

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.

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.

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 comorbidities. 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

