which is sort of counterintuitive. You would have expected an autoantibody that's present all throughout development would not be associated with a later

onset form of autism, but we actually do see that more frequently in that population than that early onset. So it's very definitely counterintuitive.

We do see deficits in language. This is probably the most significant, is the increase in stereotypic behavior in this population. We see that the MET variant that Pat Levitt and Dan Campbell described is associated with the presence of these antibodies. MET in this context is an immune control gene or immune control protein, so it's a down-regulator of the immune system, of the innate immune system, and that variant causes less regulation, less immune regulation. So, speaking to what Carlos was talking about, during gestation that definitely could have an impact.

Interestingly, we see enlarged brain volume in male children. I'll talk about that a little bit more in a minute. The big thing for us was identifying what these proteins are, because by understanding what they are we can potentially intervene in these pathways. We have several animal models, not just us, but also Andy Zimmerman and Harvey Singer when Andy was at Johns

Hopkins also had a mouse model showing that when we passively transfer, meaning we take human antibodies and put them in an animal during gestation, the offspring had changes in behavior.

So that speaks to the pathologic significance of these. We're currently looking at the animal tissues to understand what the pathology is. I can talk a little bit about that, but because these slides are going to be made public and that data isn't out yet I'm not really going to go into that necessarily. But I think the translational potential for this is that we can identify children prior to conception, we can identify these antibodies prior to conception, screening women at risk. This is not -- I would say this is a good marker for risk of having a child with autism. I wouldn't go down the road of diagnostic or certainly a biomarker of risk. I think, more importantly, we're going to be able to define the pathophysiology and develop interventions specific to this type of autism, and that's definitely the direction my research is going.

Now that we know what they are, what we really

understand is that each of these proteins there are seven specific target autoantigens that we have found. LDH has an A- and a B-subtype that are both implicated. We will never see changes here because antibodies don't cross the placenta until about day 100 of gestation. So the antibodies won't have access during that early developmental period, but they do have access during neuritogenesis, dendritic branching, and especially I think it's particularly interesting from several standpoints.

This gives you a breakdown of the table. So really it isn't one particular protein. It's the combinations of them, and they seem to be additive. From everything that we've looked at, titer is very important, so how strong their response is, is very important, for the obvious reason that the more antibodies you have the more you're going to impact the system, but also the combinations.

It's -- this particular combination was what was defined in our original paper by those two bands that I showed you. It turned out that these

were what I call my little holy triad there of the three big proteins that were most significant at that time, and this is the pattern that is really associated with stereotypic behavior. When you put cypin in the mix, you end up with lethargy. So there is a behavior -- a difference and a behavior phenotype that's associated with the presence of these.

As I mentioned, we have several animal studies. This is a big question, because if they have pathologic significance that's important if we're going to try to do something in the therapeutic realm with them. We need to understand what they impact. This is a study that was done by Christine Nordahl at the MIND Institute with my group, and that we had children in that were two to four years old, two to four years of age -- this was all males in this study or in this particular data I'm going to present -- where we looked at total brain volume.

We noticed that boys whose mothers had these particular autoantibodies had a more extreme abnormal brain growth, meaning their brains were

actually larger than the boys with elevated brain size. I think the graphic is probably more telling here. These are the ones whose mothers had MAR antibody and these are the large-brain boys, and here's the typically developing population. So they're distinguished even from the rest of the ASD population.

So there's a physiological effect of having these antibodies that we can measure actually by MRI. This is just a listing -- I didn't want to go through this in detail, but this is a listing of all the animals with the most recent where we actually injected -- I have a colleague who's very good at injecting into the ventricles of developing mouse embryos on day 14, and we put them directly into the ventricles because we're putting human antibody in, so we bypass the circulation and having them removed by the mouse's immune system, and let them -- she can put them back in; they develop perfectly fine.

We saw increased stereotypic behavior in the form of spontaneous grooming and marble burying and then response to novel environment. That sort

of is where we are on the maternal autoimmune. We do know -- I don't have it published yet, but -- that these antibodies do get into the cells. They get into the radial glial cells, and they seem to be changing neuronal proliferation. So that's what we're looking at now, so we actually can see at the cellular level that they do get into those cells and seem to impact migration.

Dr. Pardo-Villamizar: We are moving from the critical period, this period of brain development and autoimmunity and perhaps the challenge of the maternal environment, we are moving to the period of adaptation. That is when the brain is already developed and during childhood. One of the challenges that we have is to understand what is going on in the brain of patients with autism, particularly with the immune system, and the interaction with the systemic responses.

Just a couple of methodological approaches -- The immune system-brain system interaction may be studied ex vivo with neuropathological studies. This is a gap. We need to collect more brains for understanding better the neuropathology of autism.

The other approach, in vivo, is to do an analysis of brain images. However, we are still quite behind using methodologies for brain imaging and evaluating the role of the immune system in the brain.

There are several lines to study microglia, but we are still a little bit behind having a very good technology to do mapping of these immunological reactions in the brain. So we are left with the studies of blood, we are left with studies of CSF. This is another gap. We have no access to spinal fluid analysis in patients with autism. We have access to blood. But, as I will demonstrate later, blood studies are not equivalent to the spinal fluid analysis.

Many of the studies from neuropathology are derived from a very few brains obtained from the ATP and from the collection that has been derived from Autism Speaks. These studies have focused mostly in evaluation of neuroglial responses, and perhaps the first demonstration of an immune system hyperreaction in the brain was our study in 2005 that demonstrates clearly that neuroglial

cell populations were active in many areas of the brain in patients with autism. That later has been validated by other studies that have used more sophisticated stereological techniques and demonstrated that microglial cell populations are really increased in areas of the white matter in the brain of patients with autism.

In addition to the observation that there are neuroglial reactions, we have also observed that many subsets of cytokines and chemokines are selectively expressed in some areas of the brain, particularly in the frontal lobe or in the cerebellum, and these are relevant for immunological function, like the role of microphage chemotactic protein or some of the pro-inflammatory cytokines like IL-6.

But the most interesting observation is those cytokines and those chemokines have not necessarily derived from the blood. The central nervous system, the neuronal cell populations, the glial cell populations are in CHARGE of producing many of those cytokines chemokines. That is interesting because one of the most relevant

studies in the past few years for analysis of the transcriptome in brains of patients with autism came from Dan Geschwind, that demonstrated that there are obviously abnormalities in the transcriptome of synapses, but one of the surprising findings for his study is that there was an overwhelming presence of immunological genes or immune-related genes that were very prominent to be present in those brains and those areas of these particular cohort of brains that he evaluated.

So these demonstrate once again that there is a close interaction between synaptic and immune functions of the central nervous system genes and immune genes. This is the list of the most relevant genes, and again you are able to recognize that some of the immune-mediated genes are very prominent in the brains of patients with autism. More recently, there has been a lot of interest in understanding from an imaging point of view what is the expression of microglia. Again, this is another area in which there is a gap because we don't have very good tools.

This is a paper that was published a couple of years ago that demonstrates with a ligand that is assumed to be a relatively fair ligand for detecting microglia, and demonstrates once again that many areas of the brain appear to be with an increased presence of microglial cell populations. This ligand, unfortunately, is not necessarily the best one. My understanding is there are several new ligands that are being produced for better understanding of microglia.

Now, the question now is what is the evidence that we have and what's the cause of the problem? Many years ago when we published our first paper, we never committed to explained what is the reason for the neuroglial activation or microglial presence? But there were several explanations, perhaps related with brain development or perhaps related with development of some immunological responses. Perhaps one of the most interesting findings in the last couple of years is the demonstration that the synaptic organization follows a pattern in which there is a very important role for elements of dendrites and

perhaps elimination of those dendrites.

This is a beautiful paper that was published a couple of weeks ago that demonstrates the role of mTOR-dependent macroautophagy in brains of a patient with autism. This is a demonstration that in many of those brains there is an excessive amount of synapsis and this is a very nice demonstration because this is probably one of the suspects that may involve the role of microglia. So one of the hypotheses that I have raised in the past is the microglia response in the brain of patient with autism is just a response to maintain homeostasis and perhaps to maintain the enormous synaptic activity that should happen in the brain of these patients.

Another paper that was published also a couple of years ago is a paper from Betty Stevens from Children's Hospital in Boston, that demonstrated the critical role of complements of as well as elements of microglia in the process of synaptic pruning and synaptic modeling by that microglia.

So these come to the conclusion that many of those elements of microglia are perhaps associated

with neurons for maintaining this equilibrium of dendritic organization and synaptic activity, and this communication, interestingly, is mediated by many of the immunological mediators that we mentioned before, including presence of cytokines, including elements of the complement cascade, and including elements of cytokines networks. So this is another demonstration that the role of the immune system in the brain is more for homeostasis of that function rather than an immunological response.

Now, I'm going to move quickly in some research that has been done in reference to the presence of blood reactions in spinal fluid. This is in very close collaboration with Sue Swedo and the program at the National Institute of Mental Health here at NIH.

This group, led by Dr. Swedo, has collected a very important cohort of patients in which many elements of the immune system have been evaluated, and particularly for understanding what is the role of this compartment, systemic compartment, versus the spinal fluid compartment. What we have

learned -- and this is preliminary information -- is that the compartment of immunological proteins in the spinal fluid versus the compartment in the blood is completely, completely different. So the assumption that we can use the blood for understanding elements of the central nervous system or assuming that the blood is going to reflect what is going on in the brain is completely wrong. So the profile of expression of immune mediators in the blood compartment is very different to the expression in the spinal fluid. Interestingly, many of those elements of the immune response in the cervico spinal fluid are very well recognized to be elements associated with innate immune activity, particularly because many of these cytokines and chemokines are critical for the processing of monocytes and processing of microglial activation in the brain of patients. We need to move very quickly. We have only 30 seconds now.

Dr. Van de Water: Just to sort of wrap up where we are and what we know -- and I think autism is the perfect example of how much

difference there is just even among kids with autism. When I look at them, we see -- I wanted to go through this quickly.

These are the number of studies that have been done. You'll see, I highlighted -- there's a lot of overlap between labs doing the same thing. Some of the work was great and some of it was early. But one of the interesting things -- this is just serum cytokine and chemokine levels -- we're starting to be able to relate it to behavior. We're starting to be able to understand that changes in, I think particularly interesting, this TGF beta, that low TGF beta is an issue when it comes to behavior, is related to irritability, lethargy, and hyperactivity.

When we activate the cells -- this is I think a better measure than just measuring plasma cytokines. I think actually asking the cells to do something gives us a better picture of what those cells look like, and that we again see changes in behavior associated with -- and this is a number of different groups. That we see changes in behavior that are related to some of these changes

in cytokine and chemokine levels, and I'm not going to go through that more.

But what I do want to show you is an example of something that we're doing in the Children's Center at Davis, and that we actually see a differential immune response in the presence of a Tox-BDE 49, where we have children with ASD versus typically developing subjects, and we co-culture with this particular polybrominated diphenyl ether, or flame retardant, and to use this as an example of genetic susceptibility, there's something that we don't understand that is creating this very, very differential picture.

We've taken the cells incubated for four hours with BDE49. We've done nothing else to the cells except let them go for 48 hours after that and gather the supernates and check for cytokines. And you can see the AU group responds very -- the autism kids respond absolutely opposite for several of the cytokines and chemokines that we've looked at. This is just a small picture.

But not only do they have a difference, they go in the opposite direction. So there's something

fundamentally different about how the kids' immune systems see these particular exposures. So what we're doing in the Children's Center is trying to understand genetically what is it that differentiates these two populations so dramatically. So that's just to give you an idea of some of the kinds of things that we're looking at to understand the fundamental differences.

Dr. Pardo-Villamizar: It's okay if we go for two more minutes? All right. One of the issues is what is triggering immunological responses. One of the questions that actually we outlined here with the NIMH group and Dr. Swedo is if there was any element of gastrointestinal pathology increasing the amount of cytokine response and eventually producing abnormalities in the brain function. This is still a work in progress, but one of the questions that we asked was, was there any element of the gastrointestinal system translocating into the system that is going to be recognized by the immune system and generating an immunological response? That is called microbial translocation. In other words, if there is intestinal

inflammation is there any way that an intestinal inflammation may trigger systemic responses that eventually are going to trigger immunological hyperactivity in the brain?

To study that we have several tools in immunology: We can study the expression of LPS or LPS-binding protein or CV-14 or other elements of microbial translocation. So we did that study at the National Institute of Mental Health, and what we found is that there is absolutely no evidence that elements of microbial translocations are present in patients with autism. This is basically comparing a group of patients with autism and a group of patients that represent controls or, even better, comparing the patients that were labeled autism with regression versus no regression. There was no difference at all in presence of that.

We went to more sophisticated technology and we did analysis of the 16-S RNA looking for bacteria circulating in plasma, and again we found no evidence of that type of reaction. So in other words, the hypothesis that there are elements of microbial translocation triggering immunological

reactions is not demonstrated in this cohort of patients. So the rationale for using empiric antibiotic in patients with the hypothesis that there is a leaky gut or an occult infection is not proven in this cohort of patients.

Now, let me finish my presentation with this slide, because this is a slide related with treatment. There has been a lot of concern about immunological reactions in patients with autism, and there is an empirical use of oral steroid treatment or even suggestions of treatment with immunosuppressive medications, with the assumption that we are going to be treating some elements of the central nervous system. I think that in my view as a clinician working in immunology this is a very dangerous route. At this moment there is absolutely no evidence that we are dealing with an autoimmune disorder in autism and there is no evidence that the brain abnormalities and immune abnormalities that we are seeing in autism are related with any process that involves adaptive immunity or presence of hyperactivity of the immune system in the brain.

There are interesting concepts, for example the use of IVIG. I think that we may need to understand this better because IVIG modulates complement cascades. Based on work by Beth Stevens, we need to understand better the role of complement in the process of synaptogenesis. So this is something for the future, to have a better understanding of the potential role of this immunological modulator.

We already know that minocycline, based on a study that was published here at NIMH, doesn't have any role in microglial activation or at least modifying the outcome of patients with autism. So in other words, the conclusion that we have is at this moment it's much better to wait and have a better understanding of the immune role in autism rather than jump in in using medication that we don't know what is the outcome. In other words, my motto is: Don't mess with the immune system.

The conclusion that we have is, yes, we have areas that the neuroglia and the innate immune response is present in patients with autism. We know that maternal antibodies are present in a

subset of mothers and this is probably relevant as a risk. We know that there is no autoimmune process, and probably the immune system – is not a pathogenic process. The immune system perhaps in autism is perhaps following a pattern in a dysregulation of this function, rather than a pathogenic effect that is producing damage of the brain.

Again, I think that we may need to work more in the gastrointestinal pathology. The main conclusion, as I mentioned before, is at this time there is not any role for immunological therapy or treatment of patients with immunosuppressant medications or antibiotics. Thank you.

[Applause]

Dr. Insel: I'm sure we all have a lot of questions. But let's go on to the final presentation and then we'll take time then to ask questions of all three of you.

[Pause]

Dr. Naviaux: Thank you very much to Tom and Gerry and John and the members of the organizing committee. It's a real honor to be able to speak

to you today about what I'm tasked to speak to you, which is our recent findings in the metabolic disturbances in autism and animal models and comparison to human studies.

The overall summary to my talk today is to express the view that autism is a whole-body disease, ultimately controlled by chemistry that leads to altered neurodevelopment, GI abnormalities, and fundamental disturbances in innate immunity and cell defense pathways. The second point is: The brain can ultimately be considered a cell defense and survival engine that regulates these processes.

So the summary of the talk, in other words, is all autism subjects that have been examined to date have metabolic abnormalities. Most of the mitochondrial dysfunction found in autism is secondary and not the result of single-gene Mendelian or mitochondrial DNA defects. I go further to say that the mitochondrial dysfunction that we see is an active suppression of mitochondrial function that leaves the cell with the ability to explode, react explosively to

environmental stimuli.

Redox, glutathione, and methylation disturbances are common in more than half the kids. I was specifically asked by Lyn to talk about a pioneer in this field, Dr. Jill James, and some of her work in ASD biochemistry. I'll introduce the Cell Dangerous hypothesis and will talk a little bit about how autism-like behavior, metabolism, and synaptic defects have been corrected by a particular treatment designed to address the cell danger response; and that NexGen Metabolomics, using mass spectrometry, identifies the disturbances, and that mouse models and humans with autism have the same core metabolic pathway abnormalities; and that previously identified effector pathways of the cell danger response are these pathways.

I've been in communication with Dr. James and what she specifically asked me to say is: Please do not place my work in the category of oxidative stress school of autism that is that reactive oxygen species cause disease. She was a pioneer in finding some of the first oxidative changes in

glutathione and the methionine cycle in the majority of children with autism in 2004, and that in a recent paper published last year she used methyl-B12 and folinic acid to restore that glutathione imbalance, and that that was correlated with some benefits, and we'll talk about that.

This is a picture from a recent publication of Richard Frye and Jill James that talks about the metabolic cycle, the folate cycle involved in purine and pyrimidine synthesis and biopteran synthesis, how the methylation cycle is involved with methionine, and how that ultimately feeds into transulfuration, cistine, and glutathione metabolism. I'll introduce Dr. James' work by her first publication in this area was in 2004, that identified a decreased ratio of reduced oxidized glutathione in the plasma of children with autism. She followed this up with an open label clinical trial that was published this last year in Autism Research and Treatment. The design of that study is an open label treatment without placebo. There are 65 screens. She eliminated those without

glutathione abnormalities and enrolled 48, gave treatment with methyl-B12 and folinic acid for three months, and obtained the following results using the Vineland Adaptive Behavioral Scales as before and after, and saw a significant increase and improvement in the VABS scale scores; and that correlations in improvement in glutathione redox status were associated with expressive communication scores and others.

I'm going to follow this with an important cautionary tale from my field of mitochondrial medicine, is that in a recent publication by Pfeffer in Nature Reviews and Neurology in 2013 we looked at -- well, our community looked at over 1,000 clinical trials in mitochondrial medicine. Only 35 of those clinical trials were described in sufficient detail to give what's known as a HADAD score of clinical trial quality. A HADAD score is characterized -- you get up to two points for being prospectively randomized, up to two points for being double blinded and placebo-controlled, and another point for paying attention to how -- why the subjects dropped out of the study and not

losing them from the denominator of the study.

In mitochondrial medicine, when we looked at the low HADAD score treatment trials, we found many of them that were successful, that passed the .05 conclusion threshold. But in the studies that were prospectively randomized and double blinded and placebo-controlled, none of them, none of them, passed the effective treatment conclusion. So this is a heartfelt message to everyone, and actually most of the investigators know this, is that we can identify maybe safety and toxicity in open label trials, but we can't determine efficacy, which is what everybody really wants. So if we want to move forward with treatment, we have to be doing prospectively randomized, placebo-controlled clinical trials, HADAD scores hopefully around five if you can get them.

In order to understand the metabolism, you have to understand how cells smell the world, how they see and smell. Actually, "see" is not a bad metaphor, because it all started with little receptors to light, opsins. They are G protein-coupled receptors. They are 7 trans-membrane

domain. Imagine yourself as an angel shrunken down to the size of the cell. How do you know what's going on in your environment? Well, it turns out there are receptors that act like the cellular equivalent of little mass spectrometers, that literally measure the molecules used that cells use as building blocks for cell growth and metabolism and function.

So we have four different opsin receptors. We have 388 odorant receptors. Humans only have two pheromone receptors. In taste we have 25. But, interestingly, the class of molecules designed to interrogate the metabolic milieu of the cell connects all of these, all of these chemosensory receptors. Some of the most fundamental ones are actually in similar groups, so chemokines, ATP, UTP, short chain fatty acids, nicotine, and bradykinin are all in one little group. Down here -- I haven't indicated it, but here we have muscarinic receptors, so acetylcholine, cholinergic cellular responses are tightly, intimately tied to chemosensory integration in the cell.

So we formed this little term called "mitokine receptors," and they're like little extra-nasal odorant receptors. These are in every single cell in the body. And they're 7-trans-membrane G protein-coupled receptors. They respond to ATP, UTP, short chain butyrate, beta hydroxybutyrate, a lot of important actors that a lot of people know about. But these are all related phylogenetically. Interestingly, the purinergic receptors, those that respond to nucleotides like ATP and UTP, are the most diversely distributed in all cell types in the body.

So we asked a question tied to how does the cell know safety and danger? I'll say that at the onset: Safety and danger are not anthropomorphic constructs in the way that I'm using them. They are chemical definitions of the instantaneous concentration of metabolites matching the collective KM's and KD's of cellular receptors and enzymes, versus being too high or too low, below the KD's and KM's of the collective receptors responding to them.

So we started looking for ways to understand

how cells respond to danger. We noticed that the cells seem to respond differently according to, ultimately, the availability of electrons. The world of chemistry is written in the electrons.

I'll refer you to this little paper that we're very pleased has been remarkably popular, "Metabolic Features of Cell Danger Response in Mitochondria." Last year it's had over 6,000 downloads and over 30,000 views in less than a year. Basically, we talk about conditions of scarce calories that happened evolutionarily over the winter. We identified about 30 different pivotal metabolites that can be treated in one direction under conditions of low electron availability and under -- and move down another pathway under conditions of caloric plenty. So electrons equate to carbon-carbon, carbon-oxygen bonds, so this is why we're getting to that. So mitochondria turn out to respond instantaneously with a voltage drop whenever an infection occurs or when electrons are diverted from them. They'll decrease their oxygen consumption. Oxygen consumption will begin to rise in the cell. That

will result in an increase in oxidation that results in the opening of channels in the cell that release ATP to the outside of the cell.

This also leads to a cascade of events that include changes in sulfur and glutathione metabolism, vitamin D metabolism, folate and B12. But we wanted to focus on, what is it that might be coordinating this or maintaining the pathological persistence of what is naturally universal in response to any kind of cell injury. So the danger response is a metabolic response that's universal, but in some cases can be pathologically preserved.

We went looking for, so if ATP signaling on the outside of a cell -- so another point of this talk is that ATP has -- two and a half minutes -- has an energy carrier function inside the cell, but an informational function outside the cell. We found that there is one compound in the world that's available that was a competitive antagonist of ATP that could be used both in animals and in humans. That compound is suramin. It's one that cannot be used for any other function other than

the treatment of African sleeping sickness and river blindness currently, but we are using it as a lead compound to open up a class of drugs that can be made safer and better. When we treat animals with the maternal immune activation model, the one that involves the treatment of pregnant animals with a simulated virus infection with poly-IC, double-strand RNA, the resulting offspring have autism-like behaviors and they lose Purkinje cells postnatally. So Purkinje cells here are lost, but if we give drug we can completely prevent that. We can also have -- so these are abnormal synaptosomes with hypermorphic postsynaptic densities and electron-dense matrices. We can prevent that in treating the animals with anti-purinergic therapy. The Fragile X model, they have the same kind of electron-dense matrix and hypomorphic postsynaptic density, and we can return that to normal with anti-purinergic therapy. The animals in the MIA model are less sociable, as you saw earlier, and we can restore that with anti-purinergic therapy. The fragile-X they are less social and we can restore

that with anti-purinergic therapy.

If we get down to what cells do, but use what is relatively not as easy to do for humans and use a mass spectrometer in order to interrogate cellular chemistry, we can identify about 700 different endogenous metabolites and 63 different biochemical pathways, and we can characterize the metabolic disturbances by systems analysis. When we do that, we see in the Fragile X model -- I guess I missed one.

In the MIA model, we can move the abnormal autism-like phenotype for metabitite in the direction of control, from red to green here. Also, in the Fragile X model we can move in the direction of the red, being autism-like Fragile X, toward the control. We see when we analyze this that the most influenced pathway, those are pyrimidine biosynthesis. There's also a microbiome component, and in Fragile X there's a fatty acid oxidation component. I'll point out that the purinergic signaling gene expression abnormalities were identified by Marv Natowicz in a paper that we just recently heard about, actually, from

Sophia Colamarino. So thank you, Sophia.

But that's a human study that identified that purinergic signaling gene expression abnormalities were highly correlated with behavioral abnormalities in children with autism, in the brains of children with autism.

So if we correlate the biochemical pathways that have been identified over the last 50 years in children with autism, there are about two dozen different pathways. But it turns out that 75 percent of those pathways are shared with the maternal immune activation model and another 75 percent are shared with the Fragile X model, and that 50 percent are actually shared by all, across all groups. Those include disturbances in purine metabolism, the microbiome, phospholipids, cholesterol glycolysis, NAD, niacin metabolism, and glutathione metabolism. These are all features of the metabolic -- of the cell danger response.

Basically, these metabolic pathways are coordinately regulated, that they actually tell -- tell the cell which proteins to express. So the small molecules are first. There are changes in

small molecules that tell the cell what proteins to express, and it's triggered by a redistribution of electron flow and oxygen and substrate concentrations. In our case so far, we've seen it that hyper-purinergia plays an important role in that.

The messages are: The brain controls metabolism. So the corollary is all brain disorders have metabolic disturbances. Cells smell the world through conserved chemosensory receptors that continuously monitor metabolism; and that purinergic signaling in mitokines controls cellular response to safety and danger, and they're not anthropomorphic constructs, but actually mismatches of the instantaneous chemical concentration of the effector molecules, the small molecules, and the receptors, the evolved KD's, the affinities, the KD's and KM's. And about a dozen core metabolic pathways are shared by environmental, MIA model, the genetic Fragile X model, and then human autism. That's it. Thanks.

[Applause]

Dr. Insel: Thank you to all three of you. A

terrific set of presentations. Let's open this up for discussion. Jose.

Dr. Cordero: Fascinating presentations. I have lots of questions, but I'd like to go to just one. It's the immune changes that you observed and that relate to autism. Are they specific for autism or can they be seen in other conditions, like intellectual disability?

I'm sort of thinking of work that was done way back, I think Harry Nelson, looking at neuropeptides using blood spots from a newborn screening and then looking at children that had autism. In the group that had mental retardation, there were some elevated neuropeptides, just like in autism, but not in cerebral palsy.

I'm just curious to see whether what you're describing is specific for autism or it's in the spectrum of other brain conditions.

Dr. Van de Water: Sorry, I didn’t hear the antibodies part of that. So it's very specific to autism, actually. We don't see it in developmental delay. There is one pattern we found that may correlate with ADHD. And these antibodies

definitely correlate with stereotypic behavior. But it's very, very autism-specific.

Dr. Scahill: I'm reminded of the great country western song: "It's a shame that all the blame falls on the women."

Dr. Insel: Dan.

Dr. Coury: Along the lines of Jose's question, something that has confused me. There have also been the reports of maternal inflammation, as in mothers who've had something like the flu during their pregnancy or some other illness with fever, and the question of how that might be related to autism. The work that you're showing with the cytokines and such, how do I know that that's autoimmune-generated as opposed to generated by something like an infection that the mother is having? Whoever can answer this, because it's beyond me.

Dr. Van de Water: That's why we did the primer on immunology when we started. You marry the brain and the immune system and it's just like, oh, yeah.

I think that's a very good question, though.

There have been a number of studies looking at inflammation in schizophrenia and inflammation in autism during gestation. The important caveat is there are a lot of people who get sick who don't have a child with autism. So that means there's some underlying susceptibility or way that their immune system is regulated that likely contributes to that. So it's not as simple as infection.

I think it's an interesting model. Whether it's schizophrenia or autism depends on when that occurs. When you ask if we're measuring -- the cytokine discussion that I was talking about was kids, so that was -- the cytokines I was presenting are what is going on in the children. We do have studies looking at what's going on in gestation in women, and we've had the study that Lisa Croen and I did a while back, and now we're sort of recapitulating that study in a larger study and so we're writing that up now. It's not a simple answer. Can you tell what their reacting to? I'll say, for the children that come -- the children that come through charge, they only will have -- they can't be sick when they come in for a

blood draw and they can't have been sick within two weeks. So we try to get them at a baseline as best we can. We all know that kids could be like deathly ill the next day and it's been incubating in there, because it's very quick for them.

But you're right, you can't rule out when we do the measures. That's why I don't think they're a good measure for biomarkers, but more -- I like to use how they respond to the things that we do to them, the cells, as a measure of what might be wrong. So what pathways might be dysregulated.

I think that one thing -- I'm not sure that it came out in the presentations. Immune cells and neurons -- immune cells in the brain and neurons share many of the same pathways. mTOR is critical for healthy immune cell development as well. So many of the pathways that we think might be dysregulated could be dysregulated in both arms.

So that's why sort of it's early for us to use this as any kind of measure, as a biomarker, as far as just looking at immune molecules themselves.

Dr. Pardo-Villamizar: In the case of maternal

infection or any toxic exposure to mothers, we need to be a little bit conscious with the interpretation of data generated from blot. The reason is placenta is a very active immune organ, and any type of challenge to the mother, actually the placenta produces a lot of cytokines and chemokines, and eventually that is going to be affecting the fetus. We are not going to see that too much in the bloodstream from the mother. So I think that in the future the animal model probably will help us to understand a little bit of that interface, and definitely maternal infection from an epidemiological point of view is an interesting topic for research on autism, and I hope that probably Lisa may provide some information, because you have been involved in some of the epidemiological studies of maternal infection as a risk factor in autism.

Dr. Croen: The epidemiologic data do suggest that maternal infection or fever during pregnancy is associated with an increased risk for autism. The types of organisms and the time periods that have been associated with increased risk for

autism differ across studies. Sometimes -- so there are some inconsistency, but there is a body of evidence that shows some kind of relationship.

What hasn't been done to my knowledge, and I think in some of these new prospective pregnancy cohort studies we'll be able to do this, is link the biomarkers in the blood or placenta, the levels of cytokines and other immune molecules, with the clinical disease or fever in the mom with outcome in the child, and bringing those three pieces together I think will be informative on how this all fits together.

Dr. Insel: Lyn.

Ms. Redwood: Hi, a lot of comments, great presentations. Thanks to everyone. With regard to the immune activation, I was thinking about the work of Paul Patterson in animal models, where he actually found that it was not the infection itself, but it was the release, it was the immune activation, the release of the cytokines that actually caused the neurological injury in the offspring.

So, following that line of work, one of the

questions that I have is administering flu vaccines and now DTaP vaccines during pregnancy. There's recommendations now for, depending on the stage of pregnancy, two flu vaccines and a DTaP vaccine, which we know causes an immune response. So whether or not that should be something that we should be looking at as well.

Also, the fact that vaccination is known to result in an elevated C-reactive protein levels, which in a Norwegian study was also a risk factor for the development of autism. In one study where they looked at women who had a history of depression and they followed the C-reactive protein levels after flu vaccine, they found that they had a much -- a very prolonged elevated C-reactive protein level and it lasted longer than women that did not have a history of depression. So that sort of feeds into what we know about autism, too, in terms of there's strong family histories of the mothers also having depression. So I'm putting in a plug for that to be looked at and to get input from the committee on that as well.

With regard to Dr. James' research that you mentioned, she acknowledged, quote, "Clearly, this intervention requires further study and double blind, placebo-controlled trials to eliminate the potential bias associated with an open label study." So I think it is important that it move forward and we do more types of investigations looking at correcting some of these identified metabolic abnormalities in children, especially if they're resulting in improved behaviors.

And I was wondering if Dr. Naviaux could also talk a little bit about the mitochondrial abnormalities in individuals with autism?

Dr. Naviaux: It was actually the disconnect between what we observed in children with inherited forms of respiratory chain disorder, oxidative phosphorylation, mitochondrial disease children, clinically and the clinical features of autism that got me into autism. Maybe this is the appropriate time to also thank Autism Speaks for giving us our start in autism with the funding of our Trailblazer Award.

The children with inherited forms of

mitochondrial disease come in with multi-organ system involvement, a decrease in hearing, sight, skin sensation, taste. They respond actually with a blunted immune response to most immunizations, so the actual percentage of immune conversion, titer conversion after, say, pneumovax is decreased in children with autism -- excuse me -- with mitochondrial disease.

When we look at children with autism, in the peripheral blood we actually see an increase in mitochondrial DNA copy number among the white blood cells. However, when you look at the cellular function with the cell membranes intact it appears that the mitochondria are actually respiring less. They have what we call an increased reserve capacity, but when you uncouple them they can react explosively. Also, when you place them under load they can dramatically increase the level of reactive oxygen production.

Dr. Insel: Could you just clarify, to go back to Jose's question - how specific are any of these findings for autism? I was struck by your comment at the end that all brain disorders have metabolic

disturbances. What's unique about autism?

Dr. Naviaux: The rank order of the metabolic pathway disturbances. We see there is an overlap with something, for example, that we study also in post-traumatic stress disorder in Marines returning from Iraq and Afghanistan. So there are also some overlapping abnormalities that are different, because those didn't affect neurodevelopment, but do affect function of individuals with the disturbances.

In terms of -- if you're asking how broad, for example, metabolic disturbances associated with this cell danger response are, it's very broad. But if you're asking is there a specific signature in autism, I'd say that it's probably premature to say just how specific it is, but we see, if we look at cohorts of sufficient number -- my training in human genetics has taught me to expect sub-clusters within the super-cluster. So when we look at the dots that separate the metabotypes of controls in children with autism, we'll find sub-clusters of different, slight differences, children with, for example, stereotopies being

different from those with lethargy potentially. But overall, the message is preserved that there's a metabolic separation between, a metabolic separation.

Dr. Insel: Sue Swedo is going to join us, since your work has been cited heavily in this session.

Dr. Sue Swedo: I just wanted to first ask about the assumption on the "all brain disorders are metabolic disorders," because the brain controls the metabolism. It doesn't actually control the metabolism of the entire body in every cell. At the point that you take very broad systems, you find links in path one-quarter, then three-quarters.

We were commenting back there that if you expand it broad enough, everybody would have 100 percent of the area they're consuming water, carbon dioxide, and some of the others. So again, going back to the question of specificity, I would like to see the evidence for your initial assumption that all individuals with autism have abnormalities in metabolism.

Dr. Naviaux: Subconsciously, our brain stem is continuously monitoring the chemistry of the body. A big part of autonomic tone is generated in response to the chemosensory monitoring of neurons in eight different circumventricular organs that lack blood-brain barrier, including the fourth ventricle and the area postrema, but others as well. What's interesting to me -- so I'll answer that by: First, we don't have all that data to be able to actually fully demonstrate that, because we haven't tested enough children, nor have we tested all cases of PTSD. But in the cases that we have, we see the abnormalities.

Dr. Swedo: Specifically what kind of abnormalities? Because we've tested a large number of children in the intramural program and haven't found any meaningful metabolic abnormalities.

Dr. Naviaux: We invented the platform that allows us to actually look in a broad-based way at 700 different metabolites. So it's not possible when you just focus on one thing or another. You'll see those one things or another. But if you broaden the lens so that you're actually

interrogating as many different metabolic pathways as you possibly can without bias or assumption in the beginning –

Dr. Insel: And that's in blood or CSI?

Dr. Naviaux: This is plasma, it turns out. So even though the mapping is not one to one, there is -- there's a signature in plasma that correlates with a different signature in CSF.

Dr. Insel: I thought what we saw from Carlos' presentation was this striking difference in heat maps.

Dr. Naviaux: That's because you're asking the TNF-alpha outside in the plasma to be correlated with the TNF-alpha inside the CSF. That doesn't happen. But what we see is, for example, tryptophane levels on the outside correlated with serotonin levels on the inside. There will be metabolic correlations that are not the same metabolites outside and inside.

Dr. Swedo: I apologize for being the interloper, but I also just wanted to make a comment on Dr. Van de Water's gorgeous data, and then just ask her for her comments. You frequently

used the term "risk factor" and that this could be a biomarker, and every paper I've been able to find from your group and from others, we do not yet have prospective data, where mothers are followed through their pregnancies. Other than the cytokine-chemokines, for which there were actually no group differences, we don't know that maternal antibodies are present during gestation. We only know that they were higher in a group of moms whose children had autism when those children were 6 to 12 years old.

Dr. Van de Water: You mean -- yes, they were two to five, but yes. We actually do have the data. I just don't present them in a public form yet because they aren't done. It looks really good, actually, as far as being very -- at least in the Marble study so far.

Dr. Swedo: I hope that comes out really fast, because just on a personal note, we had one of our patients who got the profile and terminated a pregnancy on the basis that she had a, quote, "96 percent risk of having a child with autism." I'm just concerned about that kind of interpretation

of data that's retrospective.

Dr. Van de Water: Where was she from? Was she in a study that we did? She must have been.

Dr. Swedo: She may have been.

Dr. Van de Water: Because it's all research and they know that. First of all, we don't actually, yes, do it during pregnancy, because we don't have to. It's not fetal-based. So it would be somebody who --

Dr. Swedo: No, it was a mom and she had them in her blood.

Dr. Van de Water: Right, So anybody who we've tested. We do have mothers who test during pregnancy, but we don't tell them, actually, so none of the mothers in the study, for obvious reason. We actually don't even test them until they're through the study. I mean, I don't even run them until they're done.

But, no -- you're right it's a tricky, tricky thing. The data coming out on the prospective is very good, actually better than the retrospective, because one of the things that we know in the typically developing moms is we did them

postnatally. We had no idea what their next child looked like. So I think I agree, but those studies take a long time because we bring them in before a pregnancy and we don't even do a final diagnosis until they're three.

Dr. Swedo: Right. We've talked before. We were talking about gaps in the research literature. I think that using the Norway cohort and the Danish cohort and some of the others where there were maternal samples obtained during pregnancy and now those children are old enough that they've passed through the age at risk, if I were still here I would be putting that as the highest priority for this group to fund and to get done.

Dr. Croen: I want to add, the IMA study that we're doing with banked serum from mid-pregnancy from MSAP testing in California, and we have the outcome, so it's a retrospective cohort study, so Judy's done all the antibody testing, and we'll in the process -- we'll be analyzing that very soon.

Dr. Insel: Can you give a couple clarifications about how this is done, Judy? After the pregnancy you're collecting blood to find

maternal antibodies, and I guess the question is do subsequent children; do they have a higher rate of autism in those moms?

Dr. Van de Water: They do. This was done originally through the CHARGE study. It was sort of the discovery, do they exist. All the data was based on just finding them in the first place. We did go back to a group of moms and actually inquire as to their second child. Interestingly, some of them wouldn't answer whether their second child -- and we knew they had another child, but they wouldn't answer whether they were or were not. But we actually -- it was very predictive in that cohort. We didn't do that in a way we would publish it. When MARBLES began, that was when we really looked at it, because we measure it all before that pregnancy and through that pregnancy. Those are high-risk moms, mind you. But we also have just begun enrolling 100 typically developing moms in that population.

So yes, it was the original study was really based on seeing if those antibodies even exist.

Dr. Insel: People are starting to drift out

and I'm watching the clock. But there are still questions, so I want to make sure we get those on the table. Gerry.

Dr. Dawson: This is a question I think for Carlos. When you think about the neuro-immune hypothesis in autism, particularly from an etiological perspective or a developmental perspective, as you showed in your diagrams, do you think of this as a common pathway for many forms of autism or do you think this is a model that applies to a subgroup? And do you have the sense of what size that subgroup? How do you think about it in the context of the broader population of autism?

Dr. Pardo-Villamizar: I think it applies to all forms of autism. The future basically needs to focus on -- future studies need to focus in timing, for example combining different risk factors like maternal infection, environmental factors, or difficult pregnancies, or even difficult deliveries, because during all of that process the immune system is going to be reacting differently. And the timing in brain development

is going to be different as well, and the target may be different, because every region of the brain follows a very, very well-organized pattern of lamination and organization.

So I believe that a maternal infection, for example, at age 28 of gestation may have different implications as compared with 36. The same may happen for potential neurotoxicants, any toxic material. It depends on the age of the exposure. So I think that the model may apply to everything. The critical step in the future is to define a very good clinical epidemiological study that analyzes that timing and perhaps animal models that target that issue as well.

Dr. Insel: Final comments before we go to the general discussion. Lyn.

Ms. Redwood: Just with regard to immune system activation, Carlos, and the comments that you were making that the take-home message was: Leave it alone, don't mess with it. There's just so many of these other abnormalities that come up, like myelin-based protein antibodies that we see in children, these elevated cytokine levels. What do

we do with that information? How do we follow up on it? What's the next steps with regard to research to determine whether or not it's something we need to support or something we need to blunt?

We know that parents out there now are using treatments for microglial activation, and they don't -- nobody knows. Because of the absence of that information, they're acting on their own. So what are the next steps to get that vital information and disseminate it to the public?

Dr. Pardo-Villamizar: The main issue is that we need to understand completely how the process is. We have a lot of pieces floating around and we need to put the pieces together. Microglial activation is a very good example of that. Ten years ago when we were writing the paper, we never committed to say microglia is doing bad things because we never had any evidence of that.

And actually, it was a very good approach, because right now, in the past two years, we are learning tons about microglia. We are learning that they are critical for synaptic pruning. We

know that they're very important for the process of dendritogenesis, etcetera.

So I think that that element is an element that is telling us that all of those small pieces of information need to come in a very good explanation of pathogenesis. Antibodies. If you screen the population of the neuroscience at age 15, you are going to find 15 percent of that population may have auto-antibodies. Are those antibodies pathogenic? Probably not. The immune system has the ability to encounter many antigens and generated immunological responses that eventually are going to go away without any significant impact on the clinical outcome.

So I believe that if we are starting looking for antibodies, we need to focus on antibodies that are relevant for the disease process, and obviously we need to be very critical and validate that process of understanding these antibodies. In the adult population, if you take a look at antibodies against thyroid hormones you are going to have about 25 percent of the population have antibodies for thyroid hormone.

So we need to have a better understanding of the clinical implications of those small findings.

Dr. Insel: Jose.

Dr. Cordero: I just have a general observation, and it's that --

Dr. Insel: Are we going to move into the general discussion? Yes, absolutely. You can kick it off. Go ahead.

Dr. Cordero: I'm just trying to be general here. I think it's really amazing. It's been an amazing meeting, and I think that again reinforces and reminds me of the importance of having a very multidisciplinary, transdisciplinary types of groups, because bringing together people that are working in what seems to be quite different and distant research from one another, it all connects on autism. Particularly this afternoon, it went from mitochondria to immune system. It's just been terrific.

I think that we need to have more of these kinds of discussions and opportunities where people from very different disciplines can intersect and connect and see where the

connections are that actually bring really new ideas.

Dr. Insel: Thank you. Really, that's an invitation for everybody to join into a general discussion. Alison.

Ms. Singer: I had a question for Dr. Kohane. Unfortunately, he left, so I'll put it out to the general group. He brought up the idea of the phenotype-first approach. My question was really about the reliability of a phenotype-first approach, because it seems to me that all of the suspected causes of autism or the majority -- I won't say all; the majority, the ones I can think of, like advanced maternal age or in genetics the Simons Foundation recently reported with regard to the 16P11 -- that there were diverse phenotypes, radically diverse phenotypes. So what is the benefit of the phenotype-first strategy?

Dr. Insel: Does anybody? I'd be happy to take that on if no one else wants to. NIMH has been deeply involved in that question for about three years or four years, and we finally gave it a brand and launched this research domain criteria

project, essentially to say that the future has to be getting beyond symptom-based diagnoses for any of these brain disorders, and that to the extent that we're limited to symptoms we'll never be able to have biomarkers because they aren't going to map onto the symptom clusters in any consistent way.

We already know that. As you said 16p11. But you could pick your favorite thing that looks like a causative gene, and you'll get very different kinds of outcomes. So what do you do in that case? Well, you do -- and actually, Zack talked about it. He had a slide of what's happening in the world of oncology using precision medicine. The concept there is to build an information commons, a huge database, in which you bring in all kinds of stuff -- immune factors, neuro-imaging, genetics you do bring in clinical symptoms, treatment response.

You put it all on the table, and then you ask a very good computer to tell you where the classifiers are. You begin to sort all of that data through machine learning to come up with what

are the right entities.

We just did this recently for all of the psychotic disorders, and it turns out we put in -- there are basically three or four that form the realm of psychosis in adulthood, and we came out with three or four categories, but they weren't in any way mapped onto the ones that we went in with. They're actually not the diagnostic categories we have. And yet those are the ones that seem to have some biological validity because they follow not just the genes, but the connectomes, they follow cognitive function, and a whole bunch of other things.

I think that's a kind of way forward here that we ought to think about. It wasn't in the strategic plan to create a kind of information commons, but you can imagine, with NDAR and some other things that are there, it wouldn't be that difficult to do to put all the data into a pool and then to begin to see how it sorts out. But it's not going to happen based on the presence or absence of one or two or three symptoms. That's just not the way that any brain disorder works, at

least none that we've seen so far. Yes?

Dr. Cordero: I think that actually from people like me that were at work in the previous century, I think that the examples of what happened with clinical genetics and syndromes and this morphology actually is a good example. We started sort of trying to specify a lot of syndromes, and actually that helped when we went into what were the molecular bases of them, to actually beginning to identify specific genes.

Then after that was done, well, we find that actually there are two genes that are -- or the same gene that actually causes two phenotypes. But actually it was very, very helpful because it sort of narrowed and created groups that were more manageable to then look into what is the basic biology, but also the genetics.

Dr. Insel: With all of the bashing of DSM-5, if you sit down and you read the autism section in DSM-5 it basically says this. It says: We don't know enough yet to know how to break out all the categories. So it's essentially -- it's a really well written section, and I have a hunch that Sue

Swedo wrote it, but I'm not sure about that.

But what it says is: Given the state of our ignorance in autism, let's not even try to pretend that we know where to break it into parts. Let's put everything into this bucket that we'll call autism spectrum disorder. But the charge to the field is to deconstruct this over the next few years and to collect the data in such a way that we can decide about the autisms and whether that's 8 or 10 or 15 different disorders.

It may very much be like hypertension, where 5 percent of the time we'll start to peel off as we get really connectomes, as we get really good genetics, as we get a lot more information about immune metabolic factors, all of that.

But this leads, I think, to the question that has kind of been inherent in everything we heard today: How much of what we're hearing that we're calling co-occurring is really something that can help us to untangle this very heterogeneous group?

Larry, you spoke to this directly. I guess we're still not there. It's sort of striking how there are lots of clues and interesting leads, but

it's not -- well, I'll put the question out on the table: Are we at a point now where any of this helps us to identify that subgroup that now has a new name, like Fragile X or Rett, that we can put a name around it, even if we don't have genetics, because we know something about cause and mechanism, syndrome, and treatment?

Ms. Singer: From the point of view of families who are looking for treatment at the point of care, I think what many families want is for someone to be able to say to us: Your child presents with symptom A, symptom B, and symptom C, and therefore should have this treatment, as opposed to presenting with D, E, and F, and that person should have this treatment. So really treatments that are evidence-based based on the presentation.

I guess my question is, does the phenotype-first strategy lead us that way or does a more traditional strategy lead us in that direction? Because ultimately that's what's going to affect treatment at the point of care.

Dr. Insel: Phenotype-first could do that if

included in the phenotype is treatment response as one of the ways you define your syndrome, and if you don't limit yourself to symptoms. If you collect lots of different kinds of data, you could get there. And that's worked. That's worked in lots of other areas. So it could work here. We do have to have a way to collect that data in an aggregated way, so that it moves quickly, so that this isn't just a series of papers that drip out over 20 years, but that there is a collective effort to really drive this home over a very short period.

I think it could be done. It's not being done yet in quite that way. But it could be. Larry.

Dr. Scahill: Two purposes for the phenotype story. The phenotype-backed causation, I think maybe not, maybe that's not so fruitful. The phenotyping for naming target symptoms that are the objects of treatment that I still think is worthwhile.

Dr. Insel: Gerry.

Dr. Dawson: I just have a few responses. One, I think it's important to keep in mind when you

think about treatment and families that many of the co-morbidities that individuals with autism are presenting with are treatable with common kinds of treatments. So I think that we can make very rapid progress by getting the information out to pediatricians that you can look at sleep hygiene or prescribe melatonin or, for constipation, the treatment is how you would treat another child with constipation, correct? So I think that that's something we could do immediately, is get those things out there.

The other thing is I really wanted to underscore what you were saying about the idea of trying to do a phenotype-first kind of approach by looking at who responded to the treatment and who doesn't. If we were, maybe NIH, would mandate that in addition to collecting -- I don't know whether people are collecting genetic information now for those kinds of trials always. But they maybe should collect these co-morbidities in a very systematic way, and it goes into NDAR. So we start to collect lots of data on whether there are certain kinds of subtypes that are responding to

trials in a different way.

Dr. Insel: Beth, go ahead.

Dr. Malow: Just to build on Gerry's comment, for example, if I were going to do a sleep trial after today I'd be really excited about collecting phenotype data, so does the child have more of a bipolar phenotype if they have a short sleep duration, for example. In other words, can I pull other phenotype information together that I might not normally have thought to collect.

I think that's an opportunity, is in our treatment trials think about these other things. Think about your anxiety measure, for example. Then the other thing would be a lot of us or several of us mentioned the whole hyperarousal, electrodermal activity, heart rate, heart rate variability, and thinking about those autonomic measures. Again, doing the treatment trial, because I think Gerry's point is very well taken, that's what the public wants, that's what our families want. They want the treatments. They don't want us to wait to do the treatments until we figure out what's driving the pathology; but in

the process of doing the treatments, collect those data, so that it will inform maybe who's going to be responsive to those treatments.

Dr. Insel: Bob.

Dr. Naviaux: On the phenotype-first point, just to underscore, there are dimensions of phenotype. Just as we're so often, we collect what we can see and with the tools that we have, but it's important to try to unpack the phenotype from as many layers as we can, so looking from chemistry to electrophysiology to functional imaging to behavior. It turns out those studies are hard to do, to actually do metabolomics with diffusion tensor imaging and an intervention study. But it's the future. It's what we have to, we really have to do, in order to understand the interconnectedness of all those layers of phenotype.

Dr. Alan Guttmacher: Just to underscore that and bring it back to Alison's comment, of course I think it's very important to do that in a multi-layered kind of way, multidimensional, because in the end it may not be this constellation of

symptom A, B, and C. It may be symptom A and biomarker H and molecular something or other J that really helps us figure out what treatment makes sense and, very importantly, develop new treatments.

I think it's very important, to Gerry's point, that we use those treatments we know now on a somewhat empirical basis work. Maybe they work for certain characteristics of kids that we can figure out or whatever, but they tend to work. But then, particularly if we think about more biochemically based or other kinds of treatments, we're going to have to break it down on a very -- I think sometimes when we talk about phenotype people just think about manifest symptoms.

Obviously, you want to eventually make it much richer than that.

The challenge is figuring out in this multidimensional kinds of things which ones are really going to pay off, which ones. So we have to cast a pretty wide net, which makes it more complicated and more expensive. But if we're going to do this, I do think, particularly for ASD, that

we need to cast a fairly wide net.

Certainly people who are doing studies now looking at particular parts of phenotype, we want to -- besides having one large, deep phenotyping kind of study or something, we want to go as deep as we can in those other studies and try to collect as much information as we can.

Dr. Insel: There's a wonderful paper out last week or two weeks ago in Cell, which we can distribute here, which has done just this thing for cancer. It's the Cancer Genome Atlas Project. They took I think 12 different cancers from different parts of the body and they just tried to characterize them.

They had six or eight different platforms, to figure out how to define these different cancers. It turns out that the neck cancer was identical to one of the bladder cancers. A completely different phenotype, appearance. The cells looked different, the cancer looked different. But at a molecular, cellular, and treatment response level, identical tumor. Whereas within the bladder there are completely -- there are three completely different

kinds of cancers that were present.

So it is this idea of pulling all of these pieces together. I think oncology has gotten there first in helping to show the importance of using that kind of information, molecular, cellular, treatment response information, and using that to sort out your diagnostics. As they say in oncology, the best path to better treatments is better diagnosis. We need to do that here as well, because we're still dealing with this incredibly heterogeneous category. Lisa.

Dr. Croen: I think this is the way to go, but practically how to implement this? We're talking about a behaviorally defined disorder with a lot of physical and biochemical and some hard -- something that you can measure. But we don't typically -- in cancer you can take a biopsy and you have a specimen and then you can look at genetics and you can look at -- it's easier to collect those data, in other words, I think on large numbers of people than in our autism studies, where we're often studying children, number one; and we're looking at behaviors and

doing brain imaging and collecting biosamples and looking at molecular and cellular and genetic.

It's just, having been involved in studies where we're collecting lots of data at different levels it's incredibly expensive and hard to get funded. And you can't look at large numbers. So I'm just wondering practically how we would implement a strategy of collecting information at all these different levels of phenotype and then doing the computing.

Dr. Dawson: This is perhaps where the Zack Kohane approach is important. If you can take very large data sets and say, okay, we're finding that kids with GI are also having infections and they seem to be very distinct from this other group that has epilepsy, you have this very large data set, and it looks like they're going to do it even more, and if things pop out as relevant subtypes those might be things to prioritize, that NIH says, look, for every clinical trial we fund we want to know, does the kid have seizures, does the kid have GI disorders and a history of infection.

You have to have some way of prioritizing

these, but maybe the big data analyses will point in really important directions.

Dr. Insel: One of the surprising things about people who do autism research is that they don't appreciate their successes. I've talked a lot to people in the dementia field. There are no interventions for Alzheimer's. There's nothing that will move dementia 10 percent. We, maybe out of just pure luck and serendipity, have ended up with some pretty good outcomes for a lot of kids who do actually pretty well.

When it comes to the co-occurring conditions, we can do really well. So it's worth thinking about how these will predict who are the kids who do best, so you can help to select treatments, I mean -- even as great as it is to have these biomarkers and to have tissue for cancer, good luck with pancreatic cancer. If you can get a 21-day longer survival, that's considered a fantastic success. We're in a really much better place in terms of treatments and the fact that we've got a lot of symptoms that are relatively malleable. I don't think we appreciate that nearly enough here,

and the question is really how to optimize it. Rob.

Dr. Ring: I think Gerry just hit something very important. It builds off of something, a theme that's kind of emerging here in this conversation. We've certainly been facing it with our 10,000 genomes program, which is building a giant cloud-based database with Google all on whole-genome sequencing. I think what we're running into is that need for standardization on the collection of data.

I think we can be creative across the funding ecosystem, if you will, and regardless of where that funding originates, creating requirements for the collection of data and the collection of biosamples on top of existing research activity seems like a very quick way to start to build up a repository of information and means to collect additional information.

But it will all fall down unless the standardization of that collection is achieved ahead of that, and that we as a field have reached some consensus on standardization for some of the

core collection activities. That starts with the ADI and NADOS. That's the foundation on which all harmonization might be based for cases on the diagnosis.

But I think that's a huge challenge. I know, Tom, we've dealt with this around the Biomarkers Consortium activities. Can we agree on what that core set of end points would be? Whether or not you lead in on phenome or you lead in on genome, whatever the omics preference is, standardization is absolutely key. I think if we don't have that none of this would really be able to achieve the scale I think necessary for all of us to mine it in an open access kind of way and arrive at the answers to some of these questions.

Dr. Insel: I think this is a really important point for the afternoon session here that we heard, is that we don't have that yet for most of the measures that floated up, even for sleep, where it should be relatively easy to standardize it.

Dr. Malow: I think one of the challenges -- I'm sorry, I didn't see your hand. Can I just

follow up on that really quick? I think one of the challenges, particularly in a field like sleep, as I showed; we could have a particular gene that's going to predict short sleep duration, for example, but then all of the environmental things. It's really hard to sort out the environmental influences, and I'm talking about simple things like iPad use.

But one of the things I think we're trying to do and others are trying to do is look at some of these questionnaires like the CSHQ that was included in Autism Speaks' data collection and say, what are the most robust? So for example, a kid who sleeps three hours is probably going to sleep three hours whether they're using the iPad or not. In other words, there may be some strong predictors.

I think that not just applies to sleep, but other fields and other co-morbidities as well. So focusing on those areas might be fruitful and really digging into those question areas.

Dr. Insel: Anjali.

Dr. Jain: I was just going to say that I think

that we seem to be not talking about big data sets and genome data sets and claims and clinical information. It seems like a lot of this is really about linking these different levels of information and kinds of data together around the children themselves or the adults with autism.

I like the cancer model because, at least for childhood cancers, there aren't a lot of kids at any particular center, but it's in developing a registry that then you begin to standardize naturally by having kids collected and dealt with in the same way, where all that information is available at the child level. So I wonder if we can sort of expand on that model, because a lot of these kids are getting worked up, they are getting tests, they are getting MRI's, to even begin to put them in one place, that we can draw from the collective experience and link it to claims or the genome big databases as well.

Dr. Insel: I think NDAR is now at the 35 or 40,000 subject level for autism and it's probably at well over 100,000 for total subjects. So that's an attempt to do that. Maybe it doesn't have

everything in it, but it has a lot of the levels that we're talking about -- genetics, certainly imaging, clinical features, a whole range of things. And it has then with a fair amount of standardization.

The challenge is we still don't have all the right measures and we're not sure what those measures might need to be in the future.

Dr. Scahill: Some are onerous. Larry, go ahead.

Dr. Scahill: Some are onerous.

Dr. Insel: Some are onerous, yes. Evdokia, go ahead.

Dr. Anagnostou: I guess my thought regarding Rob's comment is that there are multiple initiatives around the world that agree with that idea. So we have a clinical trials network embedded in a large biomarker core across multiple sites. The EU Ames Project in Europe has a clinical trials, emergent clinical trials network embedded in a huge biomarker core across Europe.

The Fasthill program has several sites, clinical trials, biomarker, and precedents for

determining treatment response. Across multiple networks, we've been thinking in similar ways, but we haven't gotten together to say, is there a bare minimum of the biomarker core? We're all going to grow them the same, right, and we all have our interests? But is there a bare minimum that we all agree, out of consensus, not out of obligation, because we have very different regulatory responsibilities and funding agencies that we all are going to collect? And are we going -- in fact, all of us have obligations for public domain dumping after. So you guys have one, I have a different one, and the European Union has a different public domain obligation. So our data will end up in the public domain, but unlikely to end up in places where we can combine across unless we do it from the beginning, unless we consciously think about how we're going to combine this data.

Dr. Insel: We've actually had several meetings about that and an initiative with the Simons Foundation, Autism Speaks, and NIH is just launching. So that'll be organized by the

Foundation for NIH, and EU Ames has been in as part of that as well. So we need to get the Canadian piece to be part of that as well. We'd love to do that. But there's certainly been a lot of meetings and conversation.

One might ask whether this should be such a forum and whether the IACC should be the place to do that. But it really hasn't been the place to bring the science together in that way. It's been I think a little too polarized for that.

Dr. Jain: I wonder if we're coming up with sort of best practice guidelines, if that could incorporate some sort of simple standard workup for testing that should be done as part of that.

Dr. Dawson: I just feel compelled to say this, which is I think one of the reasons why it's been so difficult, besides the heterogeneity and the fact that there are so many autisms, sort of speak -- is the fact that this is a developmental disorder, and that's something that we really have to keep in mind, especially as -- I love the big data approach and the biomarker approach and response to treatment, but ultimately that has to

be complemented with studies that really understand development.

I think it's going to be not only human developmental studies, but also animal model studies, because a lot of the action and some of the interesting things that are being found out now about how toxins affect the immune system during fetal development, all of that really has immediate implications, but it really comes through the animal studies that are developmental in nature, because it's a developmental disorder.

Dr. Insel: We're coming to the very end of our meeting and actually the end of the current IACC. I want to leave about five minutes for people just to reflect if there's anything we should talk about from today's proceedings. Susan and her team will be working on a meeting summary that will be shared, so you'll have a chance to see that. I think this has been a very rich day, so there will be a lot to describe in what we've heard.

But let me open it up to others for their comments. Matt.

Dr. Carey: Again, I think we could have done a

day on everything we did here today, all four sessions. I think we could probably all keep talking for a long time. So I'll try to be quick and keep it to one thing.

We're still talking a lot about getting the tools into the hands of the pediatricians so that they can help the children. We need to really change that into getting the tools to doctors so they can help all the autistics. We have to start including more adults.

We learned a lot today about adult-specific, especially these things like increased Parkinson's and dementia. Those are exactly the kinds of things that, frankly, scare the heck out of me, and I'd like to know more about and know if there's something on the horizon that I need to know about, and if there's a way to intervene with adults.

Dr. Insel: Beth.

Dr. Malow: This is really exciting to comment. I guess what I heard, the public wants treatments now and we should go with things that we have and then potentially collect data, such as biomarkers,

as we're doing those treatments, even if they're indirect, and look at what we have and our best shot and move forward.

Then I also heard -- I think Larry is a great example -- to try to incorporate the autism community and the public in putting together, through focus groups and whatever, outcomes measures, so that they feel like they're working hand in hand with the scientists. I think that's really important and it would build bridges.

So those are the two messages I came away with.

Dr. Insel: Dan.

Dr. Coury: I agree. What we've also heard and what Matthew has said and what Anjali has said is this need for some better practice guidelines. There just isn't a lot of evidence for specific treatments at this point. But as we continue to get more clinicians to use the basics that we know already work -- a fair number of these kids, for example, with constipation, do respond to treatment. It's more difficult because of their behaviors in terms of getting them to take the

medications and the laxatives and so forth. We're at this point now where we don't have necessarily novel treatments, but more that we can treat with treatments that we know work. What you find then is that the ones that are left are the true resistant cases, where we start getting into more specific or innovative treatments.

The same is true with sleep. We still find that a number of these kids will respond to behavioral strategies that work with typically developing kids.

When we really get to that and have exhausted that, that's when we get to the ones where there must be something else going on and start looking at whether it's SMT genes that or abnormal melatonin metabolism or other problems that then are going to require a different strategy and innovative strategies that we're working on.

But right now, as long as we've got really the kids who don't have that problem mixed in because they're not even getting the basic treatment, then we've really missed them, and that's where we get confused as to what works and what doesn't. I

think that part of that is knowing that up front, that you're resistant, and more biomarkers and more genetic studies unfortunately are still part of that.

Dr. Insel: I think one of the messages from the day -- it actually was what drove us into this day -- is that so many of problems which are in fact treatable are undetected or no one even identifies them as being separate from the core of autism. So thinking about a way to get that message out, I thought Zack's idea of having a little card that goes out to parents, rather than to doctors, is probably a way of increasing -- maybe driving a bigger change than anything else that we try to do.

Dr. Jain: I think we also have to pay attention to the time and reimbursement that's allowed for primary care docs to really look at this autism. That's a huge variable in their ability to pick up on anything.

Dr. Insel: And to their capacity. I heard this from somebody who was sitting around the room, that as a pediatrician if you see the problem and

you want to refer, getting a really good referral for a GI problem in a kid with autism there's not a long list of people to refer to, and they are all very busy. So there's a capacity problem as well. Anshu.

Dr. Batra: Again, I want to thank Susan and the staff for setting this up. I think this has been something that really will help me in practice. One thing that Dan had mentioned that resonated was looking at the whole child, whole body approach, which I think it was nice to hear everyone echoing that.

Number two, the dissemination of information to the physician I think is key in the card. I think whoever wants to follow up on that, that will help us in the community.

The other key component that I heard was the need to subtype the different autisms because, in answer to Alison's question, why phenotype-first, phenotype- first because then that helps drive and customize the therapy, which is really what the families want, I want, the community wants. And of course we want to know etiology, of course. That's

of course.

But as John said, being an adult living with autism, at this point he wants the treatment, and most adults who live with autism don't -- they're not as focused on why, but really what do I do about it so I can have a better functioning life. That's really what as a physician and as a parent, that is exactly what my focus is and our focus is, to help do the best we can to help better the life of the individual with the autism.

Dr. Insel: Thank you for that. I also just want to echo I thought a really important comment made by one of our public commenters today about the importance of prevention. We can't duck that. It's true that we have to deal with the needs of people today, but also at the IACC you want to be thinking 10, 20 years out and how do we bend the curve to make sure that fewer people are going to be struggling with the same issues.

Well, we're at the closing hour. I wanted to say this has been really a terrific day of discussion, lots of interesting ideas, great science, some issues for the here and now as well

as issues for more research.

I want to thank all of you who came from far and wide, especially the experts who came in. You're part of a really important process that's been going on for many years through the Department of Health and Human Services and other federal agencies, the IACC.

For the IACC metabolics, my goodness; thank you for your public service, which will terminate. Hopefully, many of you will be back for the next round of this committee. That's up to the Secretary, except for those of you who are federal members. I think that's up to me. So you're the ones who are likely to get called.

But it's been a great experience to serve with all of you and, even if we're not working together on the committee, I hope we'll be interacting again in the future. So I wanted to thank you deeply on behalf of those of us who are in federal service that you became what are called temporary government employees for the days that you were here. It's been great to have your dedication and your compassion and your smarts, which has made

all of this go really well.

We are adjourned. Thank you.

[Whereupon, at 5:02 p.m., the meeting was adjourned.]