

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

FULL COMMITTEE MEETING

WEDNESDAY, OCTOBER 26, 2016

The full Interagency Autism Coordinating Committee (IACC) convened in Bethesda, Maryland, at the National Institutes of Health (NIH), Building 31, C Wing, 6<sup>th</sup> Floor, 31 Center Drive, Conference Room 6, at 9:00 a.m., Joshua Gordon, M.D., Ph.D., Chair, presiding.

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DAVID MANDELL, Sc.D., University of Pennsylvania

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BRIAN PARNELL, M.S.W., C.S.W., Utah Department of  
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KEVIN PELPHREY, Ph.D., George Washington  
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EDLYN PENA, Ph.D., California Lutheran University

ROBERT RING, Ph.D., Autism Speaks

JOHN ELDER ROBISON, College of William and Mary

ROBYN SCHULHOF, M.A. (for Laura Kavanagh, M.P.P.),

Health Resources and Service Administration  
(HRSA)

STUART SHAPIRA, M.D., Ph.D., Centers for Disease  
Control and Prevention (CDC)

ALISON TEPPER SINGER, M.B.A., Autism Science  
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CATHERINE SPONG, M.D., Eunice Kennedy Shriver  
National Institute of Child Health and Human  
Development (NICHD) National Institutes of  
Health (NIH)

JULIE LOUNDS TAYLOR, Ph.D., Vanderbilt University

LARRY WEXLER, Ed.D., U.S. Department of Education  
(DoE)

NICOLE WILLIAMS, Ph.D., U.S. Department of Defense  
(DoD)

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## PROCEEDINGS

DR. SUSAN DANIELS: Good morning and welcome to everyone around the table, to our committee members and to our listening audience, people on webcast. Thank you for being here for this meeting of the IACC. Are we ready to start? Good morning and welcome to everyone who is here for this meeting today. It's my great pleasure to introduce to you our new IACC chair, Dr. Joshua Gordon, who is going to be giving you a few remarks later this morning. And I also wanted to take a moment to thank Bruce Cuthbert for his support of the committee over the past year, and of the Office of Autism Research Coordination. We really appreciated all your input and your thoughtful comments throughout meetings in the past year. Thank you for everything you have done, Bruce.

(Applause.)

I would like to start this morning with a roll call to see who is here and who is on the phone. So we will start with Bruce Cuthbert.

DR. BRUCE CUTHBERT: Here.

DR. DANIELS: Joshua Gordon.

DR. JOSHUA GORDON: Here.

DR. DANIELS: Jim Battey or Judith Cooper.

DR. JAMES BATTEY: I am here. Judith is here, too.

DR. DANIELS: Great. Cindy Lawler.

DR. CINDY LAWLER: Here.

DR. DANIELS: Jennifer Johnson.

DR. JENNIFER JOHNSON: Here.

DR. DANIELS: Josie Briggs.

(No response.)

DR. DANIEL: Ruth Etzel.

(No response.)

DR. DANIELS: Tiffany Farchione.

(No response.)

DR. DANIELS: Melissa Harris.

(No response.)

DR. DANIELS: Laura Pincock for Elizabeth Kato.

(No response.)

DR. DANIELS: Robyn Schulhof for Laura  
Kavanagh.

DR. ROBYN SCHULHOF: Here.

DR. DANIELS: Thank you. Walter Koroshetz or  
Laura Mamounas.

DR. LAURA MAMOUNAS: Here.

DR. DANIELS: Stuart Shapira.

DR. STUART SHAPIRA: Here.

DR. DANIELS: And Linda Smith is not going to  
be here today. Catherine Spong.

DR. CATHERINE SPONG: Here.

DR. DANIELS: Larry Wexler.

DR. LARRY WEXLER: Here.

DR. DANIELS: Nicole Williams.

DR. NICOLE WILLIAMS: Here.

DR. DANIELS: Alright and for public members.  
David Amaral.

DR. DAVID AMARAL: Here.



DR. DANIELS: Jim Ball. Will be on the phone today - I think he is absent today. Samantha Crane.

UNKNOWN SPEAKER: She was here.

DR. DANIELS: She is here. Okay. Great. Geri Dawson, I think is going to be joining us on the phone.

DR. GERI DAWSON: I am here. Good morning. Sorry I can't be there in person.

DR. DANIELS: Thank you. Feel free to comment throughout the meeting. Amy Goodman is ill today but will be on the phone. Amy, are you on the line?

(No response)

DR. DANIELS: Shannon Haworth.

MS. SHANNON HAWORTH: Here.

DR. DANIELS: David Mandell.

DR. DAVID MANDELL: Here.

DR. DANIELS: Brian Parnell.

MR. BRIAN PARNELL: Here.

DR. DANIELS: Kevin Pelphrey.

DR. KEVIN PELPHREY: Here.

DR. DANIELS: Edlyn Pena.

DR. EDLYN PENA: Here.

DR. DANIELS: Louis Reichardt is not going to be here today. Rob Ring.

DR. ROBERT RING: Here.

DR. DANIELS: John Robison.

MR. ROBISON: I am here.

DR. DANIELS: Alison Singer.

MS. ALISON SINGER: I am here.

DR. DANIELS: Julie Taylor.

DR. JULIE TAYLOR: Here.

DR. DANIELS: We have a pretty full group today. I'd like to now turn your attention to the minutes that were from the July 19<sup>th</sup> meeting. I received one correction from Samantha Crane, which will be made. It was just a factual error. Any other comments about the minutes? Any suggestions? Can we have a motion on the floor to accept the minutes? Second? All in favor? Any opposed? Any abstaining? The motion carries to accept the

minutes as written with the correction that Samantha provided. These will be posted on the IACC website as soon as possible after the meeting. Thank you. Now, we have a few minutes to hear from Dr. Gordon.

DR. GORDON: First, I want to say thank you all for attending and for coming and for your hard work on this committee. I have spent some time, as much time as my schedules allowed of familiarizing myself with the business of the committee, the strategic aims that have been produced, getting briefed on the process of revising those aims, and of the strategic plan I should say. I am excited to be part of this group and to be here working on autism, which is an incredibly important issue for consumers and incredibly actually compelling issue for scientists too as I am sure you know.

I thought I would first actually introduce - actually, first, I am going to let Bruce say a little something about what it has been like for him. I think he knows that I was going to ask him

to do that. Then I am going to come back and I will introduce myself a little bit, tell you a little bit about myself and then I'll take the prerogative of the chair to ask each of you to do the same, but because there are so many more of you than there are of me, maybe I should work a little harder to get to know you. I will say it again, but we will keep those brief so we can get on with the rest of the day.

DR. CUTHBERT: Thanks very much, Josh, and good morning again everyone. It's really been a pleasure and a privilege for me to lead this group during your year of transition. It's a transition not only obviously for NIMH with our leadership, but for this group because of course, you are newly reconstituted committee after the legislation had lapsed. We had to all start up together. It has been really gratifying to lead this group.

I think we have made a really good start. We have identified a lot of areas and opened up some

new directions, most importantly I think in areas of services research, not only research, but program for services.

This is really a unique group. For us at NIH, it is particularly interesting and gratifying to be able to lead it because so many of our groups are simply within NIH or related areas of the federal government like the FDA and SAMHSA and so forth. But really this is truly an interagency and public group with the input from people and other sectors of this government such as the Department of Education for our scientific contributors and most importantly I think especially for all of you who have children on the spectrum or are on the spectrum yourselves. We depend upon on your input. It has really been to me very important to hear about your experiences both as parents and as participants contributing. We really have identified important areas. We have had discussions about things like housing and the nature of supported housing or independent housing

and living issues, for instance, that really are salient and highlighted by many of you.

It has really been an experience, but I think we have really bonded well together as a group and are working hard. I know that under Dr. Gordon's leadership, you will only continue this progress.

I am really excited that I think we can really make some differences not only in future scientific directions, but in the here and now and the practical day-to-day needs of people on the spectrum and their families. Thank you very much for the opportunity. It has been a pleasure to work with you.

DR. GORDON: I would add my word of thanks to Bruce for leading both the NIMH and this committee so well over the past year.

To introduce myself, as many of you may know, I have been a neuroscientist and psychiatrist on the faculty of Columbia for the past 20 years or almost 20 years I should say. I come to NIMH with really experience in education, in clinical care

for adults to confess and in research. I came to neuroscience before that and psychiatry before that really from the perspective of curiosity and the recognition that curiosity alone isn't all that helpful to society. I started out being interested in the wave of modern biology that was happening in the mid-80s and late-80s as I was in high school and then college and felt like this was an incredibly exciting time to study life and biology. That was my primary motivation.

But in college, I worked with an MD who was doing research on cancer and I became enthralled by the idea that one could study life at the same time that one worked towards advances that actually meant something to real people. In this case, this MD was doing basic molecular oncology work, trying to understand the genetic underpinnings of a particular kind of childhood cancer and discovered something that actually was a direct relevance to patient care and ended up getting samples of tumors from all over the world

really and doing some genetic analysis of those tumors and then sending that information back to the physicians who were sending the samples so they could have conversations with their patients about the meaning of that genetic work because it had direct implications for the prognosis for their children. That experience drove me to get an MD and a PhD and eventually I switched from being interested in cancer to being interested in neuroscience, but I never switched from the idea that basic studies and clinic studies could inform each other.

My really only experience I am sad to say directly with autism and families who are dealing with it and children who are suffering from its disabilities as well as potentially although at that age it was hard to say, learning about its differences that can be advantageous. I worked in a clinic once a month as a graduate student with an autism clinic or I should say an autism spectrum diagnostic clinic where we saw children



who were being brought in typically at that time at the age of 3, 4, or 5, looking for a diagnosis, looking for answers, and looking for treatment referrals. I did that once a month with a child psychiatrist who was also a neuroscientist. I have some direct experience, but it's old. I know that a lot has changed since then.

I am looking forward to learning from you all here and from my staff at the NIMH about what the current issues are and trying to make sure that we, at NIMH, have a research agenda that applies to that and that we, as a group, set an agenda, not just on research, but on care priorities. I think you will see that from the agenda that really Susan has assembled today that we are really at the insistence of this group, moving towards looking at autism across the lifespan. We are doing it at NIMH from a research perspective and we should be doing it as a group of agencies from the care perspective as well.

Again, I am really excited to work with this group. I am really excited to learn from this group and to see what we can do together to improve the lives of individuals with autism and related disorders.

With that, what I would like to do is have us go around the table and also on the phone. Obviously, you responded to the roll call. Some of you I can see the placards. Give me your name, what agency or organization you are with if you are and maybe a one-sentence description, maybe two about what you bring to the table here. Okay? Maybe we should start with Brian.

MR. PARNELL: Good morning. I am Brian Parnell. I am from Utah where I work for the Department of Human Services. For the last four years, I managed their recent Autism Waiver and was busy just putting that to bed as autism waivers are being phased out. And then two weeks ago, I began a job working with Child and Family Services, managing domestic violence programs. A primary interest now

in this committee is that of our seven children, three of those are on the autism spectrum.

DR. GORDON: Thank you.

DR. TAYLOR: Hello. My name is Julie Taylor from Vanderbilt University. I am a researcher whose work is focused on understanding how to improve the transition to adulthood and various outcomes for adults with ASD.

DR. WEXLER: Good morning. Larry Wexler from the US Department of Education, the Office of Special Education Program. I direct the discretionary grants program under the Individuals with Disabilities Education Act.

MR. ROBISON: I am John Robison. I am the Neurodiversity Scholar at William and Mary in Virginia. I teach about autism, neurodiversity, and the role of autistic people in society while at the same time I serve on committees like this as an advocate for science to help improve the lives of those of us living with autism and those

of us who will come along tomorrow and live with autism.

DR. ETZEL: Good morning. My name is Ruth Etzel. I represent the US Environmental Protection Agency. My background is in pediatrics and preventive medicine. I spent much of the last 25 years looking at the environmental etiologies of childhood illness and disability.

DR. AMARAL: Good morning. My name is David Amaral. I am a neuroscientist and professor in the Department of Psychiatry at UC Davis. My background is in systems neuroscience of memory and emotion and social behavior. But I was fortunate in 1998 to be asked to be the founding research director of the MIND Institute, which was a parent initiative, to understand the causes of autism, to get better interventions. Since that time, autism has taken over my life and I have been a very enthusiastic researcher primarily in neuroimaging. Subsequently, I was a past president of the INSAR, which is the International Society

for Autism Research. I am currently the editor-in-chief of Autism Research, which is the society's journal.

MS. CRANE: I am Samantha Crane. I am the director of public policy and legal director for the Autistic Self Advocacy Network. We are the nation's leading advocacy organization run both by and for autistic people ourselves across the entire spectrum. I am also a person on the autism spectrum.

MR. MANDELL: Welcome. My name is David Mandell. I am at the University of Pennsylvania where I direct the Center for Mental Health Policy and Services Research. My research is about improving policies and practices that result in better care, better outcomes for people with autism in the communities where they live.

DR. MAMOUNAS: Hi. I am Laura Mamounas. I am sitting in for Dr. Walter Koroshetz, who is the director of the NINDS. Walter asked me to mention a couple of interesting clinical trials that we

are now funding at NINDS as well as clinical studies. At NINDS, we are a large part of the autism portfolio, which focuses on monogenetic and syndromic disorders associated with autism, including tuberous sclerosis complex, fragile X, Phelan-McDermid syndrome, Rett syndrome. We are funding some very interesting biomarker and natural history studies in disorders like tuberous sclerosis complex, Phelan-McDermid syndrome to identify biomarkers that can tell us whether a child will develop autism as well as children that will develop epilepsy and disorders like TSC. We also just this year funded two very interesting exploratory clinical trials, one in fragile X and that it is to revisit mGluR5 antagonists in fragile X. If you remember, Novartis and Roche have conducted clinical trials in adolescents and adults, using behavioral outcomes. We are revisiting that to look at whether mGluR5 antagonists in very young children with fragile X can boost language learning in these children. We

are combining the drug with an intensive language learning intervention. This trial is co-funded by NIDCD as well as NICHD. We are very grateful for that.

The other trial is to see whether in TSC if we can prevent and we have a biomarker that can tell us when infants with TSC will develop epilepsy. If we prevent the onset of epilepsy whether when they are 2, 3 years old, we get better neurocognitive outcomes including whether they are less likely to develop autism.

DR. GORDON: Thank you.

MS. HAWORTH: Hello. I am Shannon Haworth. I am the senior program manager for disability and public health at the Association for University Centers on Disabilities. Most importantly, I am the parent of a child with autism and my spouse also has autism. I am interested in autism and services and supports throughout the lifespan.

DR. BATTEY: Good morning. I am Jim Battey. I am the director of the National Institute on

Deafness and Other Communication Disorders. Our particular interest in autism is as it pertains to autism being a communication disorder. My background is in genetics and molecular biology although it has been a number of years since I obtained that background.

DR. SPONG: I am Cathy Spong. I am the acting director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. As an institute that is not disease or organ specific, we are one that has a very broad representation and clearly autism is very rich in our portfolio. My background is I am an obstetrician, gynecologist, maternal fetal medicine subspecialist and perhaps more importantly a mother of four.

DR. PELPHREY: Hi. I am Kevin Pelphrey. I am the Carbonell Family Professor of Autism and Neurodevelopmental Disorders at George Washington University and Children's National Health System. I am also the founding director of the Autism



Institute at those two institutions. My background is in cognitive neuroscience, mostly understanding how people understand each other and the brain systems involved. About ten years ago, I changed my career path to study autism as the result of having a daughter diagnosed of autism. I am the father of five kids all together, two of whom are on the autism spectrum.

DR. WILLIAMS: Hi. My name is Nicole Williams. I am the program manager for the DoD's Autism Research Program for one of the federal funding agencies.

MS. SINGER: Good morning. I am Alison Singer. I am the co-founder and president of the Autism Science Foundation. Our foundation focuses on funding autism research, predominantly early career investigators. We also focus on building up infrastructure to support the needs of researchers and we also focus on disseminating research findings to stakeholders in the community. I am the mother of a beautiful 19-year-old daughter

diagnosed with autism. I also have an older brother who was diagnosed with autism.

DR. LAWLER: Cindy Lawler. I am here representing Linda Birnbaum, the director of the National Institute of Environmental Health Sciences. I am a chief of Genes, Environment, and Health Branch and I also manage a growing portfolio of grants, looking at environmental risks for autism and gene environment interactions that may underlie etiology. Our institute is a little bit unique at NIH because we do have a public health perspective. Part of our strategy is always to think about how our research findings can translate under a public health framework.

DR. SHAPIRA: Good morning. I am Stuart Shapira. I am the CDC in the National Center on Birth Defects and Developmental Disabilities where I serve as the associate director for science and the chief medical officer. My background is I am a pediatrician, a clinical geneticist, and a metabolic specialist.

The CDC receives appropriations for work in three areas that I will mention in just three sentences. The first is the Study to Explore Early Development or SEED, which is a multi-site case controlled study to evaluate genetic and environmental risk factors for autism. The second is the Autism and Developmental Disabilities or ADDM Monitoring Network. It is a multi-site community surveillance system for ASD in 8 year olds in children in 11 communities in the United States and a subset of these communities also evaluate 4 year olds. And then the third area is CDC's Learn the Signs Act Early Program, which focuses on lowering the age of first evaluation and getting children into needed early intervention services.

DR. PEÑA: Good morning. My name is Edlyn Pena. I am associate professor at California Lutheran University and co-director of the Autism and Communication Center at California. I do research on access and success in post-secondary education

for people with autism. I also do work on augmentative and alternative communication supports for people with autism who are minimally or non-speaking. I have an 8-year-old son with autism. Nice to meet you.

DR. GORDON: Likewise.

DR. RING: Good morning. My name is Rob Ring. I am a neuroscientist by background. I most recently started my own private consultancy practice that works with small companies and foundations, looking to stand up programs and medical product development activities in the autism, neurodevelopmental, and rare disease space. Until earlier this year, I was the chief science officer at Autism Speaks for five years. Half of that was as a CSO. Before that, I spent over a decade in the pharmaceutical industry. My background is in medicine's discovery and development. I headed the Autism Research Unit at Pfizer's Global Research and Development Organization and over nine years

at Wyeth, mostly working in mood disorders and in schizophrenia.

MS. SCHULHOF: Good morning. My name is Robyn Schulhof and I am with the Health Resources and Services Administration of HRSA and particularly the Maternal and Child Health Bureau, MCHB. Today, I am sitting in for Laura Kavanagh, who is our deputy associate administrator. In brief, MCHB has CARES Act-funded programs in three areas, which are health professions training, autism intervention research, and state implementation grants.

DR. JOHNSON: Hi. I am Jennifer Johnson. I am the deputy director of the Administration on Intellectual and Developmental Disabilities. We are in the Administration on Disabilities and the Administration for Community Living, which is a relatively new agency in HHS. We were created in 2012. We focus on policies that promote services and supports and community living for people who are aging and people with disabilities across the

lifespan. We do not have a particular focus on autism, but our work supports community living for people with autism.

DR. BRIGGS: Good morning. I am Josie Briggs. I am the director of the National Center for Complementary and Integrative Health here at the NIH. On this committee, I have the task of being Dr. Francis Collins' representative.

DR. CUTHBERT: One other thing that I forgot to mention in my remarks, is that one of the major things I learned this year is the incredible amount of work that it takes to support the activities of this committee. I really want to compliment and thank Susan Daniels and her entire staff and her office for all the work they do. It is amazing to see how much they do and with what dedication they do it. Susan, thank you.

DR. GORDON: I believe there are a couple of members on the phone who might also introduce themselves.

DR. DAWSON: Hi everyone. This is Geri Dawson. I am a professor at Duke University in the Department of Psychiatry and Behavioral Sciences. I have been a scientist and a practicing clinical psychologist in the field of autism for many years. I was the founding director of the University of Washington Autism Center, which continues to be a very thriving clinical and research center. I was the first chief science officer for Autism Speaks. I served in that position for five and a half years before returning to academia in my current role as director of the Duke Center for Autism and Brain Development where our focus is on clinical trials that are testing cellular and molecular and behavioral therapies for autism. Also, I serve as the president of the International Society for Autism Research. I want to welcome you to the NIMH and also to the IACC. We are very pleased to have you here.

DR. GORDON: Thanks. Anyone else on the phone? I appreciate everyone introducing themselves. I know that it takes a little bit of time to do, but it is helpful for me to hear from everyone and at least get a start on getting to know you. One of the things of course that comes out of that is the tremendous range of experiences and expertise that we have in this group, everything from individuals with autism to experts who have been studying it for years at all different levels. I think that is really wonderful that we can all get together and talk about important topics in the field.

DR. DANIELS: We would also like to welcome Dr. Novotny, deputy assistant secretary of Health who is going to talk to us about his update from the Office of the National Autism Coordinator.

DR. THOMAS NOVOTNY: Good morning and thanks again for allowing me to come and visit the committee and see a few familiar faces again.



Hopefully each time, I will get to know a few more people a little bit more personally.

We are making a little bit of progress. This is a slow process of trying to just staff up and become responsive to the autism CARES Act, which we are determined to do. I just want to let you know that we have finally been able to recruit some internal expertise for the production of the report that was required on the transition period of people on the autism spectrum. We are fortunate to now have some representatives from HRSA and also from my office who are now dedicated to the production of our report and the collection of information behind it.

This report, the way we are framing it, is a report to Congress that is required under the Autism CARES Act, as I mentioned, dealing with the transition period specifically. What we intend to do is a pretty thorough reporting on what the current federal activities are across multiple agencies. This requires what are sometimes

difficult processes to get information from across not just the Department of Health and Human Services now, but also from the Department of Labor, Department of Education, Department of Defense and others that we can then put together as more or less a review of where the federal government stands with this particular niche in the support for those on the autism spectrum.

At the same time or subsequent to that, we would look at the gaps, the duplication. This is something that GAO is also very interested in. But as several of you have indicated to me, sometimes duplication is actually probably the right thing to do. Especially in science, we definitely seek duplication and replication so that we can actually rely on the results that we get.

In terms of services, maybe we need to look at those in a more critical way, but nevertheless, we do need to make this report reflect what is really going on and what the gaps are that need to be addressed in the future.

I am certainly learning a lot about autism - I think I mentioned to you that this is not my subject matter of expertise. I am a physician with a fair amount of clinical experience, but an epidemiologist who appreciates the value of data and information in terms of planning policy.

We have been able to also - I just recently sent out a data call. We call that here in government speak, which is basically a request for information. We are looking forward to our agencies being able to provide us with the information that we need to be able to compile this report. It will not be a 200-page or 300-page compendium. It is going to be what I hope as a very focused, sharp document that we can carry over into the next administration.

As you all know, we are about to have an election. That means those of us in government who are staying here - I am not a political appointee. I get to stay, I hope. We will continue on with the issues that are important and we are trying to

put these into place so that we can continue to do our work despite very substantial disruptions that occur as a result of changing administrations no matter what the parties are. But nevertheless, this is a requirement that we are going to fulfill, led through my office at HHS, but involving the cooperation of so many other federal agencies in this process.

You may ask are you going to also get some input from stakeholders. Yes. As we get further on down the line, we are able to get some advice from stakeholders. This is not the work of a federal advisory committee, which has a very set structure and set of rules that need to be adhered to, everything from conflict of interest vetting, et cetera, but we will be able to at least invite some input from stakeholders as we get a little bit farther along on our activities.

I want to just mention that a couple of weeks ago, I had the pleasure of speaking at the Advocacy Leadership Network meeting here in

Washington. This was a two-day meeting that was a multi-national meeting. There were representatives from 40 countries there. I had an opportunity to hear about the global health perspective on this. It is a global issue. It is not something that is restricted to the United States. What we do here is of course looked upon as leadership whether it is in research or programmatic activities, but that there are also things that we can learn from other countries that deal with some of the same issues.

One of those countries is Canada. I had the pleasure of meeting Mike Lake. I think maybe many of you know him. He is a very outspoken advocate in the parliament. He is in the opposition party now, but he is a very clear thinker and very persuasive and effective advocate. His son is on the spectrum and brings him with him to do official presentations and TED talks and everything else that he does so very effectively.

We had a very important discussion about how to actually look at this as a global health issue. Sometime along the line maybe you all ought to talk about here in the committee is another angle. Things that happen outside of our borders also affect us and conversely what happens inside our borders affects the rest of the world.

We are hoping to get - I finish things. We are going to get a draft in January. This is the best we can do I think given the complexity of collecting information and have that at least as a draft and something I will be able to report to a little bit more on at the January meeting. That is more or less what I have to say.

I just want to let you know we are working on it. It takes time. Resources are, how can I put it, constrained. We are headed into a period of bureaucratic disruption coming up, but we are going to push through and respond to the Autism CARES Act as directed. Thank you very much for your time. If there are any questions, I would be

happy to answer them. Also, we need to sit down and get ourselves oriented as well.

DR. GORDON: Thank you, Dr. Novotny. I am looking forward to that as well. Susan, you had a comment or a question.

DR. DANIELS: I just have a comment, Dr. Novotny. We will be sharing with you some of the comments that the IACC has collected over the summer about various topics, but we have some comments on transition from our request for public comment. I think that might be helpful to the working group that will be putting together this report.

DR. NOVOTNY: I saw the list here and I am looking forward to getting those in detail.

DR. DANIELS: We will be able to provide them as double duty to make sure the comments do their job.

DR. GORDON: We have the rare pleasure of having a little bit of extra time before the next presentation is due to start. Dr. Novotny already

offered to take questions. I should say that I am happy as well to take questions if you have about my experience or comments about where you, as committee members, would like to see the committee under my tenure to go. If there are questions from any of the committee members, I am happy to take them now.

(No response.)

DR. GORDON: We are getting started early. I think our next presentation will inspire enough questions to fill the extra time if you guys are ready. Actually, Dr. Novotny's comment about autism being a global issue, and that while we are often seen as leaders in a field, we can certainly learn from our colleagues in other countries is a perfect introduction to our presentations this morning on tackling early death in autism. We responded to the interest amongst the committee to hear about global approaches to autism by inviting Jon Spiers and James Cusack from Autistica in the United Kingdom.



Jon Spiers is an experienced, I was going to say something more polite but lobbyist, in the health care sphere working for the most part on the behalf of nonprofits, trying to get the issues of patients and consumer advocates and families on the agenda of law makers in the UK. He is now the chief executive officer of Autistica.

James Cusack, a fellow neuroscientist, is a director of science for the organization.

Autistica is a UK charity that funds and advocates for medical research to better understand autism develop needed tools and interventions that improve the lives of people on the autism spectrum. We note in inviting him to speak to us that this is the first of what we hope will be several maybe many international presentations that the IACC hosted. We hope it will open the doors to future dialogue with Autistica and certainly in the UK community, but also further members of the global community. Jon and James, please take it away.

DR. JAMES CUSACK: Good morning everyone. Thank you very much for inviting me. We are really honored to be here today. It is really to talk about what is quite a serious subject.

Before I go into the data, what I would really like to do is to share my own personal journey and Jon's personal journey as well in terms of understanding what is obviously quite a sensitive topic area. For me, it really started almost a year ago. We have this thing in the UK called Guy Fawkes Night. I do not know if you have it in the US, but you have fireworks and an enormous bonfire. My family was trying to get me out the door. I have a 3-year-old daughter and a wife who had their jackets and shoes on. But I had my head in the phone because I was doing this thing, which I am sure you are all familiar with, which is reading PubMed. One had come up for autism. There was this paper which had really grabbed my attention on early death and autism. When I read the results and I saw the outcomes, to me it was

really quite startling. We finally made it to the fireworks display. Once the fireworks were going off in the background, I really was not paying attention because I was looking at these results and emailing Jon. An overwhelming sense on that day is that we simply had to do something. It was our responsibility as a research charity to highlight this issue.

When we spoke to our science advisory group, which has some of the UK's leading autism researchers, they agreed. When we consulted with the community so did they. That is effectively why we are here today.

My background is a researcher as Josh said is in autism research. I also have a background in policy. I was involved in Scotland's first ever autism strategy. I have been involved in autism in three different ways from working in hospitals, schools, social care, working with families. I have been doing this since I was 16 in various different ways.

But last year I joined Autistica. Autistica is the UK's leading autism research charity. The reason I joined Autistica is because they have a very similar mission and vision to me, which is that to believe that power of research ultimately is to show that people affected by autism have an equal opportunity and chance to live a long, happy, and healthy life. And to ensure that, we try and ensure that our research strategies are driven by the views of the autism community. That means working with autistic people, parents and people working in the field, autism researchers, together to devise an autism research strategy. That is what we have done to date. On that basis, we currently focus our research on three main areas, which are autism in aging, mental health and autism and early intervention autism. I guess in that respect particularly looking at the lifespan side of things, this topic here is really research strategy as well.

In the context of this presentation, really what I wanted to do is to talk about the data on mortality. I will be going through this in quite a clinical fashion so do forgive me for that, but I think it is important to objectively just present the data as it stands. It is not to suggest that I do not find it personally disturbing. It is just to put the data on the table.

We will be talking about potential new research directions. Then I will hand it over to Jon who will tell us a little bit about the report, the campaign, what we are doing from a policy perspective to deliver an impact in the UK and potentially what we could do, I guess, and we are a global sense as well.

Now we get to the data on mortality. I am aware this is quite a busy slide, but I think it is a very important slide as well. Really basically the story is quite a serious one. Prior to this paper coming out last year, if you look at the bottom right, there has been a range of

different research studies, which you generally find a similar thing, which is that people with autism have an increased risk of dying early and of early death.

If you look at the results from Denmark, USA, and Sweden, the results have been fairly consistent, although the risk ratios have differed widely, there has been a consistency in the story, which is to say there is an increased likelihood of early death in autism. But these were all based on small sample sizes.

This paper from Sweden to me really confirmed what this preliminary research we are seeing, which is that there is a serious problem. If you look at this figure here, Figure 2.56, the take home message from that is simply to say that people with autism have over two and a half times increased likelihood of dying early. And the impacts on that and the indications for that are quite serious. If you look at the results from this particular study, you are looking at people

with autism dying as much as 16 years earlier than the general population, which to me is a tragic loss, not only for autistic people and their families, but also for society as well.

If you have autism and intellectual disability, the results are even more serious sadly. Your likelihood of early death developed is over five and a half times with the leading cause of death not particular surprisingly being epilepsy because we know in this population, there is a particularly high prevalence of epilepsy in autism.

Autistic people who do not have an intellectual disability I guess classically would be defined as people with Asperger syndrome. The paper found that was an increased likelihood of suicide in this group with this paper, finding a quite startling figure that there is over nine times likelihood of suicide in this particular group, over two times increased likelihood of premature death.

When you try and break this down as a research funder, you are trying to think about breaking it down into really strategic areas and ways in which you can make the biggest difference and have ultimately the biggest impact. That is what we have tried to do and that is what I have tried to do throughout this presentation.

When you look at something like autism and epilepsy, which are really one of the leading causes of premature death in autism, again, it is not surprising. The epidemiological data shows that 20 to 40 percent of autistic people tend to end up having epilepsy. Patrick Bolton and science advisory group has been really useful in terms of advising me on this and looking at the research findings. There appears to be as an altered developmental trajectory as well, where you often see epilepsy later in autism. There are a range of things, which appear to be different about epilepsy and autism as opposed to epilepsy (inaudible) so things like seizures being present



in different areas and it being more treatment resistant, harder to identify. There are very specific features, which we can really target and which can lead to potential tractable research questions as well.

If we look at the other disproportionately high causes of death within autism, it is suicide. Again, it is a very sensitive topic. If you look at the data behind this, particularly related to mental health, these results are again sadly not particularly surprising. Work from Emily Simonoff at King's has found that if you have a child with autism, you have 70 percent chance of having a mental health problem at a given point. You have 40 percent likelihood of having two or more. And approximately half of 5 to 10 year olds do have an anxiety disorder.

If you look at that from a developmental perspective what you see is the early emergence of a range of mental health problems, which may have biological basis and as well environmental basis,

in terms of the stressors this particularly group faces. You get in this very early impact of mental health, which is perhaps not surprisingly least of the tragic outcome.

That is what you see as well in adults. You see a massive high report of self-report of psychiatric disorders and particularly depression and anxiety. This is from a report in the Netherlands. Hilda Geurts did some great work aging in autism, lifespan research in autism.

When we look at the work from Sarah Cassidy, she is really the only academic, aside from the UK, looking at suicide and suicidality in autism. She has found that if you look at certain groups of people, again, with Asperger's syndrome I guess now classically defined as autism with no intellectual disability, you find that 66 percent of these adults have considered suicide and 35 percent have made plans or attempts at suicide.

When you put this data in context, what you find is that this is a higher likelihood than

people with chronic pain or people with psychosis even. What you are seeing is a really particularly increased likelihood within the context of this group.

This paper also finds - the Swedish paper also find an increased likelihood of death across the board. If you look at this table on the top right what you are finding is a particularly high portion of death almost across the board. It is not just specific causes of death. You are looking at generally poorer physical health in the population as well.

These results are perhaps not particularly surprising particularly when you consider even various social issues, things like access to health care or things which people of autism commonly report as being exceptionally challenging and anxiety provoking. We certainly know in the UK that going to visit a GP is something which provokes an enormous amount of anxiety for

autistic adults. But the causes again, . are likely to be very complex and poorly understood.

Again, I have just probably spent five or ten minutes telling some pretty sad negative things, very sad, negative data. I do not share this data because I want to share it. I think it is important to share this data because we have an enormous opportunity to change these outcomes and improve things for people affected by autism. That is why we released our report to raise and leverage ten million pounds in the next five years to fund research into these major causes of death for autistic people.

In terms of our own specific research strategy, I think we really break it down into three areas. We need to make very scalable with a small research fund during the context of autism research. We have decided to focus on epilepsy, suicide, and other diseases or other causes of early death in autism.

I guess it is a bit scoping the research need from a research strategy perspective. For each arrow that you see here is that we are looking at very different things. For epilepsy, it is the case of looking across the translational spectrum. But in suicide, you are looking at potentially more applied research, simple things like risk factors and prevention strategies. And then the more general causes of death is potentially again looking at risk factors, but maybe some more health services, things like social care, which are not necessarily optimized to care for autistic adults.

We have just really completed this early scoping exercise. For us, it is not about holding stakeholder meetings to develop research strategies in these specific areas. What we aim to do is to really bring together as many people as possible around these areas of research funders, researchers, internationally, not just in the UK, to develop a research strategy and what we thought

would be a global plan to really deal with these issues.

And then we can develop and commission potential research. I have just come up with these things as hypothetical endpoints from these meetings, but they are things, which are still having entire conversations about them and talking about when we speak to different academics.

And really ultimately the result of this is that autistic people will live longer, happier, healthier lives, which really gets back to what Austica's mission ultimately is. It is something which we must prioritize from my perspective, not only because of the empirical data, which I presented. It is not the only thing that drives me personally. I will have had not just professional experience working with autism.

When I was 12 years old, I received a diagnosis of autism myself. I know what it is like to be in a family to receive the news of the diagnosis. I know what it is like to face some of

the challenges, which many autistic people face. I have grown up with other autistic people who face some of the challenges, which I do not face. The outcomes, which they are currently facing, are very serious. This is what I am talking about, which, I guess in essence, the ultimate per outcome for autistic people. It really drives home to me why we must take action here because for this year and for this room and for my career today, I have heard too many stories, which have this conclusion.

The positive message and I guess the message of hope here is that for science, we have enormous opportunity to change this outcome and that is what we should be trying to do. This is what science is ultimately for is to really target these outcomes.

But it is not only science. It is also policy as well. I will be honest. I do not know enough about that. It is just as well that Jon is here. I am going to hand over to him. He will be able to

talk to policy and the more of the campaign side of things and how we are going to take that forward. Thank you.

(Applause)

DR. JON SPIERS: Thank you, James. I am going to use my kind of standard. Please wave if suddenly I go out of volume. I am enormously proud of Autistica's commitment that we have made. Ten million pounds, which for those of you who are not very good at exchange rates is roughly about \$12 million. It was \$14 million when we made the commitment, but then we decided to leave the European Union. It is worth a little bit less now. That amount is a huge number for us. That is more than we have spent on research in the entire history of the organization and it is roughly 50 percent of the money that will be spend in the UK across the board. So by government funders, charitable funders and industry as well. It is an enormous contribution towards the UK spend.



But really it represents a very tiny portion of the financial fire power in the room today and the financial fire power around the world. We really want to communicate that this is not simply a challenge for one organization. Autistica is absolutely focused on doing what we can, but we must drive a global response and that is really why James and I are so excited to be here today and why we are having this conversation and making this presentation as often as we can, in as many places as we can.

I hope that by working together and harnessing the individual strengths of different nations and of different organizations, we can create something greater than the sum of its parts. There are certain things we are able to do in the UK because we have a nationalized health system that you are not necessarily able to do here. Equally, there are enormous strengths in the US. Your genomics and genetics are years ahead of what we are doing in the UK in multiple areas. The science

base in the US is absolutely world leading. We want to try and help everybody around the world who is active in autism science to understand the role that they could play if we all work together. Ultimately, we should not be accepting these outcomes. It is appalling to me that we are talking about mortality gaps as big as 30 years.

If you look at the Hirvikoski data that was published last year, that group that James talked about, those who have autism and an intellectual disability, they die on average at 39 years of age. We have not had an average mortality rate of 39 since about the 16<sup>th</sup> century in the UK. It strikes me that we absolutely should not accept it in the 21<sup>st</sup>.

We created this report. We were very conscious that we are relatively familiar, James and I, and the scientists that we deal with are relatively familiar in reading and interpreting scientific literature. But the broader public is not and the autism community is not. We wanted to make the

data that we had visible and accessible to as many people as possible. We have hard copies of the report for those who are interested just down here. But James has taken you through I guess the major highlights.

What we wanted to do through the report is really make clear to everybody involved that this is not a pure research challenge. This is a challenge for everybody involved in autism. Yes, of course, we do need to understand how and why these mortality rates are so different and that is going to involve basic research and translational research. But that research is going to take time. We know that people are dying right now. The report as well as calling for more research calls for action from health care providers, from those who commission and design health care systems, from families and from the charities and nonprofits who support autistic people as well because there is an onus on those of us who provide care and design care for people with

autism to understand this problem, to think about risk in a different way. We want to say to people that there should be lessons that we can take from other conditions. I will talk a little bit about some of the work that has been in intellectual disability, which I think is a really powerful driver of useful lessons for us here.

We have done a huge amount of policy influencing in the UK and I am very pleased that the UK government and the UK opposition has really seized the opportunity to do something about this. The response has been quite impressive. In six months, we have achieved an enormous amount. I want to pull out a couple of particular examples from this slide that I think have relevance more broadly in other jurisdictions as well.

We called among various things for premature death in autism to become a national priority and crucially for that to be much better data collection and analysis. It is not really a surprise to us in the UK that it took a Swedish

study to give us good population-level data on mortality risk. We cannot do those population-level studies in the UK because our data collection is not good enough quality.

We also call to things like training support and more research. We secured a number of advances. One that we are very proud of is autism is a theme in a piece of work we have going on called the National Mortality Review for Learning Disability. Just for those of you who are sensitive semantics, the UK term "learning disability" is the equivalent to the US term "intellectual disability".

This is a national review, which has been built on about ten years of campaigning by the intellectual disability community who really felt it was unacceptable that the outcomes were so poor in that group. They have secured the national mortality review. In a nutshell what that means is that any death of someone who has a diagnosed intellectual disability is investigated and

considered by a multi-disciplinary team than would normally be the case. And any lessons learned are then shared back into the medical and care community.

We have managed to secure autism as a specific theme in that. Anyone who has autism and intellectual disability recorded in their medical records is not automatically going to be included in the mortality review from next year. We will start to generate the sorts of insights that we need to understand why this group is dying so young.

The third bullet as well is crucial. We have managed to secure two new commitments from the UK government: one in primary care and one in acute mental health care to improve the collection of autism status. At the moment, it is actually very hard to record autism's status in a UK health record essentially for historical reasons. And the government has realized that our inability to mine that data and really dig into the large-scale data

that we have within our national health service is holding us back in tackling this problem. It will take us time to build up a good corpus of this data because we are only going to start collecting it from next year. But it hopefully moves us a step closer to being able to do the sorts of analysis that the Swedes and the Danes and some other countries are able to do.

We were genuinely surprised when we brought out the report, just how incredibly interested the media were. We anticipated given that this was such a negative topic and given that autism still remains a relatively niche area of interest in the UK, we did not expect this to be front page news, but it was. It was in every major newspaper. It was on the television. It was on the radio. It got picked up worldwide. The day we published the report, we got media requests from Malaysia, from Russia, from South America, from people who had never ever heard this news before and were desperate for more information.

Off the back of the media coverage that we got, we had a huge number of approaches from organizations across Europe. James and I were lucky enough to present the report and the version of this presentation to the Autism-Europe Congress, which is a group of several thousand advocates, families, autism charities and researchers who met in Edinburgh a month or so ago. We are absolutely committed and partly that is why we are here today to spreading the word nationally and internationally, not just to say what we know, but actually to find out what others may know that we might not be aware of because it is perfectly possible that there is better data out there than we currently have and there are studies out there that we do not know about.

One really crucial thing and I suspect a lot of you in the room are feeling this today if this was the first time you had encountered this data, this is new to the vast majority of people in the autism community. For a very long time, parents



have been told to expect that their autistic children will live a normal lifespan. They have been told when they are making their care plans, when they are making their financial plans to expect that their children will outlive them. That is true in the UK. I suspect that is true here. And what this data is telling us is that is probably not true for an awful lot of families.

What has been interesting for us in going out and talking about this is the enormous tsunami of people who have come to us who lost their loved ones, their brothers, their sisters, their children at very young ages, in their teens, in their 20s, in their early 30s and who were told by their doctors at the time you were just tragically unlucky. It was an outlier and the fact that your child had a nocturnal seizure at 32 and died, the fact that your autistic daughter took her own life at 24 is just dreadful bad luck. But actually, what these numbers suggest is it is not dreadful bad luck at all. It suggests it is part of a

pattern that we did not see because we were not asking the right questions.

But we do need to be incredibly careful how we communicate about this. We learned a lot of lessons through the process of preparing and disseminating our report about how this information landed with an awful lot of people in the community because we do not know everything.

We need to be sensitive and honest about what we do and we do not know. We, of course, need to remember that for a lot of autistic people, trying to deal with this complex data is not something that is necessarily going to be easy to do. I think that probably applies to a lot of non-autistic people as well.

We are looking at creating new information resources both in standard versions and in easy ready versions because fundamentally we want to empower as many people as possible to access this information. We would be delighted to make those available free of copyright to anybody who wants

to take those on and make them applicable in their jurisdictions. We are not creating things to the UK. We want to create information resources for the world.

And really that is part of the global response that we want to see. We are committed, as I said before, to doing things ourselves, but I am much more excited by the opportunity to be working with as many other people around the world on this. I think it is exciting from a research perspective. It gives us the opportunity to get large-scale trials off the ground, capitalizing on the particular advantages of different countries and of different health care systems. I think we know that when we collaborate internationally, we really drive progress. If there is an area where we need to drive progress, this is it. It feels to me like international collaboration has to be the way forward.

I alluded to our information leaflets. I think we have the opportunity to create resources, which

are of use for every country in the world, those which have very developed health economies at the US and UK, but those who are just starting out. There is not any information on this and there is not any need to make the information that we collect proprietary in any way. We should just be making it available as widely as we possibly can.

Hopefully, through the report and through the conversations we are having with policymakers, we can start to show indications of where policy can go. We can drive the coordinated policy response. A lot of the recommendations that we made in our report actually are not particularly complex things. There are things like we should be offering annual health checks for people at high risk. We should be making sure that care providers understand what a risk plan is and how to put one together. Those sorts of policy responses are broadly applicable in any health economy. They should not be something that is UK only. Hopefully, we have begun some of that work. But we

want to begin conversations and gain ideas and galvanize a response from across the world. If someone else in Europe or in America or in Australia comes up with an amazing policy concept, we can apply it in the UK as well.

I want to just close on a quote from Barack Obama that we have been reflecting on in the office a lot and I think probably many of you will be very familiar with. It is a quote where he said - he was talking about change and the need for people to embrace change themselves rather than waiting for others to act. He said change will not come if we wait for some other person or some other time. We are the ones we have been waiting for. We are the change we seek. I hope you can join us in making that change. Thank you very much.

(Applause.)

DR. GORDON: Thank you so much for a really informative and compelling presentation. We will open it up for questions. I see David.

DR. AMARAL: First of all, thank you for your presentation, Jon and James. I think it really is timely and a beautiful presentation. It brings to mind two issues. The first is with epilepsy. We do not at this point in time, have good predictors of the 20 to 30 percent of people on the autism perspective who will actually suffer from epilepsy and as you know, but maybe others do not. It often comes out of the blue when the individuals are in their late teens or even early 20s. It often happens where there is really no predictive sign.

We should be able to do something about understanding the biology that would lead to that. It really highlights the need for long-term longitudinal biomedical studies, not only epidemiology, but to actually be taking biomeasures through the life course of an individual on the autism spectrum to ultimately come to an understanding of what are the risk factors that lead epilepsy in a 20 year old and who are those who may be safe from that

occurrence. That is one thing. I think nobody yet is doing enough in terms of lifespan, longitudinal biomedical research to try to answer those questions.

The other issue is this issue of the lifespan being shorter in autism. I think part of that can be explained by seizure-induced death, the suicide issue that you brought up. I wanted to let you know that this committee has talked about having a task force that will deal more intensively with health care issue in autism. I think it is still an open question of whether some of this premature death is simply because individuals on the autism spectrum are not getting the same level of health care either because they are nonverbal or whatever than other individuals. Therefore, a disorder that could be cured early on goes undiagnosed and leads to early death. I think the issue of why people are dying earlier on the autism spectrum is really complex, but it really is time that we address the issues around it.

DR. CUSACK: There is a multitude of hypothesis that you can develop in the context of that and certainly from the quality of data, which is out there. You certainly get a sense of access in health care, something which autistic people can find exceptionally challenging in terms of simple things such as just going to see a GP. And then you have this whole issue of diagnostic overshadowing as well. That is just because they are autistic. I have a very personal anecdote myself, which is that I used to get coughs and colds and for ten years I got coughs and colds and thought it is because I get very stressed all the time. It turned out I had asthma. But you can have this form of misattribution. I am saying that as a personal anecdote but, actually, that is a story you generally hear when you look at the qualitative research more generally. There is this enormous range of potential. When you actually think about it, the range of potential blockers to



health care and access to health care are quite enormous.

DR. AMARAL: Just as another side to that, we are dealing intensively now with trying to distinguish anxiety and autism. Oftentimes there is diagnostic overshadowing. Clear symptoms of anxiety are just attributed to the autism, but that leads to lack of treatment of the anxiety symptoms. I think that this happens over and over again.

DR. GORDON: David Mandel and then John.

DR. ROBISON: I would like to thank you guys for coming and presenting what is really another important study on a topic of pressing interest. I would like to offer the comment that while we do not know the causes of this autism mortality, my own family experience suggests that there is no one answer. My father was autistic. He was a college professor, a successful person in anyone's eyes. He died of a disease at 69. One of my cousins, little Bob, he and I went to the Emory

Autism Clinic before it was an autism clinic just when it was special ed for kids like us who were different. He died of pneumonia at 40 after never finding his way in life. Another of my first cousins on my mother side - he walked into a car before he was 40.

The thing is you look at those things and they are all different causes of death, but the fact is we have this family where somehow we all die early for whatever reason. I know that I myself have contemplated suicide successful as I seem. I fully understand that.

Another thing that I wonder about is now having had relationship trouble through my wife and I have had the experience of getting married three times now and I am practiced at it. I have a wife who watches me very closely. One thing that I have learned in her watching me is that I do not have a very good sense of when things are wrong with me. I am concerned that that is symptomatic of something that affects a lot of autistics where

people like me were singled out as being bad kids and noncompliant because we were autistic and because our precise speech made people assume we were smart and capable and so anything we did wrong was deliberate.

I think the same thing may happen with health care. People look at a person like me and they think he is so smart. He is articulate. He is here at the National Institutes of Health. He has obvious access to the best of medicine. How could he possibly ignore his health problems and yet I am not even aware of them? If I am not aware of them, how many tens of thousands of adults are there like me with even less access to get the care if they even knew? I think that is a very real concern.

DR. CUSACK: I think those are all excellent and very relevant points. I think that the self-report issue and self-analysis of your own health is something which I think people with autism frankly find difficult. We have all been in a

situation where you have told to go and see your general practitioner. If you are isolated socially, it is good that that can be an issue, but I think you are right to say it is also specific issue in autism. If you look at the suicide data, actually there is not a particularly high correlation between depressive symptoms and suicidal ideation in autistic people. It is lower than you will find in the general population.

I think from having worked and assessed people with depression in the past, potentially it reflects the fact that the questions are quite vague really, and in fact a quite vague concepts. How have you been feeling over the last week? If you reflect on your behavior over the last week, have you been feeling sad or down? These sorts of questions might be more difficult for this particular population to answer. I think that that probably is too far range other health questionnaires, instead of specific questions related to that.

DR. GORDON: Thank you. David, you had some comments.

DR. MANDELL: This is very compelling presentation of these data. It struck me that the mortality gap is very similar to what we observe in people with schizophrenia, bipolar disorder and major depressive disorder. Those are three groups that are at much higher risk for suicide than people with autism and yet the major causes of death in those three groups are not suicide. It is metabolic disease and heart disease. And the underlying causes of those metabolic disease and heart disease are sometimes health care. But it is more likely malleable environmental factors related to social capital, to access to appropriate food, to having meaningful employment and meaningful relationships. And that over the last 60 or 70 years in mortality research, the primary determinants of mortality have always turned out to be in the general population and in other populations, not access to health care, not

things like suicide or seizures, which are very salient, but still relatively rare, but those social determinants.

And I wonder as you think about your research agenda for reducing mortality how addressing issues related to social capital and employment, access to good food, to appropriate housing figure into what potentially causes mortality and how to prevent it.

DR. CUSACK: That is a really good question. One of Autistica's three strategic priorities is aging in adult autism. One of the things which we did as part of that is we set up a lifespan cohort. It is an interesting project. It is driven by researchers, but it also has some co-produced research with autistic adults as well and they work together to set the agenda and discuss some of the issues. Part of that is looking at the specific issues. It is things like quality of life, access to employment. We are getting some interesting findings regarding mental health and

quality of life and how that relates to access to employment as well.

The housing question we have not focused on yet, but I think you are right to suggest that there is a priority and it is something which we consistently hear from the community is that housing is an enormous issue. We just not quite have gotten to it yet.

DR. MANDELL: Will you then try to link that to mortality and quality of life?

DR. CUSACK: We will see that as part of our agenda. Next year, we are hoping to hold an aging autism meeting in the UK as part of that. One of the things which we really hope to do is to bring all of these things together with a real focus on health, well-being, and ultimately mortality.

DR. HAWORTH: I wanted to thank you so much for bringing to our attention. I know personally a lot of families and parents do not know that there is this high chance of mental health issues with their children with autism. I have a ten-year-old,

and I almost lost him last summer because he tried to jump out of a four-story window. He has comorbid - they call it disruptive behavior disorder, but it has been called so many things. Mood disorder. And it is probably bipolar, but he is so young. He was not trying to kill himself. He was just impulsive and was looking for a way out, running away from something. A lot of parents and families I talk to are just so surprised that there is a 70 percent chance that they are going to have at least one comorbid mental health issue. I really thank you for bringing this information to the public.

I had two questions. One question was about other causes of early death. Are you looking into Ehlers-Danlos at all as a genetic disorder? It is a connective tissue disorder. It affects muscles and the heart is a muscle as well. My son has that. I have noticed there is some research going on that a lot of people on the spectrum might have that in some way, but there is no real test for



it. They found that I had it and that is how they found out he had it.

And my other question goes with Dr. Mandell's. Are you looking at culture and ethnicity and those differences and how they affect the health of people and their health care access?

DR. CUSACK: We are very much at the start of things. What we have done has literally been in the last year. It is very early stage for us in terms of refining our strategy in respect to this. The answer is basically we have not really looked at it yet. I thank you for bringing that to our attention and perhaps that is something that we can look at. The second question was on --

DR. HAWORTH: It was about culture and ethnicity and how that affects health care access and in general. It follows with what Dr. Mandell was talking about.

DR. CUSACK: That is a really interesting question. At the moment, we have not done an awful lot on that, but we do collect that as part of our

cohort data. It is about mining that data. So we are in the process of building this cohort up. We need to get that critical mass before we can really gain valuable insights in that respect. But I think that should absolutely be something, which is on the agenda.

I guess there are some interesting cultural differences in respect to the UK and the US, insomuch as we have a nationalized health service. That makes things slightly different. If I remember right, David, you published a paper looking at social economic status and likelihood of diagnosis.

The interesting thing is that in the UK is that we are finding is not great. What we are finding from the data is you do not tend to get such an effect. I think that is just about the general access to health care in the point of access. You have to be at three and a half and four years to get diagnosis unfortunately, but at least there is a sense of equality about it.

I think all these things and all the comments, which everyone has made, ultimately is about I guess it is about marginal gains. Doing a series of very small things, which can ultimately have an enormous impact. I think that is certainly how we have seen it when we have discussed it and with other researchers.

DR. GORDON: On this issue of health care access, what I heard from John was not just about access, but actually successful utilization. We must have data on access amongst this group. I am wondering though even if you control for access and for biology, which is hard to do, would you see an inefficient use of resources because of these issues around anxiety or difficult to communication, et cetera?

DR. CUSACK: One of the things that we have in the UK is we have this thing called the Farr Institute. I cannot say an enormous amount about it, but there is some interesting data suggesting that access to health care is different

potentially with an increased likelihood of access to tertiary health care, as opposed to primary health care.

I do not particularly like it. I know the use of the economics argument is somewhat controversial, but in terms of influence and policymakers, there is potentially an opportunity there in being able to say you are losing money because it is getting to this stage. And actually, if you made access to primary health care more efficient and more appropriate, then you would not have a situation where people are ending up in these tertiary health care systems, be it mental health services or specialists' services or accident in emergency where various things are coming up.

DR. ROBISON: I just would point out that while asking about different cultural and demographic groups, I think that is a valid question. But if my life experience as a GUIDe being autistic, frankly trumps that. I look at all of my dead

family members, and those people you could say were from, in America, what is a least disadvantaged or most privileged group.

I look at my experience getting health care, my experience advocating for my autistic son in school. I cannot do all those things. I think that the fact that I am an affluent white guy is overridden totally by the fact that I am autistic and I just cannot do that. I sound great and I look fine, but I cannot do it. Whether I was from a different culture or whatever, I do not know, could it disadvantage me more? I am sure it could.

But I am pretty disadvantaged the way I am. That is not obvious to people.

DR. CUSACK: Sure. I think that is very interesting. I thank you for that. I think that is a very valid point. I think the one thing I would say and I cannot speak for the US culture so much, but there are certainly specific cultures where there is a stigma associated with autism, which may have an effect above and beyond the very

serious implications which autism has for being able to do the things that you undertake as well. But I do agree. It is a very valid point.

DR. CRANE: I had a point about the correlation between intellectual disability and mortality from seizures. I was wondering if there is any way tell yet or if this is something you are investigating, whether it is because people with intellectual disability are more likely to have seizures or whether it is because when a person has an intellectual disability, their seizures are less likely to be recognized.

I know in a lot of institutional settings in the United States, for example, there is a very high mortality rate associated with situations with a person is having a seizure or having a serious health concern, and it is treated as a behavioral problem and the person ends up dying as a result.

DR. CUSACK: I think that potentially one of the things that you might find in that population

is the increased of having a rare genetic disorder, which potentially increases the likelihood of having some sort of biologically engrained problem with seizures. But I think there is an interest in hypotheses such as the one - I think there are things like medication use, things like how is antipsychotic use affecting the likelihood of seizures managing or not. I think, John, you spoke a lot with charities.

DR. SPIERS: We have had quite interesting conversations with our epilepsy research sector, which in the UK is rather better developed than the autism research sector. We have had some fascinating conversations with them and with industry, actually. I asked a very naïve question to a couple of fairly big companies who make a decent amount of money from epilepsy. I said to them, how many trials have you done of your standard anti-epileptics in autistic populations? They looked at me like I asked them a really stupid question. We have not done any. I said, you

have not done any trials at all. Autism is an exclusion factor in epilepsy trials, completely standard process.

I said so 40 percent of people with epilepsy have autism. Most of them are medicated and most of the medications do not work very well. But you are telling me that you have never tested those meds on that population. Therefore, I am not hugely surprised now that they do not work very effectively.

We got into a technical conversation then about whether or not the epilepsy we see in autism is biologically distinct from the epilepsy that we see in the non-autistic population. There are reasons to argue it both ways. As well as having conversations with government funders and charitable funders, I actually think industry has a real role to play here if nothing else because there is actually a commercial imperative to them that there is a huge group of people with epilepsy



who are going essentially untreated. They are being given meds that do not work.

It ought to be possible to do trials in autism. It ought to be possible to go back and look at existing molecules and potentially go back and revisit molecules sitting on shelves that look like they did not work and test them in autistic populations. We have cohort databases. You guys have good cohort databases here as well.

It ought to be possible to recruit those populations and run those trials probably for not vast amounts of money, probably for tens of millions of dollars rather than hundreds of millions of dollars. But I was genuinely quite surprised and appalled to find that. It was just taking as read. The charities did not think it was hugely shocking either. It was just taken as read that there is this group of people with epilepsy who are really hard to treat and who quite often die as a result of seizure. That is where we stopped rather than thinking doesn't that mean we

should be looking at biologically what is different doesn't that mean we should be looking at treatment options.

I think there is a real opportunity pharmacologically and also we were talking before about seizure detection. I think we have new tech coming through. Wearable technologies, patches, things that can start to give us real-time information about what is going on electrically in the brain, but are now getting to the point where they are cheap enough for us to probably stop putting them into widespread use and using that as a research opportunity as well.

We have had a couple of approaches from the organized biotech organizations, looking at devices that do exactly that. I think that is probably quite a useful step in helping us understand is that widespread epileptic activity.

We think that probably is. When does it move from epileptic activity into full blown epilepsy? There is a lot to do.

I think it is about trying to build a coalition of support that does encompass industry and biotech and devices as well because they are the people who will drive innovation faster. Some have the most to invest arguably.

DR. DAWSON: I wonder if I could make a comment. I wanted to remind people of the presentation that Lisa Croen made to the IACC about a year ago. It was a pretty comprehensive epidemiological study looking at a variety of health conditions in adults with autism. As I recall across all of the health outcomes and this included heart disease, cancer, metabolic conditions and so forth, people with autism had higher rates of all of these conditions. One area in which they did better than the general population was in addictions so alcoholism, which was very interesting.

But in any case, when we think about early mortality and health care, I think it is going to be important to really think about a developmental

and preventive approach where along the developmental pathway if we could have GUIDance, for example, for physicians and psychologists and others that are working with people with autism about the variety of risk factors that are contributing to poor health outcomes, which as we know, can be things like wandering, which leads to accidents and drownings. It can be the need for exercise or the side effects of some of the medications such as weight gain and so forth. I think this more preventive approach that deals with a variety of factors is going to be critical. And the other side of that has to do with the education of primary care physicians both for children and for adults and internal medicine and having them have greater awareness and also comfort and skill in providing care for people with autism.

DR. CUTHBERT: Thank you, Geri. This is Bruce. Back to the comments about the overlaps among the epilepsy and autism spectrum, Dr. Mandell

mentioned the comorbidity clinically. It is autism with schizophrenia and bipolar disorder. There is also enhanced relationship of course between epilepsy and schizophrenia. Those odds ratios have increased as well. If we are looking at combining databases to try to look at some understanding of the genetic and other biological factors related to the epilepsy autism connection, you might also want to look in that schizophrenia epilepsy connection to see how that relates.

DR. SPIERS: There is just about to be a new center based in London, which is looking at exactly that of epilepsy, schizophrenia, and autism to understand whether or not doing some basic biological research can start to interrelationship between the three.

DR. GORDON: Oscar is doing some really nice work in this area and he has a whole institute that he is building around these issues of translating genetics through to these behavior and

epilepsy and neurofunction, which is really fascinating.

But to broaden the discussion back out a little bit, we can think of the autism epilepsy premature death association as an example of the complexity of the situation. On the one hand, it is really related to the comorbidity with intellectual disability and the notion that it is arising from genetics that there is a not well-defined subset, but nonetheless a subset of individuals with autism with genetic liability that presupposes to those three things together.

You can think of that as a most likely predominantly biological factor leading to increased death. While intervention research and understanding how we can improve access to care, et cetera, may help a little bit really demands a biologic research answer, which is as you have elucidated well, what is different about epilepsy in this population that makes it difficult to treat and difficult to predict and more deadly.

And then there are other aspects where it is a little bit less clear whether a biological approach is going to make headway or a more treatment-oriented or care-oriented approach. I would put currently into those categories until we understand it better things like cardiovascular or respiratory risk and these other features. They may have strong biological components that biological studies would help with, but we do not have data yet to really support that notion. I think we can think of some of these things as being obvious or perhaps at least obvious to me anyway that a biological approach is going to be really crucial to make headway and others where we even need really more data to understand whether these variables are around access to care or efficient use of care or appropriate responses to illness in individuals with autism versus more biological predispositions that are shared between these different kinds of illnesses.

DR. AMARAL: I agree 100 percent with what you just said. But I do want to have a point of clarification. I am not aware of the literature that suggests that epilepsy and autism is more difficult to treat. We have heard that on a number of occasions. I do not know if anybody has actually tried it as you were alluding to in terms of clinical trials. That fact of whether once you identify could you prevent or could you treat adequately even using available drugs needs to be established. If it turns out that it is more difficult to treat then obviously other strategies have to be pursued. But I do not even think that there is a literature on common anti-epileptics that is working. It gets tried. There are clinicians doing this all the time, but I do not know whether the data have been gathered.

DR. SPIERS: I think there have certainly been some smaller scale studies. I do not know of any large-scale studies, but we can go and look at what we have found in the literature that we done.



Certainly, anecdotally, we were very struck by the fact that the epilepsy specialists we spoke to said things to us like good seizure control in this population might be a handful of seizures a week. Good seizure control in the population who only has epilepsy is zero. When you are using the same meds, which we do in the UK so that the populations are treated equivalently with the same medications, the outcomes definitely are different based on that anecdotal feedback from the specialists.

There is something interesting within the health care system around who is treating these people. There are strong indications in the UK. At least the neurologists may be less likely to be used in the treatment of epilepsy for people who also have an intellectual disability. It may be more likely they are being treated by psychologists, for example, which you would expect to lead to slightly poor outcomes because they are less expert in neurological disorders.

DR. AMARAL: If that is true and if that is your experience, it should be put on record - if that is true and it very well may be then it should be put on record. There should be a publication even sort of a commentary or something like that. I do not think it is generally unappreciated.

DR. CUSACK: I think there is a range of unanswered research questions. I think what we are talking about and a lot of this is a range of hypotheses in terms of beginning to understand this a little bit more. Yes, I do agree. There are unanswered research questions in respect to that. There are a lot of indications in the data, but it is all indicative rather than confirmatory.

DR. GORDON: Julie Taylor, you are next.

DR. TAYLOR: I think you already spoke about this and I missed it. But is there a research right now to suggest that the risk of death from epilepsy is greater for somebody with autism and an intellectual disability, relative to somebody

with an intellectual disability that does not have autism? Is this an autism and intellectual disability issue or is this an intellectual disability issue more generally?

DR. CUSACK: I think that is a really good question. We do not have data specifically, at the moment, to understand that. I think there has been some data from SUDEP Action what the indications are from that is worse than the autistic group. But like you said, it is indicative again. It does not give you sufficient strength to confirm.

DR. SPIERS: The Hirvikoski data, for example, shows a big mortality gap for those who have autism and an intellectual disability than other studies have shown in intellectual disability alone. But I think we have not yet got truly comparative data. There is a suggestion that autism has an additive effect, but I do not think we understand the extent of that.

MS. SINGER: My question is about whether - now that you have this compelling -- given that you

have this very compelling data and that you are able to secure incredibly broad-based media coverage, I am wondering if you are sensing an improved receptiveness on the part of policymakers to actually implement change in the face of this data?

One thing that we have struggled with here in the US is the advocacy community has gotten better at collecting data and presenting data and sharing the data with policymakers, but we have not been able to really cross the threshold of actually implementing policy change.

One topic specifically was with regard to safety. Back in 2010, this group several members who are organizations who are sitting at this table got together and funded a study to look at issues of wandering. And the data were very clear. It showed that children with autism had a 50 percent increase likelihood of wandering. We know that those wandering cases do not end well. Many of the children die. They drown. They are hit by

cards. They are subject to freezing in the winter. We got great media coverage.

Many of our advocacy groups specifically the National Autism Association led by Lori McIlwain and Stuart Spielman at Autism Speaks have been working tirelessly to try to implement policy change to protect our children. We are not where we need to be. I am wondering if things are different in the UK because I think that would provide a lot of hope to those of us who are in the US.

DR. SPIERS: I will try and provide that hope. We have essentially only been talking about this for six months. We published that report at the end of March. We have had a very complex period of UK politics with various things that has been going on. I personally having been a lobbyist for almost 20 years am very pleased to see the speed of the response from government and from the various arms of our civil service that are responsible for the design of health care.

I think there is a long way to go and I certainly think more data would be useful. We have on occasions had people come back and say that is based on Swedish data. How applicable is that going to be in the UK? Everyone knows the Swedes commit suicide more than we do. We have had those sort of if I am honest those responses sometimes.

We have had to say, yes, there are gaps in what we know, but this is incredibly strong and indicative of a broader trend we knew was there anyway. You show me a better study than a Swedish study for this sort of epidemiology. I think there is a little bit of a credibility threshold that we have had to pass. I think we have now passed that and we are now being invited to go and see the right kind of people who have the influence that we need.

The challenge we have is I have no policy team. James and I, have to fit the meetings in around all the other things that we do with all these different people who are based all across

the country. It is a capacity issue for us to try and push that forward.

But I think the good news is that when we have done it, it has been very well received and this is a sort of message, which has been taken very seriously by our policymakers and politicians who are interested in autism. For a long time, I think they have been very focused quite rightly on quality of life. Lots and lots of various inquiries and investigations that our government has done have been around things like education, transition employment. I think when we have brought this to them as James have said before, the ultimate bad outcome, actually that has really kicked them into gear and I think they have realized there is an opportunity to do something.

I guess the lesson we have learned is there needs to be so what do we do now. We have not been ready to do it so what do we do now and probably until relatively recently. I do not think we are even entirely sure yet. I think there is a need to

be a little bit clearer on what does the policy response need to look like before we can really make genuine progress. As I alluded to, they have made changes already in data collection. There are going to be changes in some of the various programs that are already up and running to encompass autism for the first time. Lots and lots of different bodies within government are looking at this as part of their autism strategy.

What we are hoping to see over the next 12 to 24 months is mortality becoming embedded in our national autism strategy and our legislation that we have around autism so that it becomes part of our conversation that everyone is having, not just us going in and seeing people and trying to convince them. I think there is reason for hope, but we probably need more answers as well as being able to focus where we have more questions.

DR. CUSACK: I think one of the other things that is quite good is sometimes it does not necessarily need to be us doing the advocating. It



is about motivating other people to do it. We had this wonderful GP who just very much on her own has been working with the Department of Health to getting to trial annual health checks and GP surgeries and adopt those sorts of things. We do not know if that is going to go ahead, but it certainly on the discussion. Hopefully, catalyzing a response as well, but it is generally myself and yourself.

DR. SPIERS: Which is why we keep saying we do not own this. We have no ego in this at all to be the people who are talking about because we want everybody talking about it because that is ultimately how you drive progress.

DR. ROBISON: One thing that I would like to see from UK. You folks have come up with some really broad population studies that are particularly relevant because of your consistent national health care so that health care is not such a factor when you survey people. You certainly brought us some fascinating insights

when you looked at the rates of autism in the population. Now, when I look at what you have presented us today, frankly, I have a hard time believing that the statistics that you cite for say, epilepsy, depression, and anxiety are truly real among autistic people. I believe those numbers are closer to 100 percent than 50 percent. I do not know that I could identify a single autistic person who I have met that has not lived at least with incidence of anxiety and depression. Many of us have shakes and twitches and stuff. I think autism isolates us and causes us to not report those things. Your presentation makes me wonder.

If we did a study like (inaudible) where we screened not only for autism, but we then we sub-screened and we looked at - have those folks have incidence of depression? Have they had incidence of anxiety? Have they shown symptoms that we could call mild epilepsy? I will bet you that that would reveal some shocking numbers. It might be that

that would give us an important insight into one of the explanations for this mortality. I think that that is a study that is maybe better done in the UK than the USA because of your health service.

DR. SPIERS: I think it would be. The challenge we have briefly, as I said before, we have not been very good at recording autism status. We have a real challenge particularly for adults. We are not as bad when it comes to kids because we are better at diagnosing kids, but when it comes to adults, there is actually very limited recorded data on autism status. I agree that we are a good place to do that study. I do not think yet we have the data to do it unfortunately. But Hirvikoski is probably a strong - that pattern I think is probably broadly what we would see in the UK in terms of comorbidity. The Swedish health care system roughly equivalent on a lot of levels, to the UK system.

DR. CUSACK: Terry is the chair of our Science Review Panel, so we are well advised in that respect as well. I think you raise a very important point.

DR. ROBISON: You brought us really a very important thing. Lisa Croen came to us with similar troubling statistics for adults a year and a half ago. You have reaffirmed them today. It is absolutely something that has to become part of our mission in the United States, the UK, and the rest of the world.

DR. GORDON: Josie.

DR. BRIGGS: This has been wonderful and terrific presentations. I am just looking at the Hirvikoski paper. I hope I am pronouncing that correctly. It is a superb study, and I think it really is teaching us an enormous amount. I think these kinds of population-based surveys are just incredibly important for ultimately and I understand the frustration at the slowness of it, but driving policy change.

I do want to mention that I have had the honor of being part of the team launching the Precision Medicine Initiative here. I am also aware of the strengths of this more in-depth look at population determinants of health, including a fair amount of interaction with the group leading the UK Biobank.

There are two very complementary approaches to understanding more the population level what drive illness. I do think that as we understand this really shocking mortality difference, there is an enormous amount to untangle here. How much of this is the underlying biology and epilepsy that is harder to suppress? How much of this is a very different ability to access health care?

John, I loved your comment about your wife. We all know from our personal interactions with people in the spectrum that having good care takers and people who can be a nudge is such a determinant of health, but so are social and policy systems that allow good supports.

I do think that the population service of the sort you see here are one piece and so will the in-depth cohort studies that allow us to build natural history. I think both the UK Biobank and our big start at having a million people enrolled in a national cohort will allow a teasing apart of some of the factors in this. Autism is a common enough disorder that if we enroll a million people, we will have a pretty probably thousands in the autism spectrum. A lot of important questions can be answered. It has been a great discussion and I think it is really important and shows the power of this kind of epidemiology.

DR. CUSACK: Briefly, on the Biobank, I think the Biobank is an enormous opportunity. Basically, when I came in, one of the first things I did was put in a Freedom Of Information request to understand how many autistic people were recorded as having - how many autistic people you had in that cohort. Out of a million people, they had 37. That shows you issues in respect to

representativeness. That is an issue which to my mind, has not really been addressed by the Biobank. I think it is an issue for all of mental health and how it has been treated into the parity.

DR. BRIGGS: Obviously, that number is too low. It may represent a non-representative sample. It may also represent failure of the EHR-based diagnostic processes and both of those have to get - people have to pay attention. We all collectively have to pay attention.

DR. CUSACK: I totally agree. We are working very hard with the relevant people to try and change that.

DR. GORDON: I would say that we are engaged really - the Precision Medicine Initiative is really in its infancy here in terms of getting launched. It is going to be launched very soon. We are deep in discussions about how to make sure we have adequate representation of all kinds of

different variables, but among them explicitly are individuals with mental illness.

It is a challenging proposition, but it is one that we really at NIH of course, but NIH-wide are deeply invested in and is making sure that when we do these deep dives into biology and cohorts that we make sure we have adequate representations of psychiatric illness. If anything, psychiatric illnesses are the ones that have the most benefit from these deep dives because there are areas where we really know the least.

Lori, you had your hand up. Did you want to say something? Then I think we will take a break.

DR. MAMOUNAS: At the Neurology Institute, we fund a lot of research in epilepsy as well as epilepsy and autism. We are supporting some natural history studies in the syndromic disorders. There is a much higher incidence of epilepsy in disorders like TSC, Rett syndrome, and Phelan-McDermid syndrome, but even in the broader epilepsies. We had a workshop maybe three or four



years ago on autism and epilepsy. But even in the broader autisms, there is a much greater incidence of epilepsy in autism particularly those subjects that had intellectual disability associated with autism.

We funded a biomarker study in TSC, which was just published. Using the EEG, we can predict with 100 percent sensitivity those subjects will go on to develop epilepsy with about three to five-month lead time. This has allowed us to fund this preventive trial to see whether if we can prevent the epilepsy. This is a very important question in the field whether subjects will have a better neurocognitive outcome. That is a major question.

DR. GORDON: Thanks Laura for highlighting some of the opportunities for progress in this area. I think what we will do now is we will take a 15-minute break. We will start back up here at 11:10. Thank you again to Autistica, to Jon and James for a really outstanding presentation. Thanks for everyone on the committee for a great discussion.

(Whereupon, the Subcommittee members took a brief break starting at 10:55 a.m., and reconvened at 11:10 a.m.)

DR. GORDON: Next on the agenda is the strategic plan update.

DR. ROBISON: I would just like to make a quick comment before we change subjects with respect to the previous thing. Every one of these meetings we have more autistic people in the audience. I think that is a really good thing. I want to just say that to everyone who is watching us or reading who is not here to see this.

One of the autistic folks in the audience came up to me during the break and he said something that nobody said in your discussion is how we are made to feel ashamed and how our mortality is our own fault. He said to me I have many of the health conditions that you guys were talking about and other people look at me and they say the reason you have that is because you do not take care of yourself. He said I have many friends in contrast

with Down syndrome and nobody blames them for their condition. Why is that we autistics are? I have to agree with him. That is a point nobody made. Just as we have problems of shame of autism with parents holding back recognition and therapy, we have blaming of us autistics for causing our own problems and it is wrong. I think he was right to speak out and I wanted to pass his comment onto you.

DR. GORDON: Thanks so much, John. That is really important insight. Thank you for whoever that was who is here today. Thank you for coming and for coming up to John and making the comment. Now, we are going to talk about really committee business. Susan Daniels, who is the director of the Office of Autism Research Coordination, and you know probably better than I even for the moment anyway is directing the business behind this committee. She is going to talk to us about the progress on the update of our strategic plan.

DR. DANIELS: Thank you, Josh. We will talk about committee business. I know that many of you have been involved with the committee over the past several months with the strategic plan update process. Many of you are serving on working groups and we really appreciate that. I wanted to talk to you again about what is going on so that everybody can be on the same page about what we are doing.

Just very quickly to review this slide that we have seen many times here before, the IACC responsibilities are to develop and annually update a strategic plan for ASD. These are the responsibilities in the Autism CARES Act. To develop and annually update a summary of advances in ASD research, which we will be talking about later. Monitor federal activities with respect to ASD and to make recommendations to the HHS secretary regarding research or public participation in decisions regarding ASD. We are going to talk about the strategic plan.

We have convened seven working groups composed of IACC members and invited external experts to work on the strategic plan updates. This set of working groups covers the seven-question structure of the strategic plan. We have a chapter that will be written on Question 1, which concerns screening and diagnosis, Question 2 that is related to underlying biology of autism, Question 3 on risk factors both genetic and environmental risk factors for autism, Question 4 on interventions and treatments, Question 5 about services and service system, Question 6 about lifespan issues and Question 7, which is about infrastructure, surveillance, outreach, and collaboration.

We have been holding a series of conference calls over the last couple of months to discuss various aspects of doing the strategic plan update. And the progress we have made so far is we have discussed in the working groups progress toward current strategic plan objectives. With the strategic plan that is currently in place with the

78 objectives there, what kind of progress have we made? We have talked about information from the 2013 analysis of research funded by federal and private funders. We took comments from the working groups on that to help provide some information for the chapters that you are writing.

We also have had a discussion more recently with the working groups about progress that has been made in the field including advances that have been made in research, what is going on with practice to research, different research gaps, needs, barriers and opportunities, programs and policies as well as gaps, needs, barriers and opportunity in the policy and services arena, more research evidence that can inform policy, and need to policy changes. Those are some of them.

We have talked about the aspirational goal for each of the seven chapters, which was developed by a previous committee and we wanted to revisit that and see if it needed to be updated for each of the chapters. I have also even brought the attention

of the working groups, the chapter titles in case those consumer-based questions need to be tweaked for the current time. We are actively in those discussions right now.

We are planning to have a third set of conference calls for each of the seven groups in the coming weeks where we are going to talk about the draft chapter outline of each question area, which will be based on the discussions that the working groups have had and our office has notes on those and we are developing those outlines and we will be getting them out to the working group chair that describe progress in the field, gaps, needs, barriers, and opportunities, which will set the stage for developing the objectives of the new strategic plan. This is kind of exciting. We had one set of objectives of the 78 that were set last changed in 2011. And now we have an opportunity to develop an entire new set of objectives. But the committee agreed that we would like to keep it a little tighter this time. We are going to be

aiming for a set of about 21 objectives total so three per chapter. These will be broad objectives. The previous objectives in the strategic plan were quite narrowly focused sometimes or they combined many different areas together. We are going to talk this time about doing broad objectives that may have more general questions associated with them, but under each we can list particular types of research projects, service or policy activities that would be responsive to give examples of what the committee is hoping to see.

Today, I did want to ask the committee as a whole if you have any particular suggestions as to areas that we should highlight in the objectives. As we go into the working groups, if there is anything that the committee wants to highlight for any of the working groups, we are happy to bring that back to the working group. I wanted to open the floor because I know there are some people here who are not on working groups or you may not be on a different working group, but you would



like to comment on. Are there any particular suggestions about areas to target in objectives?

DR. PARNELL: Julie and I were talking earlier about the fact that we frequently see comments from the public to the effect of why is the committee so focused on research for autism when there is so many unmet needs out in the community. We mentioned the possibility that the report should really highlight the fact that good research leads to good practice.

DR. DANIELS: Great. Anyone else?

DR. ROBISON: Have we already integrated the questions on mortality into our unmet needs based on Lisa Croen's work and now what we have here?

DR. DANIELS: Not formally as yet. I think that some of the different question areas as we heard the discussion today, I think Question 2, Questions 5 and 6, are probably going to want to think about this a little bit more carefully as we go into the next set of discussions and make sure that if you are interested in trying to highlight

those areas that you have that opportunity. It has come up, but just briefly so far.

DR. MANDELL: I think one of the challenges we have had in the past with the questions is that they bleed into each other and that where the boundary is between any pair of questions is sometimes unclear. I do not have a good answer for this, but I am wondering if the objectives or one of the objectives within each question could somehow recognize that. The one of which I am most familiar is the boundary between treatment and services. One of our real needs is to have treatments that can work somewhere outside a university-based lab, which has profound implications for the service system as well as for how treatment developers develop and test their treatments.

I do not know what we do about really important objectives that sit on the boundary or if you think about the ones between the more biological questions and treatment. How do we give

priority to treatment questions that are taking advantage of newest biological findings about the underpinnings of some of the disability in autism?

DR. DANIELS: One thought that just came to mind as you were talking about that is something that we could consider is rather than having objectives that are specifically tied to the questions to have the chapters each describe the problem, but then collect all the objectives together at the end. It would be a set of 20 or so. But we could collect them and not necessarily differentiate them into categories except for that makes it a little bit difficult for strategic plan coding issues. I think that would be the main problem with that.

I think that, for example, the type of example you had if we could just decide on a place for it to be, we could still put it with a particular question. That issue that you brought up certainly has been an important one in discussions. Other opinions about that?

DR. CRANE: I will say I second the concern and I will say that on the working groups, for example, the adults' working group and the services' working group have an overlap in which people are talking about what services work for adults.

And the working groups seem to have historically used certain rules to put things into one or the other, for example, a service that is for adults, ends up in the adults' question, not the services' question. I think that it is worth it to be transparent so that people who are trying to make sense of the data know that maybe not all of the research on services is being categorized under that question. You have to go under these other questions to see if there is maybe some other study that might be your criteria when you are trying to compile statistics on the advances in a particular area. You are going to have to have especially when counting the number of projects and counting the money, you are going to

have to put something in one or the other, but you have to be transparent about how that process works.

DR. DANIELS: Just to address that, we do try to be transparent about it, but I think in the long text of portfolio analyses, that probably gets lost in some footnotes that there are always projects in other chapters that relate. If we did put everything together if we did think about looking at the objectives as a whole bolus and not dividing them, we could just start a whole new way of doing the portfolio analysis where we are just looking at the objectives purely based on what they are and not trying to categorize them into these different areas. That is something to think about.

DR. AMARAL: I was also going to raise this concern from a different perspective and that is genetics keeps being brought up over and over again in the first three questions. I think what happens is then papers get assigned to each of

these that may not necessarily be most appropriate for that question, but because we are talking about genetics in Questions 1, 2, and 3. They just get distributed throughout.

What I was thinking is maybe - I do not think you necessarily have to confine genetics to risk factors and not to diagnosis. But maybe there should be a preamble of indicating what aspects of genetic analyses are being used in each question and then only those papers, for example, in diagnosis, if there are going to be genetic screens that could be used for diagnosis. It will only be papers that deal with that topic that would go into that question whereas genetics as a risk factor, which may not necessarily be a screen would go in Question 3. So some better GUIDance as to what the topics are covering or what these global topics are addressing in each of these objectives.

DR. DANIELS: That is something that is a part of what you will be writing as you describe the

scope of each question area. You would have the chance to describe what it is and if that has changed a little bit in the last few years if there are new areas that have emerged that are going to fit in that area. That will be a part of the working group's task, and of course OARC will be alongside to help and try to identify things that might have been missed to make sure that we are inclusive. Which is a little bit separate from coding rules for a portfolio analysis, which are a little bit more boring, but we have them on the internal side so that we can make sure that we are bringing things appropriately. Other comments? David?

DR. MANDELL: To build on your suggestion, one possibility also - one of the challenges is if someone is not going to read the whole report, and why wouldn't someone want to read the whole report daily. I do not understand. If you wanted a summary of what the report was about and the connectedness among the chapters, to do something

at the end where you had all of the objectives and pointed out - like a matrix of all of the objectives from all of the chapters and all of the categories. I am sure you prioritize it. You assign it to one as its primary, but you show that these particular objectives are consistent issues across topics.

That there are genetics issues in screening and diagnosis and treatment and that there are services issues and screening diagnosis and treatment in adults and infrastructure. It might go a long way towards showing the interconnectedness of the chapters in the meaningful way.

DR. GORDON: Are you suggesting, David, just to be clear, that that would be a concluding chapter or do you think it would be better to have it as an introductory chapter?

DR. MANDELL: In some ways, it could function as an executive summary that this is --



DR. GORDON: Something in the executive summary sounds right. One could imagine doing a graphic or a table that does that exactly.

DR. DANIELS: Other comments?

DR. TAYLOR: I think particularly for the adult chapter that would be really helpful because I think almost every study that is in the adult chapter, many of them could fit into treatment or services. I think we pull them all together into the adult section just to highlight first of all the dearth of adult work, but to highlight what is going on in the adult world.

But realistically, almost all of the grants and the things that are in fit into other chapters. Having that summary and pulling it together and making it really clear why this work is here instead of there I think would be really helpful for us writing the chapters too.

DR. DANIELS: Around the table, are people feeling like with the objectives you would like to disconnect the objectives from the questions? The

way we have been in the office doing analysis so far anyway we have done an analysis based on the objectives, but then we did the separate subcategory analysis, which was trying to get at the whole. We could go to something where we are tracking those very specific objectives, but then just track question areas. I guess subcategories would be a third set of analysis. That might be a much. We could do it that way, but then you would not be able to connect everything back. I do not know if that is something you want to do or do not want to do.

DR. CRANE: I would not want to totally disconnect them because I want to make sure that all of the question areas have objectives that are specific to them. We have some question areas that really have been really under addressed and we would not want that to be exacerbated by all of the objectives end up being about the other question areas and not the others.

On the other hand, maybe they should - it would be fine to have objectives that are a certain number per question area, but perhaps a study from another question could still fit under the objective if it made sense so that it would be more like tags than buckets if anyone is familiar with that distinction. Something could be tagged as being - was pertaining to more than one question, but we still have - are making sure that we have representation from all of the questions.

DR. DANIELS: With the tagging idea, it's something that we are developing internally with a system that we have, but it is not something that I think we could easily make available to the public at this time. I think it would take probably a year or two more of development of that system to make it usable. I think for all practical purposes, it is still going to be - there is going to be a need to tag each project with one category in order to make a meaningful analysis. It sounds like maybe I am hearing that

you would like to keep the objectives connected to the questions, but just indicate within the description of the questions where there might be overlaps with others. For example, David, like your example, perhaps that type of an objective would go in Question 4, but talks about the longer-term outlook for interventions. That would bleed into Question 5.

DR. MANDELL: Sure. To some extent, I do not really care where it goes. I just feel like we do ourselves two different kinds of disservice by the way the report is currently structured. One is we perpetuate silos that we want to get rid of. It is very unintentional and you have to organize it some way. I do not have a good answer to how to not perpetuate silos. But one way is to make sure that the areas in which - instead of trying to make these really clearly clean lines among chapters that we explore the excitement and the importance of this stuff that is transdisciplinary between the chapters. That is the first thing.

The second place where we do ourselves a disservice is when somebody looks only at the grants that you mark in the services chapter, for example, as what NIH funds and services. Whereas I as a services research, if I looked at the screening ones and I looked at the treatment ones and I looked at the adult ones, there are all sorts of things in there that I would say those are important services questions. We ought to count them as part of our services portfolio. I know that ultimately grants have to go in one category or another for accounting purposes. But if we thought about this as a searchable document and I type in give me all the stuff that has been funded on services, I would want all the stuff that comes from those other chapters that service is related to come up even if financially it was not being counted in the services bucket. It is just an unfortunate firewall in a lot of ways.

DR. GORDON: I know what you are talking about. I get frustrated when people say you only spend X

amount of dollars on Y. Actually, there are all kinds of other things in other buckets that are really part of Y, which should be counted.

DR. DANIELS: We have the same issue even broader than autism itself. In the strategic plan, there are projects that are being done in other disease areas or for these large cross agency initiatives that are very broad that cover maybe many different disabilities or many different conditions that apply to our work. But in our portfolio analysis, we are not specifically counting the dollars for that because it would be hard to estimate how many of those dollars are really for autism. We just note that there are these other projects. I think that that is kind of a perennial problem, but in terms of organizing a document, it does need to have some kind of structure to make it make sense.

DR. GORDON: I think what I am hearing is that we want to make sure that beyond the information that is presented in individual chapters, we point

at overlap. We point at common goals. That is probably better than saying overlap. Even in the autism committee, you are doing overlap. Issues that cross these boundaries, highlight them, and make that point clear. If we can do it in a way that is easily digestible, it is even better. We will work on that.

DR. DANIELS: I think I can work with the working groups to try to identify some of those areas. Maybe on the next call, we have a few things. I think we have a two-hour call set up. We could try to collect from the working group areas that you think you would like to point out where there could be issues about boundaries and make sure we address them in the chapter. Maybe that would help to alleviate this issue.

DR. WEXLER: Thank you. The mention of silos and GAO brought out something that I did want to say regarding those strategic plans. When Tom Insel testified in front of Congress and Susan, you were there. I was there. He received a lot of

complaining statements from congressmen about too much genomic research. He answered that question.

It was just one of the most brilliant statements I had ever heard from in front of a committee relative to the interconnectedness between genomic research, biological research, behavioral research and right down the line. It really laid out how these are not silos that in fact they are interconnected. I think a one pager that is in the front of that strategic plan that kind of lays that out. I think it would be proactive in terms of criticisms that where people in the community may pick off specific lines of research. Tom talked at length about the relationship between genomic research and environmental factors. I would recommend that if the committee sees fit to include it.

DR. DANIELS: That is actually the perfect segue into what I wanted to talk about next, which might be the right place to have such a statement. The Autism CARES Act requires as a mean item in



the strategic plan that we have to provide recommendations to ensure that autism spectrum disorder research and services and support activities to the extent practicable, of the Department of Health and Human Services and of other federal departments and agencies are not unnecessarily duplicative, which is quite a mouth full.

We are required to have some kind of statement about duplication of effort in this upcoming strategic plan update. This is related to a previous report of the GAO that came out in 2013. As some of you around the table will remember, the IACC public members wrote a letter to the GAO talking about their perspective on this issue. The key points in that letter were that efforts by multiple agencies with different mission areas to address different aspects of very broad, complex issues related to ASD is important and necessary. Their letter also emphasized the need for corroboration and replication of research. With

this statement, I think you could also work in possibly a paragraph about or more than one paragraph about how interconnected research is in many of these areas.

I have been collecting feedback from the different working groups about what they think about the issue of duplication in each of their areas. They have had to look at their portfolios to whatever extent they were able to look at that and consider the issues that are related to the field that they were focusing on. These are the some of the highlights or the themes that I came up with from the discussions we have heard over the last several weeks. They reiterated that same concern about the importance of replication of research and reproducibility, which I think has been a big theme throughout the working groups in the committee before and even here at the agency like the NIH and some other federal agencies that are concerned about replicability of research.

Also, I saw a role for closer coordination of large genomic sequencing efforts to avoid resequencing the same individuals and ask for more transparency and data sharing to prevent duplication of effort. This is an area that we have been working on, but maybe there are some new opportunities for trying to build a little bit more coordination. That was slightly different from what GAO focused on. It was more specific, but that was something that came out of the working groups.

The third one here actually echoes a little bit of what you just said. Ensuring that the new strategic plan objectives have minimal overlap or maybe actually not necessarily minimal overlap, but they were concerned about that overlap, but we are talking about maybe addressing it by just discussing the overlap rather than trying not to have overlap because I think that is a pretty impossible task to make it easier to review the portfolio for potential duplication. I wanted to

see if there were any other suggestions the committee had regarding duplication of effort and any thoughts about what you might want to put into a statement.

DR. ROBISON: I think that we should clarify and perhaps the introduction is the place to do this that there is a distinct difference between duplication of basic research and duplication for the purpose of a validation study. I think that while we want to on the one hand avoid duplicative basic research, we want to encourage multiple studies to validate therapies because that is the only path to get them accepted for insurance reimbursement.

I also think with respect to what Larry Wexler just said, I think that I heard the same answers from Tom Insel and from others on the committee. I, myself, have challenged of what I believe is a disproportionate focus on basic genetic research, but at the same time, those other members have helped me understand how broadly applicable such

research can be. Having understood that though, I recognize that if we go to the analogy of polio treatment that while the genetic research may be very broadly applicable, genetics has nothing to do with the development of polio braces. And the braces we develop and the fight against polio have helped millions of people.

I would be very careful with a defense of genetic research as Larry articulated because I think that many in the community would perceive that as our attempt to justify what is to them a failed research strategy. I do not mean to say that we failed in all our research. But I will say that as an autistic person, I believe that we have failed in our duty to autistic people. If I say what has the US government's autism research done to make my life better in the last decade with the billions of dollars, frankly, we have not done shit. I know you cannot say those kinds of words as government employees so I will.

I believe though with all my heart in science and I believe that science can make our lives better. I believe that we have to turn to funding developing braces. We have to fund the development of psychological therapies, of counseling therapies. We have to study what housing options will work. We need to put our dollars there and to do that I think some of it is going to have to come from genetics. To defend that I think would expose us to well-founded widespread criticism even as I believe in its value.

DR. DANIELS: Just to comment on your comment, I think that what you have just said has been reflected in the discussions of the working groups. I think there is a lot of interest in exploring new areas in the strategic plan. I think this new strategic plan is going to have more balance in terms of the types of topics that are highlighted in the plans. I think that is already happening as we speak.

I do not think that for duplication of effort we are really focusing particularly on genetics research, but more just I think making the distinction between replication of research and wasteful duplicative work, looking for opportunities for coordination and ways to make this understandable and also emphasizing the importance of interdisciplinary work and having multiple fields provide input on various topics.

DR. ROBISON: Susan, I think we must really never lose sight of our mission to deliver tangible benefit to autistic people. That is really the thing. I know I keep saying it, but I keep it saying it because we are not doing it even though I think we all believe it here. We are not getting it accomplished.

DR. DANIELS: I think you have been heard and I think that the committee has been working on that. I think every working group has been talking about that. You are going to be working on the introduction and conclusion. Once you see how

these chapters are forming, I think tangible benefits have been on the forefront of everyone's mind.

DR. RING: Just another lens to look at some of these same issues. I know it has been covered, but I just want to emphasize it. I think to some extent the challenges with duplication emerge from the failures of the field to really adequately disrupt and innovate the legal and ethical frameworks around data access and sharing that exists today and even the culture of data sharing that permeates the field of research. Duplication often times emerges because we can publish the top line findings of this large genetic data set. But the realities of us actually sharing the raw data files is limited or we are unwilling to do that beneath some argument about the preservation of the value we have built into that or our funder's value built into that.

I think this has come up in a number of the conversations around questions, the challenges



around data sharing. The ability for us to fully realize the potential value of federating all the data that is being generated across different funded research activities is limited right now because of the challenges with access in sharing that exists today. This, I think, will be a real area. I do not know if it falls under infrastructure or how you really take that on. The other side of it too is just the challenges of standardizing how we collect data will force us into unnecessary duplication regardless of whether or not we map it to one question or not. If we do not solve some of these fundamental problems, our ability to solve it here in the United States or ability to realize federation with all the activities in Europe and elsewhere, it would be severely undermined unless we take that very seriously.

DR. DANIELS: Thank you. Josie.

DR. BRIGGS: Can I just briefly comment on that? I do think data sharing is a very important

issue. It is certainly an issue that is being very actively discussed in the setting of the Cancer Moonshot and in the precision medicine. I think it is something that should be reflected in this document.

DR. GORDON: And in the brain initiative where development of exactly the kinds of things you are talking about, structures to share data in an efficient way, is going to be coming to the fore in the coming year.

DR. DANIELS: Larry.

DR. WEXLER: Just a couple of reactions. One, I think we need to think who is the audience for this report. This is not for us necessarily. A report like this, a strategic plan like this is an opportunity to educate. I am from the Department of Education. This should not be too surprising. I think that it is important to remember that anything we want to do is based on funding. Whether it is genomic research or whether it is more basic research, intervention research. I

think it is important to remember that the audience for this report is the appropriators. When Tom was in that hearing, he posed when they criticized him for how the autism research dollars were spent, one of the things he said to them is how much money do you spend every year on AIDS research. They did not have a number. It was \$4 billion or \$5 billion. It is certainly a pretty impressive number. He said how much do you spend on autism research. It was \$200 million or something. He was very clear that money talks. I think that this is an opportunity.

I say this and I do not contest what John said in the least, but it is an opportunity to make a statement about how all of this fits together and how as a funding source it ought to be funded at greater levels in order to do the work that it needs to be done and an example too of the duplication. I am responding again. You probably are too. I have to do yet another response to GAO on this second study, which was exactly the same

as the first study and recommended the same things, but we have to respond again. I am pretty familiar with GAO.

One of the things that was said here in the discussions two years ago was it chatted about NIH's procedure in the slate process that before they fund anything, they run all sorts of searches on is there any duplication going on. A lot of agencies have those types of procedures. I think it would be beneficial to include that kind of thing in a cover to this kind of strategic plan.

Again, we are educating especially the appropriators so they understand that we are not - I like Vanderbilt and you like University of Pennsylvania. Let's give them both the identical grant to do the same thing for the same amount of money. That is not what is happening. I think we should not miss the opportunity to put information out that would be useful.

DR. DANIELS: Thank you, Larry. I think we have had a good discussion here. The next steps that we

have are to prepare a statement on recommendations to ensure that unnecessary duplication of effort is minimized and to highlight some areas where we have opportunities for improved coordination, data sharing and other things that we mentioned.

It does not have to happen here at this table, but I will need a volunteer too to help draft a statement for feedback from the working groups. Volunteers to draft a statement for those strategic plans and we can circulate that to the working groups and then come back in January. It is something that might be a few paragraphs.

We do have the text of the IACC previous letter available as a starting point that can be used for part of the information and then if you have more to add based on some of this or I can provide with you notes from this discussion. Is there anyone here who is interested in perhaps doing that? Alison? I know she was instrumental in preparing the previous letter. That is great. Thank you, Alison. We will provide you with more

information and then by January, we will want to have a statement put together for the plans. Thank you.

The last item that I want to talk about very quickly here is that the Autism CARES Act requires the IACC strategic plan to include proposed budgetary requirements. The previous strategic plan provided estimated budgetary requirements for each of the objectives. I wanted to talk with you a little bit about whether the committee wants to develop budgetary requirements based on the objectives this time, on question areas, the overall plan, keeping in mind that the new objectives are going to be broad and inclusive of both research and services activities.

I also wanted to see if you wanted to try to estimate actual budgets or perhaps project percentage increases or decreases or something like that. Our office will be able to provide you with some baseline data. The first year that the strategic plan is in effect we will go ahead and

do analysis and provide you with a baseline. But you could use that to then look at percentages of increase or we would have a dollar figure at that point and if you wanted to try to do something with dollar figures. I wanted to see if people had any thoughts, ideas about what to do with this. It is something we can also revisit in January.

DR. CRANE: I think we definitely still need the budget requirements to be by objective or at least by question. Even though the law says that the objectives need to include research and services activities, I think we should also be clear about how much of objective budget should be allocated to each one or at least to show that there should be a proportional balance because we do not want any one objective to have all services and no research or vice versa.

DR. DANIELS: One of the challenges for us is going to be - our office has been tracking the research portfolio for many years. We have not been tracking budgets related to services and how

to draw boundaries around services whether we are talking about just service programs within the federal government. I do not think it is realistic that we could possibly look at every state and local program that exists to serve people with autism or other disabilities and try to collect that information. I think that we would be limited. If in the future we collect information on services, it would probably be limited to federal. But then are we talking about reimbursement programs too or just the ones that are service based if you know what I mean? This is something I will be looking to the committee for GUIDance as to a realistic way that we can do something with it.

I think we will have research information for sure. I do not know what kind of services information we are going to have as yet because we have not really had a chance to develop a plan for that.



DR. AMARAL: When you talk about the services activities, are you talking about research related to services activities or all service activities?

DR. DANIELS: All service activities. In the new strategic plan, one of the requirements under the new law was that the strategic plan is now not going to be just a strategic plan on research. It is a strategic plan for autism spectrum disorder that covers services. We have been approaching it that way with all of the working groups. I think with Questions 2 and 3, there is a little bit less of a service component to them. In those working groups, we have not discussed it as much. But in most of the other question areas, there is certainly a larger part that is devoted to services.

We are supposed to be at least discussing services activities broadly in the strategic plan. In terms of tracking dollars, we have not decided how we are going to do that.

DR. BATTEY: I am probably stating the obvious here, but the boundaries of where services begin and end are far more difficult I think to either defend or define than research where you can look at grants and a defined set of things.

If we are going to do this and I guess the law says we are going to do it so when the law says we do it, we do it. We had better be clear what we are defining as services as part of making that statement so that it is clear exactly what we counted and how we counted it. I see some vulnerability there. I will just leave it at that.

DR. DANIELS: Thinking about that, it might be helpful for the budgetary requirements, we may need to have separate budgetary requirements for research and service programs. I think it will be very easy to at least separate those programs. I think that the things that we have been counting in research so far are pretty clearly separated out from service programs. It would just be a matter of what we are collecting.

DR. CUTHBERT: If you can GUIDE the committee just a little bit more, you mentioned reimbursements. But presumably, we would not claim on Medicaid reimbursements for individual services. Presumably, we would be talking about programs that are established, programs through DOE to provide services, which would imply also that we would want to - but given Jim's acknowledged good point, we would want to project something like percentage increases rather than actual budgets, which would be so much more difficult. Even the track down let alone establish what services and what are not.

DR. DANIELS: Exactly. That is why I brought that up because in our office since we will be doing the practical part of this and trying to do those things, I think that trying to use percentage increases might just be easier on all of us than attempting to calculate things with dollars. We will, like I said, have a baseline that we will work with.

My current plan would be to try to collect federal programs on services that are being conducted to collect. Do an annual data call like what we do now and just ask every agency what kinds of services, activities you are engaged in and collect those programs. That would certainly be only a subset of what is going on in services unfortunately. It would be informative in terms of finding out what is going on in the federal portfolio of services activities, but certainly it is not comprehensive for all services across the country.

DR. GORDON: Susan, this comes from a naivety about starting on this thing. If we have been tasked with proposed budgetary requirements, it is not quite the same thing to me as being tasked with figuring out how much we are currently spending. To me, it sounds like they are saying if you are going to enact these recommendations, how much would it cost, which means, number one, it is very difficult because how are we going to know

how much something is going to cost if we are just proposing an idea. We can make up some numbers hopefully not out of thin air. Not make them out of thin air, but make them up from the best of our ability to figure out how much it would cost.

I think that is an important distinction because one could imagine someone coming to this committee and asking this committee how much is the federal government spending on autism period. I do not know that we know the answer to that. I think you point out that it would be very difficult endeavor to find out the answer to that.

I really want to come back to this. What are they really asking for, and to me that word proposed in front of it means that if we are proposing a new initiative or a new endeavor or an increase in the effort that they want to know how much is it going to cost and if we use that. Whether we talk about is it an increase or in hard dollars, I think that is what we should be focused on.

DR. DANIELS: One good point in terms of the baseline. The baseline would only address what research exists now. It wouldn't talk about anything that is not being done now. We do have a complex task ahead of us to try to figure this out. I do not know that we are going to be able to figure it out right here today, but I wanted to at least propose this topic as a discussion point and we can look at the actual objectives probably in January and see what we think about them.

DR. ROBISON: You have suggested that we come up with percentages of increase, but at the same time, we do not really know what the amounts of money are. Might I suggest that rather than percentages of increase, perhaps we should come up with what we view as maybe an optimum pie chart? Maybe we take our goals and we say we would like the pool of money and services and pool money in research to be allocated in this way. That might better address that than to ask for a percentage

increase when we cannot answer what the underlying number is.

DR. DANIELS: It is not that we cannot identify the underlying number. I just do not have it for you right now. We could do something with that. On the research side and on the services side, that is something that we could collect, but it would only be federal.

DR. GORDON: I aware of the fact we are now a few minutes over our closing time. Do you have more that you need to get from the committee?

DR. DANIELS: I do not think so. I think David had a comment so maybe we should let him have the last comment.

DR. MANDELL: I just do not want us to turn away what could be a really important opportunity to truly calculate federal expenditures related to autism. I think that there are enough sister agencies here that account for the bulk of spending on education and health care that we could get some rough estimates. And the reason

that is important is because if you are going to make recommendations regarding funding for services, how are you going to know if it is a lot or a little and how are you going to know where those funds should come from unless you have a sense of what the current services funding landscape at the federal level looks like? I would be really excited to work with some folks and think about how you would pull together those numbers and really present a true rather than synthesized estimate of federal spending on autism.

DR. DANIELS: I think we would be really excited to work with you on that. We will be talking. Are there any other comments before we --

DR. CUTHBERT: It is a very good point. Obviously, good. The concern is how long it might take to get that because in the government, we have requirements about releasing official numbers. We cannot just talk it up and say we are spending this. We have to go through a lot of



clearances to get that blessed and sometimes that can take a really long time. If you can do that, that would be great.

DR. GORDON: David, I think that is a fantastic idea and hopefully you can get it to work. As we say in Yiddish *zei gezunt*. Go and be well. I think if we can get that work and we could come up with a number, I think that would be a valuable number for this committee to have for the public to have and whether we can do it from a governmental standpoint or you could do it from a nongovernmental standpoint I think would be interesting to find out.

I want to just to conclude this section, which is really about the strategic plan to say that and this is in response to Bruce's point that that might have to be separated from the strategic plan. And that the strategic plan asks us what do you want to do and essentially how much is it going to cost. We should have some way in the strategic plan of detailing that. If we, as a

committee, could either on that timeframe or even on a longer timeframe if necessary come up with the numbers about how much we are spending, that might be valuable information for us and for others.

We are going to close then.

DR. DANIELS: We are going to close with the committee. I would like to ask the committee members to stay up toward the front for just a couple of minutes. We are going to get a group picture and then we can take off for lunch. Lunch is downstairs in this building on the floor is the cafeteria.

(Whereupon, the Subcommittee recessed for lunch at 12:00 p.m., and reconvened at 1:00 p.m.)

DR. GORDON: We are now entering into our oral public comment session. This is a really incredibly important part of what we do as a committee, is to hear from the public. As you are aware, we hear from the public in many ways. We have public representation on the committee

itself. We have the opportunity from the public to give oral comments to the committee at our meetings. We also have received written comments. You all should have received the written comments. I hope you go through them or that you have already done so. It is an important way for us to get feedback from the community.

Here at the meeting, we are going to hear from several people who have requested to give oral comments. I do not think we were able to accommodate everyone. We devoted five slots. We aligned the slots. Unfortunately, we did have two last minute cancellations. We only have three oral commenters today that will speak to us. But I did want to mention that Nicole O'Malley and Jim Needle were invited to give oral commentary to the committee directly, and were unable to be here today. I do believe they both have written commentary. At least I know that Jim Needle does. They both have written commentary. I encourage you

to look at their written comments which would hopefully reflect their testimony today.

I would like to invite - just a note on the format. We are going to allow them - we have asked them to aim for three minutes for their commentary. And then at the end of the oral comment period, we are going to have a summary of the written public comments by Karen Mowrer and Susan's office in the Office of Autism Research Coordination. And then we are going to hear from - Susan is going to tell us about her request for public comment on the strategic plan. And then we will have some time at the end for the committee to discuss the comments that were made. With no further ado, I will ask James Williams to come and give his comments. I believe we would like it if you could come to the microphone.

MR. WILLIAMS: Thank you. It is nice to be back at IACC after two years. My initial comment was going to be about how Anime conventions have helped many young people with autism develop

social networks that have helped a lot of people at those conventions with autism alleviate depression and anxiety. But given the discussion earlier about medical issues in autism, I decided instead to talk about how at those conventions because of that reduced depression and anxiety, I have met a lot of adults with autism who have many of the health issues that were mentioned this morning. I find interesting that although Anime conventions are not directly about health, a lot of people I have met there with autism have found that that is a safe place where they can speak up about those issues.

One thing I want to say right now is I grew up with health issues that doctors could not explain. My mother and I were often shamed for those issues. We were told that it was just psychological and we were often sent home to just deal with them and were not given treatments. There have been times that I have been in the emergency room for medical issues given no

treatment and then given a hefty bill for going to the emergency room.

When I grew up, I made friends with a girl with autism who had been shamed too. We made this deal when we were 16. She would tell me how she was shamed by issues. I listened to her if she listened to me. There were some issues that she went through that made me develop empathy. They say people with autism do not develop empathy. I was shamed a lot for having sinus issues, frequent colds, and a lot of immune issues. She opened my eyes and she revealed to me that she was shamed a lot for a lot of hormonal issues that occurred on or before her time of the month. I developed empathy for that even though I know a lot of guys who might not have developed that empathy.

I want to address the fact that people with autism are often told they are not taking care of themselves. I was the one that gave that comment John mentioned earlier. They are told we are not taking care of ourselves. It is our fault we are

sick. We just need to shape up and the truth is many people with autism have health issues and they need treatment not discipline or scolding.

I will close with a humorous comment my friends and I made when we bonded over these health issues. She told me that her time of the month was coming and that she would be sick and she wanted a listener. I told her that is fine. If I was Savant, I would tell you what day of the week it would happen next month. Thank you.

(Applause.)

DR. GORDON: Thank you. You bring up two excellent points there, one of which you brought up with your previous comment about the importance of not shaming people for their health problems and then the other point is that we need to think about out of the box ways of improving therapy and improving the ability of individuals with autism to find ways that they can function better and opportunities like Anime conventions, et cetera that might appeal to individuals with autism in a

way that allows them to open up and are important avenues to think out of the box.

Next, I will ask Mitch Burton to come and present his oral comments. First is Henry Burton. Thank you. Maybe we will have our first father/son tag team here.

MR. BURTON, H: My name is Henry Burton. I am 22 years old and I am on the autism spectrum. I graduated from a high school that specializes in helping people like me be successful in school. I tried moving into a dorm room at school, but that lasted one night because of my particular sensitivities. I could not stay there. People were too noisy after the time I wanted to go to sleep at 9:10 p.m. I could not control the temperature in my room. It became too hot. I could not find a water bottle and the mattress was wrong. After wanting to live away from my parents, I returned home.

Now, I work at a farmer's market as a bagger and I have the title of courtesy clerk. I am an



award winning runner in the Special Olympics 100-yard dash. My coach helped me with self-discipline. No sodas. Desserts and sweets only on Sundays. It makes me a better athlete.

I hope that by the time my parents die, I can live alone with someone coming in to check on things a few times a week. I do not know if I will ever fall in love again. I did once and it hurt me deeply. I will feel I will be better living alone. I never want to go through that again. Many people at my age in my religious community serve missions for two years. A mission was modified for me. I did my service for six months, three days a week, four months, four hours a day doing computer document duplication.

So far, I am lucky because I have had kind people in my life helping me become dependent. I have learned that it takes me longer to do things, but I have dreams. I want a college degree and maybe I will get that one because a nearby university has a special program to help people

like me succeed in college by teaching skills others take for granted.

I want to work in the multi-media industry and I want my own company. I cannot do it alone. I need your help and the help of my community to become the Henry I am supposed to be. I need what many other people like me need. More people need to know autistic children become adults with autism. I need schooling where I can succeed and we need more research to know how to help us be the best people we can be.

We need help to increase the nation's understanding in research for how our futures can become better. Who knows? Some of your grandkids may grow up watching the video programs I create. Invest in me and people like me making our world better. Individuals like me may make your world better as well. Thank you.

(Applause.)

DR. GORDON: Thank you, Mr. Burton, for sharing your story so poignantly. Now, we are going to hear from Mitch Burton.

MR. BURTON: Talk about nervous. I am Mitch Burton, often known as Henry's father. In the last 22 years, I have learned a lot about autism. I am a builder and a business man. I know how the world works. Yet I have been shocked to find out how little is being done for adult children on the spectrum.

Henry sounds like he has it made, but every day is a struggle. I can afford to help Henry at this point in his life, but I find thousands of Henry's across my state and around the country who are unable to go on to college because they may need help. They need people in a place to give them GUIDance academically and socially to understand adult learning deficiencies and differences. They may be living with aging and ill parents. Often parents give up careers to take care of their adult children. They may be on long

waiting lists to get housing supports. The employment opportunities are extremely limited. Employers need to be educated about adult autism. These conditions exist in large part because the country does not realize our children grow up and they are not cured and are looking at a small amount of research funding that is available. NIH funding makes me question whether the body has realized that these individuals become adults.

My wife and I have experienced through all the aspects of adult isms that there are. We have learned lately that he has fallen off the cliff. When all the services are discontinued, when the schooling is not there and the church is not there and the phones are not there, there is nothing there.

We have a large population that we know little about. It is estimated that 50,000 autistic adults becoming adults each year. As a builder, if I were constructing 50,000 units, I would know the specifications, the limitations, the potential

range of options, variable materials. I would know the labor force, understand the deadlines, who the clients would be and I would cost things out so I knew the cost of the project as a whole and individually. Here, you are dealing with human lives and potential. We are spending a lot of money on adults with autism to provide services, but actually very little is known about the implication of needed, living options, continued education, continued health concerns.

The understanding of the Down's population far surpasses the knowledge we have of about adults on the autism spectrum. With Down's, the quality of life and longevity has been greatly increased. That population in the United States is about 400,000 in total, 1 in every 691,000 births. We have more autistic people in the United States becoming adults each year than that. Three and one half million Americans are on the autistic spectrum. That equals a combined population of Delaware, South Dakota, the District of Columbia

and Vermont. It is time for some kind of a national outcry about adult autism. Either we pay some now and help these kids or we pay a lot later.

We can have people employed and active or dormant laying on a couch developing heart problems, obesity, diabetes and depression, which are all costly to treat let alone the loss of productivity and creativity that could benefit society. We need to act now with more funding with all types of research and education and job training. Those of you here have an opportunity to set a national tone on these issues.

I would like to just go off the page a minute and talk about help now or do nothing or pay a lot later because with you and the kids that I work with, we are building an autistic college in Utah right now. We had a groundbreaking scenario on April 22 of this year. It should be completed next year. We anticipated about 80 kids to sign up for autistic college. We had 700 kids sign up in one

week. We do not even know what to do with that. We do not even have those resources. We are building a 25,000 square foot building at a cost of \$13 million all funded by contributions from friends and family.

I thought about this issue. Autistic kids - most of them have huge social problems, social skills, the ability to ask, the ability to be helped. They sit downstairs and play video games. They do not really want to be downstairs playing video games. They really want to be out, be productive taxpayers, go to work, have some exercise, be out in the community, be social, be with people, be friendly, get friendships, but they cannot do it by themselves. We have to reach down there and help them out. We have to educate employers that autistic kids are great employees. For the most part, the people that I have seen and I employ some - they show up every day on time. They do not complain. They do not worry about

their hours. They do not worry about the money. They do not talk much. They do their job. Henry served a mission for six months and his mission president told me that he was the best missionary he ever had because he could come in and go on task. He got more work done than anybody else did.

I would just like to leave it with you. I have been horribly impressed with all of you and grateful to be here and see it for my own self. There is a lot of this out there, a lot of fathers out there that have autistic kids that somehow are doing this. We are all taking our resources and trying to figure it out for ourselves. We need to do this. I have seen today for the first time the body of people that can get that done. I appreciate the opportunity here. Thank you.

(Applause.)

DR. GORDON: Thank you, Mr. Burton, for your eloquence, and also for your descriptions of what can be done and the emphasis on the transition



from youth into adulthood, which is something that this committee I understand has been deliberating on across institutes where we are deeply interested in working on. You will hear some information about that a little bit later in the meeting.

At this point, I would like to have Karen Mowrer come up and present a summary of the written public comments. Karen is a health science policy analyst in the NIMH's Office of Autism Research Coordination.

DR. MOWRER: Hi everyone. Since our July meeting, the IACC received written public comments from 32 commenters. For the purpose of this summary, they have been organized into seven broad topics. The committee, as we heard, has been provided the comments in full, but I will summarize them briefly here by topic. The first topic was adult service needs, employment and quality of life. We had eight commenters under this topic. They included Mary

Barto, Christine Gilles, Jessica Simpson, Peter Mazure, an anonymous commenter, Sara Luterman, Julia Lynch, and Julia Bascom and Zoe Gross on behalf of the Autistic Self-Advocacy Network. Some of the key points from their comments included that there is a need for improved and more widely available services, social enrichment activities, vocation and rehabilitation programs, employment opportunities, long-term care, and safe housing for adults with autism across the lifespan. This was especially a concern as their caregivers age.

Recent reports describing a high rate of suicide in adults with ASD are alarming. The research, provider, and patient community should work together to begin addressing this problem. We heard a little bit about that earlier today. There is concern that according to 2012 data, only 1.8 percent of NIH autism research funding went to research on services while less 1 percent of this

funding went to studying issues facing autistic adults.

The second topic we had had to do with autism research priorities. We had eight commenters under this topic as well. They included Teresa Horowitz, Jeff Belloni, AnnMarie Sossong, Carmel Lozano, Lori Kay, ASAN, Resa Warner and Eileen Nicole Simon.

Some of the key points from these comments included the following. NIH should provide funding to continue promising research on the use of an existing anti-parasitic drug called suramin, as a potential treatment for the core symptoms of autism. The drug was thought to modulate response to environmental stress.

The IACC should prioritize research on the following topics: the ideology of autism, the neurobiology of minimally verbal individuals with autism, repetitive movements, seizures in ASD, and symptoms in severely affected individuals.

More research is also needed on lifespan outcomes, access to health care, co-occurring conditions, effective services, assistive technology, diagnostic disparities and the prevalence of autism in adults.

There is also concern that the priorities of the autistic community are not reflected in the current research planning and funding process. The IACC is urged to promote the involvement of autistic adults in grant review and other aspects of the research process.

The third topic is somewhat related, is on the IACC's strategic plan and the role of the IACC. Six individuals' comments fell into this topic. They included Brian Kelmar, Shirley Farrior, Kyle Bryan, Ann Lindsey Frost, Peggy Helm-Quest, and Linda Varsou.

Their comments made some of the following key points. Coordination between autism service organizations is inadequate and presents challenges for families. The IACC' work to address

the complex issues around ASD and the forthcoming strategic plan are appreciated and there is hope that the IACC will expand its perspective to learn from international efforts and have a global impact.

Rather than focusing on prevention or cure, the IACC strategic plan should focus on reducing the most disabling aspects of autism while valuing and appreciating autistic individuals.

The strategic plan should address the need to remove bureaucracy and recommend approaches that will benefit autistic people in society such as through the development of more compassionate service systems.

The fourth topic we had was vaccines in autism. We had five commenters under this topic. They included Sandi Marcus, April McKay Dudsic, Jacky Witherspoon, Sean Kelly, Kristie Sepulveda-Burchit on behalf of Educate Advocate, and their comments made the following key points.

The IACC should request that Congress repeal the National Childhood Vaccine Injury Act, investigate the CDC whistleblower issue and provide a full debrief of the study on autism in the MMR vaccine. Also, in general, more research should be done on vaccine safety and autism risk around vaccinated children.

The fifth topic is the court system, law enforcement in autism. We had four commenters. Andrea Colburn, Callie Mitchell, Jim N, Jim Needle, and their comments made the following points.

There is concern about dangerous interactions between law enforcement and autistic individuals. More training about autism and best practices for community interaction should be provided to first responders and community agencies.

There is also concern about the potential for an autism diagnosis to be misused and manipulated by parents and child custody cases as family

courts often do not consider children with special needs suitable for joint physical custody.

The sixth topic was childhood needs, services and interventions. We had two commenters: Tilley Steven and Patrick Feeney. Their comments included the recommendations that herbal medication should be considered at treatment strategies for ASD. There was also concern voiced about state education policies requiring disabled students to be taught in the least restrictive environment. This has caused students to be moved from self-contained classrooms to inclusive classrooms, which is not appropriate for some autistic students.

The seventh and last topic was pre and perinatal causes of autism. We had one commenter. Eileen Nicole Simon. She wanted to urge the IACC to consider complications resulting in brain injury such as asphyxia, umbilical cord clamping, thiamine deficiency and developmental disruptions when investigating causes of autism.

That concludes the summary. Thank you again to everyone who submitted comments.

DR. GORDON: Thank you, Karen. I will add my thanks to that to everyone who submitted the written comments. To me, it is interesting to hear it summarized like that and to see how many of the issues raised are issues that this committee continues to deal with, some of which we have already heard about today. That is gratifying. And of course, to also listen to where we do not is interesting to consider and things that we should be doing in addition. It is very helpful to have those comments.

We are going to have a moment for the committee to discuss. Is it all right if we hold off on the comments for now? Susan wanted to discuss the request for public comment with the strategic plan unless it is really burning?

DR. DANIELS: I just wanted to once again bring our attention to the request for public comments on the IACC strategic plan, which was run this



summer. We received over 1100 comments from the public on all seven areas of the strategic plan. I know I have been talking about this with the working groups. But then for those of you who might not be on a working group, I wanted to bring this to your attention. You have the link. Everyone in the public can also see all the comments on our website and they cover the seven question areas.

Within each question, we grouped the comments by themes. And the respondents that we have for these comments - you can see this list of all the different kinds of people who responded to our request for public comment. We feel like we got a nice cross section of the community.

I am not going to read all of these themes, but you have these in your packets and you have them as attachments within email. These are also a part of the materials that are online. These are some of the themes that we saw coming from the public on the various questions, areas where more

research is needed or priorities need to be made to address various services and policy issues. I wanted to just highlight that again as you will have an opportunity to discuss that along with all the other public comments during our discussion period. Thank you.

DR. GORDON: Now, we will open it for the committee discussion of the public comments. John, go right ahead. Start us off.

DR. ROBISON: I think that we had some very poignant comments on the issues around adult life for autistic people. I would like to raise two questions. In the written commentary, I would like to draw your particular attention to the related comment from Julia Bascom and Zoe Gross on behalf of ASAN, talking about their specific concerns about the unknowns with respect to adult autism issues.

I recognize that for us to answer the questions asked in the specific ASAN letter, and also to address some of what we heard from the

Autistica folks, as they pointed out, we do not have a database of older autistic people to turn to for research. Might I suggest that when we identify pressing issues in our strategic plan that one of those issues, which is not really included at all in the previous questions, will be the development of that as a public health issue for both the United States and indeed for every country researching autism. I think that is one big thing.

Another thing that was really brought to the fore for me by these commenters and the people who came up to me privately today is this issue of shame and blame in autism. We have talked about it before in the context of parental denial, keeping people from getting services. That is really rightly the province of the United States public health service to conduct campaigns to eliminate that kind of shame. It is very different from the autism awareness ideas that we have had to date. I think those are two issues that should be

considered for inclusion in our plan and should be discussed further going forward.

DR. GORDON: Thank you, John. Are there other comments from committee members or questions or items for discussion about the public comments?

DR. PARNELL: I just want to add that I was particularly heartened to hear from Mr. Burton who coincidentally is from Utah as well as I am. But it is encouraging, Mr. Burton, that parents of people with autism are stepping to the forefront on our efforts especially as we look at the needs of people with autism as they leave adolescents behind and enter adulthood. The housing issues are near and dear to this committee's heart. The employment issues, the whole life long well-being issues related to people once their parent caregivers are no longer here. I think I can speak on behalf of the committee and thank you for your involvement and your commitment to those issues.

DR. GORDON: Thanks Brian and I should say thanks John, not Bob. I do not know where that came from. I got it right this morning.

DR. PELPHREY: Two comments. One on the very wonderful presentation and the idea of creating a college specifically for people with autism. We are borrowing that concept and creating a residential college around autism, but also research and treatment for adults with autism, people with autism. Our preliminary assessment of this is not only is there great interest from the autism community, but by creating a common residential college around the theme of developing into a scientist who studies autism or a care provider or medical doctor were getting higher number of very highly qualified recent high school graduates as well as a lot of people who have strong political aspirations like Hillary Clinton types who are increasing our colleges' numbers, which are very important for college. It is very much a win-win situation when you start to create

these inclusive environments that promote the success of young people with autism and also early projections that our computer science department will benefit from it as well. There just seems to be no downside to this.

I think that the more private individuals as well as universities be they public or private can use the infrastructure that they have to do this, really irrespective of the federal government's contribution, will be a really welcomed thing.

And then John's point. I am always wrestling with the national registry for individuals with autism as a parent myself. I understand the public health benefits, but I also always want to throw out that word of caution. If it were to be a mandatory list of everyone who has a particular condition that makes me very nervous just because of the number of times in history that that has not worked out very well.

DR. ROBISON: A mandatory registry is a sex offender registry. We are talking about voluntary pursuit of science.

DR. PELPHREY: But oftentimes - for example, if individuals want to participate in my autism center of excellence network and they do not want to have a GUID, it becomes very challenging for them to participate in the autism center of excellence. It is not a law, but it is extremely challenging to include them. We actually have to seek clarification between our university's IRB and NIH so they could tell our university indeed it was not required. It took a while for even NIH to decide whether or not it was required. It is very shaky ground once we start talking about creating a registry as to what is required like a court order versus required if you want to access certain services, which could be another meaning of required.

DR. ROBISON: Kevin, that is a point that I should have expressed myself better. I said that

as being something that I felt should be led by our public health services because I feel that we on the one hand need this pool of people we can use for research, but we need those people since they are going to be adults to be confident that they would not be discriminating against say in the life insurance market or discriminating against in employment because people can access that as part of their health record.

We need action from our government to ensure that the identification of people participating in such a pool is separate from medical records and is anonymized and totally inaccessible to people who could use it against us because it is very clear to me that you are right. The other groups would use it against us. I think we have to be very mindful of that and yet it is a pressing concern. We need it.

DR. CUTHBERT: I want to remind everybody again that we already have a very large database set up in NIMH, the NDAR, and the National Database for



Autism Research. And of course, the data mostly involve children, but the infrastructure is completely there to be adding adult-related data as well on many of the same measures and even would apply. Dr. Greg Farber deserves a lot of credit for being very - it uses GUIDs and is completely anonymized.

MR. ROBISON: So it is safe to participate in it.

DR. CUTHBERT: Yes.

DR. MANDELL: That is a wonderful resource. Even though it does not have adults in it, it will have adults in it because those kids are going to become adults, but we will not be able to find them because it is anonymized data. I wonder if we could look at some of the - I was thinking about, for instance, the health care data that are available to us where we can identify. Some of the questions we have that are more biologically questions that may be difficult to answer with those data. But we had data sets where we could

identify kids in one year and find them as adults in other years even if they are not diagnosed with autism.

The other thing is, is there a voluntary way to use some of the more careful, clinical and biological data that we are collecting on children that would allow us to then re-contact those individuals as adults, which would then allow us to have really nice measures of what they were like as children and then see how they are doing as adults.

DR. SPONG: I was just going offer one model. NIH is funding the Down syndrome registry, DS-Connect. In that case because of the concern about recruitment, but maintaining people's privacy, what happens is that researchers apply to our research team and then the research is approved. We make sure it is IRB approved, that there is funding, all of that.

And then the very few count on one hand registry coordinators have access to the

personally identifiable information. They scan the database. We notify the families and let the families choose whether to contact the researchers or not. There are ways of doing things like that.

DR. GORDON: To mention the Precision Medicine Initiative again, eventually as I said before we do want to get adults with all kinds of mental illness diagnoses, but of course including autism into that registry. And eventually that will expand to children as well. That will give us the opportunity to follow people across the way. But I am not aware yet and someone correct me if I am wrong about an autism registry that is geared in the same way to what you just described for Down's.

DR. SHAPIRA: I did want to address David's point that if it is anticipated ahead of time at the time that children are enrolled studies and they are consented from their parents for follow up, at least in the adolescent range, we do not have it yet worked out from the standpoint of when

they become adults and have to provide their own consent. But at CDC, we are entering the third phase of our study to explore early development, the research study to evaluate risk factors and genetic and environmental for autism. In this third phase, we are re-contacting participants from Phase 1 and if they consented at the time to permit re-contact.

The purpose is to - for this follow up, a study is to understand the long-term health and developmental children identified with ASD of young ages. The children were originally 3 to 5 years of age when they were originally enrolled. They will be early teenagers at the time of follow up. It is an important step we see in providing us with the information to support children with ASD as they grow into adolescents and adulthood.

DR. GORDON: Fantastic. Other comments from the committee?

DR. CRANE: I just want to say if we are talking about doing more research on adults

especially longitudinal research, which ASAN strongly encourages, we do not want to rely on just kids who were entered into a database as kids and who become adults or on a database idea that does not involve the participation of the autistic community pretty strongly in even just the basic design because adults have very significant privacy concerns and they have been raised.

In addition, we do not want a situation where the people who are looking at our people who may not have necessarily re-consented when they became adults. We want to make really sure once someone becomes an adult that that information is not used for further research studies without a robust consent process to make sure that they are still interested.

DR. GORDON: That is a great point. That is a considerable issue with PMI, the Precision Medicine Initiative, as they contemplate enrolling children. How do you negotiate that transition and

make sure that appropriate consent is taken at all points along the way?

DR. BRIGGS: In general, the experience with re-consent is quite positive. In general, when people are contacted and say you were signed up on this before, now they you are 21 or now that you are 18, we would like to ask your permission. By and large, in other settings where this has been explored, the people do say yes. It is not an insuperable barrier. But I think all of us feel that it really is essential to maintain trust and generally consent is key for trust.

DR. GORDON: Right. And it is important to continuously establish it. We are going to move on from the public comment period. Thank you very much again to our oral commenters and to the written comments and to the committee for discussing them and also for the various committees, subcommittees working on the strategic report for paying attention to the public comment and that process as well.

We, as a committee, decided earlier this year that we wanted the opportunity to discuss articles and other evidence of science advances nominated by members of the committee. We have gone ahead and solicited nominations from the committee for discussion today. Ten articles were nominated, five from the NIMH, four from the NICHD and then several from individual members of the committee, David Amaral and Ruth Etzel. We would like at this point to take some time to discuss those so that we can consider the advances that we have gotten.

DR. DANIELS: We have a list that is in your packets. There were no nominations for Question 1

DR. GORDON: Question 2. How can I understand what is happening? And actually this first article, the Marchetto et al., was nominated by both David and by NIMH. David, do you want to tell us a little something about it if you are prepared?

DR. AMARAL: I can wing it. This is an article. It is the first of its kind. It was an article,

which individuals who had early brain overgrowth as children had fibroblast punctures taken and fibroblasts were turned into induced pluripotent stem cells. And then the stem cells were turned into neurons and what the paper reports. It is a small number of individuals. There were eight, I believe.

But the interesting thing is that we do not understand what causes early brain overgrowth. What these investigators showed was that there was dysregulation in pathways that are involved in regulating neuronal proliferation, which presents a plausible use of data to explain why there is brain overgrowth. This is one of the examples of an issue we cannot look at in living individuals.

This is a unique paper. It has not been replicated. There are a number of issues related to appropriate controls. They did not do iPSCs from individuals with autism in normal brain science, for example.



I think in many respects it certainly needs to be replicated. But it is a very exciting approach to personalized medicine. If we can start taking iPSCs and developing ideas about what metabolic pathways that actually gives us a root to novel interventions. I think as a one of a kind and as a novel approach, it was an interesting paper to highlight.

DR. GORDON: Thanks David. At the risk of over explaining to a group that many of whom probably understood that completely, I just want to emphasize that that aspect of novelty where essentially we are taking from individual patients tissue from the periphery that we can then convert into neurons in a dish and then watch the behavior of those neurons, in this case their growth behavior, and try to understand what is different about those neurons in individuals with autism from neurons in individuals without autism. One caution that David mentioned is that this is early days for this technology particularly

applying this technology to neuropsychiatric illnesses. The small sample sizes that we are able to do because currently any way these studies are tremendously laborious. The small sample sizes and the early days of the technology mean that we have to take these studies with a grain of salt. Nonetheless, they are extremely exciting that we can actually do rigorous neurobiology with actual human neurons from individual patients is tremendously exciting.

DR. BATTEY: I just want to ask a question. Were these cells excitable? They were. That is pretty good evidence that they have a lot of the phenotype of a bona fide neuron.

DR. GORDON: In terms of differentiating neurons, the field is pretty satisfied that we can differentiate, not only to neurons in general, but specific neurons. I do not know if there were specific neurons here or just general neurons.

DR. AMARAL: They were thought to be generalized progenitors of cortical neurons.

Again, one of the down sides is that not all types of neurons were looked at. Glial cells were not looked at in this particular study as well. It is just a harbinger of the field. This is the beginning of what is going to be increasingly more common.

DR. GORDON: Harbinger is probably a good word to describe it. We are seeing more and more grant applications that use this technology and we are going to see more and more data coming from it. We will get a better appreciation for how much it really tells us over time, but it is very exciting. It has a certain salience to it, which invites us into the next paper that was proposed by Alice Kau. I do not know if I am pronouncing it right.

DR. DANIELS: Alice is not here today.

DR. GORDON: I will just read the title, which is the Saliency Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Over-responsivity. I have a short description that

I can read. I might be able to elaborate on it without knowing a whole lot more. The sensory processing impairments are common among individuals with autism spectrum disorder. Their underlying biological mechanisms are poorly understood. This study used functional magnetic resonance imaging, which is of course a non-invasive way to monitor brain activity over time, to look at the patterns, not of activity within a particular brain region, but of connectivity between far-flung brain regions, and relating those patterns of connectivity to how far-flung brain regions interact with each other to behavioral markers. And the behavior that the study focused was the well-described behavior of sensory hypersensitivity in patients with ASD.

This is a great example of trying to take a behavior that is at times disabling for patients with autism and often disturbing for them and understand the neural circuit underpinnings of it. It is an attempt to say let's start with the

behavior. Let's get into the brain. It is a nice demonstration of how one could do that again in humans.

The next paper was selected by us, but the author is here in the room. We might as well. This is still on Question 2. How can I understand what is happening in autism? It is Infants' Observation of Tool-Use Events Over the First Year of Life. Kevin Pelphrey was an author on it. Do you have anything to say? You can brag. It is okay.

DR. PELPHREY: Only that I did not submit this one. What I would want to highlight is actually the first author. Klaus Libertus was a young person who was working in my lab at Duke University. We actually have another young person, Donna Werling, who worked in my lab at Duke here today as well and who will give a talk later.

But Klaus was also funded by Alison Singer's group for a fellowship as a postdoc. He is now becoming an independent faculty member at the University of Pittsburgh. After finishing up all

of that work, he finally published his honors thesis, which is this paper.

But the science of it was simply using eye tracking to understand how infants - what they know about other people's intentions and efforts to utilize tools and how that can be revealed by looking at their eye movements and whether or not their eye movements anticipate a direction.

DR. GORDON: This is similar to the previous study in trying to really understand behavior. In this case though it sounds like it is used for prediction really and potentially I suppose for diagnosis. That is another way of now trying to get at how do we diagnose children earlier.

The next paper also has an authorship of the member of the committee and it is again about functional connectivity, this idea of measuring activity over time and how it is changing together and how different brain regions are talking to each other. David, I gathered that you contributed to this paper and if you want to say anything

briefly about it. You can speak for a brief time about your small contribution.

DR. AMARAL: I will just say a couple of words. This was a study where we looked at functional connectivity in children that are having an MRI at night while they are sleeping. We are looking at how brain areas are co-active. And what we found - Mark Shen was a graduate student in my lab at the time. What we found was that connections between the amygdala and parts of the frontal lobe that are associated with social function were weaker in these kids and actually was highly correlated with their autism severity. And then when Mark actually initially showed this, we said does this happen all over the brain. He looked at the functional networks starting in the visual cortex. It turns out that there were some differences in the visual cortex networks as well, but not at all associated with autism severity, but with sensory mode disturbances in kids. There was appropriate

association between the functional disconnectivity in these two different systems.

DR. GORDON: I would say it is another example of how we can take the technologies that we have and really do nice work at trying to get into the brain in patients with autism.

Moving on to Question 3 now. There were a number of studies, one, two, three proposed by Ruth Etzel.

((Crosstalk))

DR. ETZEL: I will tell you a little tiny bit about each one, but I do not actually have them with me today. The first one comes from a very good high powered epidemiologic institute in Barcelona, Spain. They have been following a cohort from the prenatal time and looking at seafood consumption in a number of other environmental exposures. The results after looking at the kids - I believe it was under the age of 5, suggests some protection from autism spectrum traits by those who consumed large fatty fish



during pregnancy. I do not have any more details now. I am sorry about that.

The second one is a consensus study that many of you have probably seen. It was put out by people from your shop, David, Irva Hertz-Picciotto as well as a lot of collaborators including the Child Neurology Society, Endocrine Society, International Neurotoxicology Association, International Society for Children's Health and the Environment, International Society for Environmental Epidemiology, National Council of Asian Pacific Islander Physicians, National Hispanic Medical Association, and National Medical Association. It's called Project TENDR. I think we have talked about this before. It is essentially an effort to pull together all the information about select neurotoxins and their effect on child outcomes. This has been brought to EPA and many other agencies for us to use in consideration of rulemaking.

Finally, the last one is Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms from the International Journal of Epidemiology, which highlights a relationship that may or may not be causal, but something for us to consider when we think about prevention.

DR. GORDON: Thank you very much, Ruth. For Question 4, NIMH again submitted three papers. The first is on the effects of specific interventions. Actually, it was a collection of interventions and showing some preliminary findings of utility. The treatment, which I have to admit not knowing much about, used was arrhythmic-based intervention, focusing on whole body imitation, coupled with interpersonal synchrony-based activities. The finding was that they may enhance social attention in young children with ASD.

David, do you have something to add to that?

DR. AMARAL: The only thing I would like to add is that I have nothing negative to say about this

paper or positive. Even in the paper itself, it says it is a very preliminary finding.

I think, as a committee, when we highlight some of these papers, we have to be particularly cautious about treatment-oriented papers because I think people are looking for new modalities. I would say that in the case of treatments, we probably want a randomized clinical trial. But we also want a replication of that before we highlight a paper as a principle.

DR. GORDON: Thank you, David. I think that principle applies to the other two papers that we highlighted as well. One, again with a series of interventions that were actually combined and studied individually, suggesting that the combination of these three interventions led to "the greatest gains in spontaneous communication utterances" and joint attention among minimally verbal children with ASD. I suppose one of the reasons why we wanted to highlight this is because this is a look at a more severe population, more

severe sample and trying to come up with ways to intervene early with them. Again, a small study. N equals 61 in this case, which might seem like a large study, but in reality, it is small. But comparing among different interventions found that the combination was more efficacious.

Then the final study - it was on the previous slide. It was looking at social network analysis of children with autism spectrum disorder, looking at that relationship to predictors of how well they deal with particular classroom environments.

And really what we wanted to highlight with this study is the social network analysis part. The social network analysis of course is gaining increasing visibility primarily because of social media and how easy it is to do social network analysis across very large groups of people when you have electronic means of doing it. This is slightly different in looking at the social network of analysis of children through their behavior, which is more challenging, but

nonetheless using similar techniques. We might be able to get at quantitative measures of behavior that might be useful, which would be nice.

No articles nominated for Questions 5, 6, and 7.

MS. SINGER: I wanted to raise a question about the acetaminophen study on the fish study. Often when we call out those studies, we see immediate behavioral changes by stakeholders. What was the size of the N and how big of an effect were there? What was really the hypothesized underlying biological mechanism by which eating fatty fish was preventative? Those are things that we are going to get questions about and women are going to start to overconsume fish because they think it will help their children and maybe not take acetaminophen when it is called for. We saw that with the SSRI studies. If you could just talk about that.

DR. ETZEL: I do not have the studies with me. My staff accumulated these, but I doubt that there

could be any harm to women over consuming fish because the large fatty fish we generally think of as being pretty healthful.

I will talk to my staff and get back with you.

MS. SINGER: Normally, we tell women not to over consume large fatty fish. This is a change.

DR. ETZEL: Just a minute. We are not calling for people to make changes from these studies. We are pointing out these studies because they provide interesting hypotheses that need to be explored further.

DR. KOROSHETZ: This paper on the fish, it was very interesting in that the effect sizes on intelligence and in general population was quite large. The effect size on autism features was very small. I am not sure of its relevance for autism, but it was actually interesting in terms of outcomes on intelligence scales like memory and things like that in the general population. They did control for the mercury levels. I am not sure exactly how they did that, but they did control

for mercury. But actually the improved intelligence function in the kids actually went up the higher mercury level in the cord blood. That was separate from the autism.

And there is lots of biology in terms of what is in fatty fish that might be helpful. And actually the fatty fish were more - people who ate fatty fish did better than the people who ate non-fatty fish. That is really where it stands right now.

DR. GORDON: Thank you, Walter, for clarifying more about the study. I am sorry, Ruth, if I put you on the spot by asking to comment about them. Alison brings up a really good point. Again, this decision to discuss science advances was made before my presence here. I think it is a good one. I think it is good that we consider because it brings up issues like this. These papers were published. They are accessible to the community more or less depending upon the open publishing rules, but they are accessible to the community.

They are out there. It is really important that we discuss them and think about these things. But how we discuss them and how treat the science events is that we consider I think as an important question that is raised by what you brought up because are we endorsing these studies. No. The bottom of the slides says these slides do not represent decisions of the IACC. Susan actually wanted to do this for the last 10 or 15 minutes, which is now a good time to transition.

These are science advances that some of us happened to pick out that we thought were interesting or compelling or maybe even because they might be controversial. How do we, as a committee, want to deal with them? I will let Susan take over for that discussion.

DR. DANIELS: We will transition. I just want to talk with you a little bit about the process. I am always talking about process with you. I want to backtrack a little bit because we made a decision back in January to change our process and



I wanted to check in with you and see how you think this is working for you. You had asked for the OARC to begin collecting advances from you on a quarterly basis. We have been sending out data calls to you every quarter, asking you to submit nominations for the summary of advances whereas before we used to just do it in January. We would ask you for a big download of everything that you thought was important from the previous year in one sitting. I know that there were certain members of the committee who had mentioned that it is kind of hard to do that all at once if you are busy.

We have been taking time out of every committee meeting then to discuss what was nominated. From my perspective and the OARC, there are a few issues that we have run across and some that I would like to just talk about with you here. We have received fairly few nominations in many cases. You probably noticed that there were certain questions for which we did not receive any

nominations. I can say that we have sent out the data call and asked for them. I know that people's time - it is difficult for people to find time for doing this. Is there something different that the OARC can do to help other than sending out the data calls?

DR. AMARAL: As an editor of a journal, I know you have to send them out and probably more often. You have to get to the point where you are annoying people so much. I am must being facetious. Sending them out quarterly is great, but I think maybe monthly or more often.

DR. DANIELS: I think we are doing a quarterly plus a reminder. We are sending out eight a year. Do you want more emails from us about this?

DR. AMARAL: I think it is starting to work. It is going to take a transition. My comment was actually going to be that I do not think it has to be totally based on IACC's suggestions. You can do some as you have been internally as well and

present the combination as you did today. I think that that is good.

But I do think we need to work harder as a committee to be putting some of these in. I think for a while maybe you need to encourage us more.

DR. DANIELS: Staff here, correct me. We are sending them out every month. We are sending two reminders. We are sending those out. But I would encourage you to try to make some nominations. Samantha, do you have a comment here?

DR. CRANE: I was going to say that another way to do it is to make it very memorable how to submit research because sometimes people see a study and they think that is a really great study, but it is not around the same time that the call is being put out. If they wait until you send out the call, they are not going to remember it anymore. They are not going to remember where it was or what they did with it. It would be really good if people had a way to say that is a great study. I am going to send it to highlights at

IACC.HHS.gov. If it is an email that they know and they just send it all along as soon as they see it.

DR. DANIELS: You can actually just send it to me or you could send it to IACC public inquiries. We are taking these monthly data calls, but if it happens and it is a week that we did not send you an email and you see an article, you can just shoot us an email and say there is this great article and can you please put it in. We will do that. It does not have to come on the data call day.

DR. GORDON: You just need to change your name to highlights and then we are okay.

DR. BATTEY: I am just curious. What is your internal process or what has it been in the past for finding these publications? Do you a search like with key words? That is the way I might imagine you might do it. Would it be valuable, for example, to do such a search? Put out maybe the titles and the abstracts electronically of what

you find and then let people sort through that and then come back to you with ones that they find particularly interesting.

DR. DANIELS: The current process is all the nominations are coming from members of the committee. When you hear NIMH, it is because for an institute director, they are getting input from their staff. They are bringing that to the table. When we used to have Dr. Insel give science updates, our program staff here at NIMH and our office submitted things to him to present and he, of course, had his own ideas about things to present. He put together a list. We tried to make sure we were covering.

Currently, OARC is not putting forward anything at this point. But I think that there is just a lot of room for other people on the committee to be putting forward nominations. At the end of the year, we can compile a list of what is there. But what I am concerned about right now is there are a lot of gaps. For example, Questions

5 and 6 are not getting much when I know that there are publications that we have been tracking in our office that are there and the experts here probably know about a lot that is out there.

DR. ROBISON: When I look at the latter questions where we have no nominations, I wonder if there are papers that would be meaningful to the community that are in areas where we do not even look at all, for example, in electrical engineering or computer science. I wonder. Could we address that deficiency by putting a mechanism for the public to nominate advances and then for the public to vote on those advances? If people could post a recommended article and that could go in the government website and then other people, anyone, could vote that article up or down like a community like Reddit works so that then perhaps OARC reads the 50 top papers. If we get 500 nominated, the community self-selects 50 and it would not be an overwhelming burden to read the top ones. That might bring us some really

important papers that we would never otherwise see.

DR. DANIELS: With the task that is set out in the Autism CARES Act or with previous acts as well, it is for the committee to provide a summary of advances to the Congress.

DR. ROBISON: It does not say how we get it, does it?

DR. DANIELS: It is something that is a recommendation of the committee. If you are receiving information from the public and just directly transferring it without any input from the committee, it would not quite be the recommendation of the committee.

DR. ROBISON: I am not suggesting a direct transfer, Susan. What I am suggesting is if we collect these nominations from the public and then you screen them so that we have the top 50 let's say or the top 20 or whatever we decide, those could just as well be put up here for us committee members to read and discuss as any of these

others. They are just as valid as these submissions, aren't they?

DR. DANIELS: Then hypothetically, for example, if we received 100 nominations in the last quarter from people in the public, we could not discuss 100 articles here.

DR. GORDON: I think it is an interesting idea to look into ways that public can nominate papers and maybe contribute to their evaluation. I think we will think about that. That is something we have to think about how we would enact. Larry, you had something you wanted to say.

DR. WEXLER: Thank you. I would just like us to -- I think the discussion about fatty foods were high in mercury are great for you somehow, I think that the unintended consequences of this really need to be taken into consideration. It almost speaks to there are advances and then there is interesting studies. I am wondering if we could bifurcate that. One of the unintended - the kind of genetic and biological things do not affect my



world a whole lot in terms of unintended consequences. But when there are interventions put up there that seem to be with a very small end size and no randomization have gotten good results then frankly school districts end up having to pay for it. If it is endorsed by this body, it takes on a level of endorsement. We have school districts paying for kids swimming with dolphins and going to Mongolia and riding horses. This actually does happen, not to say it is not effective for certain children, but in terms of a general intervention that school districts then have to pay for. There needs to be some science behind it in order to believe that it would have a reasonable effect.

I am just suggesting that we think about bifurcating. This is a randomized control. It is a gold standard study. It really has shown this and this. You can depend on the results within.

DR. GORDON: Can I push you a little bit, Larry, which is to say I think I can completely

agree with you? I bet you most people around the table would agree with that. For example, some of these papers might be premature to say this is a scientific advance that we want to put forth to Congress.

I guess what Susan is really trying to get at is what the mechanisms by which we take these nominations - number one, how do we get more nominations because some of the areas, we are not getting them? We heard about reminders, et cetera.

We would put this out as another reminder. Please send it to us. Send it to Susan as soon as you see something. You can send us this stuff. But now we have to figure it out. If we have this list of however many papers we are going to get by January, how do we decide which ones as a committee that we put forth to Congress? It sounds like, Larry, you would have a lot of concerns about putting forth those treatment interventions that we mentioned to Congress. How do we, as a

committee, decide which ones we want to actually mark as scientific advances?

DR. DANIELS: I can kind of answer a little bit of that. We do have a process. The previous process that was in place, which still is in place for the end of the year is we usually in January we would just collect nominations from the entire committee. Our office would make a giant list and then do a selection process. We would put it out to the committee and say please choose your top 20 in this list and we would probably go through this once or twice to get it down to a list of our top 20. That is what we were planning to do this time, but we have been collecting them throughout the year. However, we have not collected that many during the course of the year. I have a feeling that there will be a large number at the next data call. I just wanted to see if there is anything we can do to even it out a little bit more or if you are happy with how it is going.

MS. SINGER: But the point of changing to the process we have now was to deal with the issue of what gets on that list to be voted on in the first place. I think the purpose of this conversation and of bringing this up at each meeting is to talk about whether some of these studies that were nominated should even be on the list.

DR. DANIELS: As a reminder for our task that we are required to do by Congress, it is submitting top advances as a part of the summary of advances, not just interesting papers. The interesting papers idea is interesting, but I do not know if we have sufficient time. If it is something that is important to the committee to also be collecting a collection of interesting papers, which is just an activity that is on the side. Our congressional mandate is to provide the summary of advances at the end of the year.

DR. AMARAL: I just want to echo what Alison said. I thought what we were going to do was actually sort of have a vote on this list that was

generated every quarter and some would stay on and some would get off.

DR. DANIELS: Right. That is what we are planning to do. In January, you will get the list of everything that has been nominated throughout the year and then you will have a chance to vote. I am a little bit worried right now that we do not have enough in some of the various categories.

DR. AMARAL: (Inaudible)

DR. DANIELS: We could do that in meetings. I do not really want to go through formal voting processes quarterly. It is onerous enough doing it once a year. But if the committee feels, for example, that certain - I have heard in the room that people feel certain studies here are preliminary. We could take them off the list earlier.

DR. ETZEL: What I am hearing is a bit disturbing because I do not believe we have a rigorous process if what we are trying to do is find the advances. It appears that there is a

double standard between basic science and epidemiologic science, which greatly disturbs me. If we are actually going to put forward advances, the process we have of volunteer is simply not adequate and I would chuck it and have a different process.

DR. DANIELS: So what kind of process would you suggest?

DR. ETZEL: We will have to have a peer review group with epidemiologists and biostatisticians and advanced scientists and actually do a rigorous job. We cannot let this committee just volunteer articles.

DR. DANIELS: Yet the responsibility given to the committee by Congress is for the committee to make these decisions or to provide the recommendations. The committee could convene working groups with experts like what we are doing for the strategic plan, but again that would be a very complicated process.

DR. AMARAL: I did not want to make things complicated. I want to encourage my colleagues on the committee to actually nominate more articles. Everybody take a pledge of at least one article in the next couple of weeks. The process before was not rigorous either. It was rushed. I agree with you. We might want to refine the process. But we need more ammunition. We need more substance to evaluate. What we can do is nominate more articles. I am sure there are more articles out there in all of our areas.

DR. ETZEL: What we have to do I think is if we are nominating articles just because somebody thinks they are interesting or important, we would need to have a peer review with epidemiologic and etiological scrutiny of every article.

MS. SINGER: I think, Ruth, the point that you are raising is one that was raised by Louis Reichardt about a year ago, when we were talking about changing the process. I think at that time the points that were raised was that this is not a

scientific journal. This is not a scientific committee. This is a committee comprised of scientists and stakeholders and members of the public and that the audience for the summary of advances was not scientists. It's Congress and the stakeholder community. The process did not need to rise to the level of peer review.

DR. DANIELS: Josie I think had a comment, sorry.

DR. BRIGGS: This is a good discussion of a complex topic. There are rigorous evidence-based medicine processes for recommendations for care. That is absolutely not what you have been asked by Congress to do. Perhaps some of the complexities can be addressed by making it very unambiguous that this committee has selected these papers as important research advances and research advances that go through a number of additional steps before they become recommendations for care.

DR. DANIELS: Yes, that's right. Bruce.



DR. CUTHBERT: Also, I think there is an issue of how high a bar we set. If you will remember that last year we got into this discussion because there was one paper that was nominated and people came back and said but the facts in this paper have actually been shown to be not true. The paper has really been essentially debunked. Maybe that is too strong. We need to avoid that.

I think this process now is helping us avoid that, but whether we want to start teasing apart studies. Did they have the right controls for the mercury or not? Maybe we are setting the bar too high. Ruth's point is well taken, but again also is Susan's that we perhaps do not have the time and resources to do a really thorough peer review. And what we really doing is saying this is interesting and there are no major flaws in this paper and it may be promising. We have to decide on a bar.

DR. GORDON: I am going to interrupt the discussion a little bit because I feel like there

are two issues I want to highlight. One is what are we really trying to propose as research advances. And the other is how do we vet them in a fair way that doesn't bias against compelling clinical studies. Am I right, Ruth? I think that is what you were trying to get at there.

DR. ETZEL: What I am getting is methodological savvy and how we are vetting each of these papers. Right now, I do not think it is being done adequately.

DR. GORDON: I am sorry, John. I want to try to move this on. We can either keep doing what we are doing, but take into account the issues that several people around the table raised about concerns with advancing specific papers and then that will go into the vote obviously in January as to whether to propose it. Or we can adopt a methodology that will be more rigorous. I say this as a bifurcation.

I think we should actually decide that now. I think we should decide between whether we want to

do something more rigorous or whether we do something that is more akin to what we have been doing, but knowing that we need more nominations and that we might carefully consider things that have direct treatment implications before we stamp our advancement on it, regardless of the fact that we do not have a rigorous method to use it.

I would actually like to have a motion about Ruth's proposal that we make it more rigorous and see how much enthusiasm there is in the room for doing that. I do not think we need to belabor the point much longer.

MR. ROBISON: (Inaudible.)

DR. BATTEY: I will put forward that motion that nothing be proposed as a science advance endorsed by this committee that does not stand the test of scientific rigor.

DR. GORDON: And that we would adopt some more rigorous approach to decide that?

DR. BATTEY: Yes.

DR. GORDON: Okay. Akin to what Ruth said with regard to a methodological review. So moved. Is there a second? We have a second. We have a motion on the table to provide for more a rigorous methodological review of any paper that we want to put forward as scientific advance. Raise your hand if you agree with the motion. I see three hands. Raise your hand if you disagree with the motion. I see more than three. Abstentions? The motion does not carry.

We are going to continue with the current plan for now. We can certainly revisit this at another time. Thank you. I appreciate that. Do you have anything to close on?

DR. DANIELS: Thank you. I think that covered what we needed to cover in this session here. We can move on.

DR. GORDON: Okay, so we are going to now have a break until 2:45, which gives us about ten minutes. And then we are going to have a panel presentation on autism in women and girls at 2:45.

I will see you all back here in the end. I am sorry if I had to cut off discussion there, but we want to keep moving.

(Whereupon, the Subcommittee members took a brief break starting at 2:00 p.m., and reconvened at 2:15 p.m.)

DR. GORDON: Today, we are very pleased to have a panel on another subject of interest that the committee has expressed interest in before and specifically looking at autism in women and girls. The panel was pulled together by Kevin Pelphrey, one of our members, who is the Carbonell Family Professor in Autism and Neurodevelopmental Disorders in the Departments of Pharmacology, Physiology and Pediatrics as well director of the Autism and Neurodevelopmental Disorders Institute at George Washington here in DC.

The panel consists of Dr. Pelphrey as well as Dr. Somer Bishop, who is an assistant professor in psychiatry at my alma mater, USCF, as well as Ms. Alison Singer, a member of IACC and the president

of the Autism Science Foundation and Dr. Donna Werling, another UCSF postdoc at UCSF. Kevin, take it away.

DR. PELPHREY: I am just going to briefly say a couple of words and then we will get started with the presentation so that we stay on time. For those watching out of the room, we are going to switch up the order just a little bit and have me, Somer, then Donna and then me and then Alison Singer.

Thank you so much for letting us have this panel today and talk about this. This is, of course, my profound restricted and repetitive interest. About four years ago, we were funded to run an autism network that is recruiting a very large number of girls and boys with autism. Those boys and girls are now transitioning through adolescence and will soon be young adult men and women with and without autism as well as unaffected siblings. This is a topic that has become a very hot area.

I was interviewed by Sports Illustrated. My mother and father were so proud that I finally got into Sports Illustrated although not for my soccer record, but rather for studying autism in girls. It is being covered today. There were five or six articles floating around via the AP about this. Something that is very important both in terms of writing the orphan status of girls with autism and also seeing how we can better help facilitate the lives of girls and women living with autism. But what we are finding and what you will hear today is some very important science that allows us to begin to understand how girls might inform our understanding of both boys and girls and fundamental aspects of autism.

With that, I will introduce Somer.

DR. BISHOP: Thank you so much for having me. I am a clinical psychologist and I am going to be talking about phenotypic differences between males and females with ASD. Particularly I am going to be focused mostly on the state of the current

knowledge and some discrepant findings with respect to phenotype and some of the methodological limitations that I think underlie those discrepancies.

Following my talk, you will probably feel confused and a bit despondent. But the good news is that I have three people following me who are going to make you feel hopeful for the future because they are going to talk about all the things that we are doing to hopefully remedy the gaps in knowledge like Kevin just alluded to. Historically, this is not a new topic of interest.

It has definitely gained a lot of attention recently and very positive attention in terms of the quality of science that is now being devoted to it. But historically I think the reason for the interest is that there have been more males diagnosed with ASD than females. This is the most consistent, I would argue, finding in all of autism research despite lots of epidemiological



changes or changes in epidemiological trends. This preponderance of males remains.

We see widely varying ratios across different samples. I think the baby sibs studies are a good example of how the sex ratio in female siblings, male and female siblings diagnosed with autism has been somewhat less than reported before. But still most studies converge around three or four or five to one boy for every girl.

Relative to the overall sex ratio in ASD, another consistent finding is that females tend to be overrepresented at the lower end of the IQ continuum and underrepresented at the higher end. There are probably a lot of sampling issues that contribute to this.

But we find this both in epidemiological studies like the ADDM Network were across states. You see the proportion of females to males at the lower end of the IQ spectrum quite different than at the higher end. And then also in large clinically ascertained and research ascertained

cohorts like the Simons Simplex Collection, which Donna will talk about where the entire IQ distribution has shifted downwards for females with ASD. Although pretty much both sexes span the whole range in general the mean IQs of females in our ascertained samples thus far have been lower.

As I mentioned too, another consistency just in the research on sex differences has been this longstanding interest in examining differences between boys and girls. But when it comes to phenotype and trying to see if there really is something different about the presentation of ASD in girls versus boys, we have findings that are wildly discrepant.

In the beginning, people consistently reported that females with ASD were more severely affected than males. A lot of that is probably due to the IQ finding that I just mentioned. But then we have everything from similar levels of ASD symptoms to now more recently, a number of researchers are coming out suggesting that the social

communication impairments in females present as less obvious or less severe particularly in adolescents and adulthood and especially in females with higher cognitive and language abilities.

It is also been reported that girls with ASD have fewer behavior problems in general so non-ASD specific behavior problems. That is important. I will come back to that later because that can also affect measurement and ascertainment.

Restricted and repetitive behavior findings have been a little bit more consistent. In general, whether you are looking at a parent report or direct observation, females tend to exhibit fewer restricted and repetitive behaviors. It seems particularly true with restricted interest.

Circumscribed interest seem to be either less commonly reported all together or the focus of the interest is just less traditionally thought of as being a restricted interest in females.

But then in other studies including one recently where it was a community-based sample of toddlers, there were no differences reported in restricted and repetitive behaviors. Still discrepancies in findings despite more consistency in this area as compared to social communication.

But despite this, I think clinicians are interested in finding differences because they feel that they see them. And parents wonder about differences between their girls and their boys with ASD also. We see this explosion of literature in the behavioral arena and elsewhere trying to find if indeed there are important phenotypic differences that we should be attending to.

And the particular worry when it comes to screening and diagnosis is that if we are missing what is really salient about the female phenotype in ASD that our measures may not be picking up those girls who are in need of service. These are submitted data. They are not yet published. This is a group of clinicians that we

surveyed, very experienced clinicians. More than 100 clinicians who we knew or who our friends knew and they had on average more than ten years of experience and saw a lot of people for diagnostic assessments every month including a mean of three females per month, which is quite a lot of females to see in a diagnostic assessment setting.

We asked them if they observed differences in core symptoms so social communication and research and repetitive behaviors or associated symptoms, which could include things like medical and psychiatric comorbidities.

Clinicians did report seeing a difference between the girls and boys in their practice. It seemed that the difference was most apparent to them in school age and adolescents. I think this in adulthood, this non-difference, likely reflects the few number of adults that clinicians are seeing and maybe not so much the lack of differences because we definitely hear this from other clinicians. This is a plea I should say for

longitudinal research that I will keep back to because these are all based on just cross sectional observations.

UNKNOWN SPEAKER: (Inaudible.) - indicates statistical -

DR. BISHOP: They are. Basically, significantly more differences were reported the observed during school age and adolescents as compared to early childhood and adulthood.

And then if you ask people about the direction of the observed differences, when it comes to social communication, clinicians were generally reporting that when there were differences that they saw less severe impairments in females as compared to males, not so much in terms of relationships, but with social reciprocity and nonverbal communication. This is just based on perceptions again.

And then with restricted and repetitive behaviors, again, the percentage of clinicians reporting less severe impairments was second in

any of these cases only to then reporting no difference in impairments. In general, when you ask clinicians do you see differences between girls and boys, the tendency is to report them as either seeing them the same or seeing the girls as having less severe difficulty, which is in contrast to the historical literature, but more in keeping with people's concerns now that girls do in fact present differently and perhaps in a less severe way than boys.

A big question just given that we have clinician - we have one off anecdotal reports and then accumulating evidence when you survey large numbers of clinicians and self-advocates and parents of these observations of differences. Why are we having such a hard time finding it in the data? We are lucky enough to have access to various large and relatively large data sets of phenotypic information. They have just yielded very inconsistent findings when it comes to sex

differences in the core autism symptoms or other things.

There are likely a number of issues that underlie this mismatch. I am going to focus on three that all go together. And that is problems with our measurement, problems with sampling and then general methodological issues that some of our panelists are going to tell you about how to address.

One of the common concerns right now is that our existing measures may lack sensitivity for detecting some females with ASD precisely because these instruments were developed largely based on male samples. When you have an underrepresentation of girls or any group - in autism, we have the same sort of issues with minimally verbal folks who are underrepresented in a lot of measured development efforts because thankfully there are few of them now. Our diagnostic constructs, which are in turn reflected on measures, could be sex biased. This is one cause for concern.



The other problem is that scores on autism symptom measures are affected by other individual-level factors like IQ and behavior problems, which can make interpreting the scores more complicated. I want to give you an example of what this looks like. It actually looks the same if we use IQ instead of emotional behavioral problems.

But over here is a group of children with either non-ASD diagnoses like ADHD or intellectual disability or anxiety disorders and a group of kids with ASD who have low parent-rated behavior problems on the CBCL, which is a measure of general child behavior.

Here is a group over here that had parent-rated behavior problems in the clinical range. This is a parent interview of autism symptoms. And what you see is that even though you see the separation within groups between the kids who do not have autism and the kids who do have autism on a measure of autism symptoms, the scores are shifted upwards for kids who have more behavior

problems. There is less of a separation then between the ASD kids with low behavior problems and the non-ASD kids with high behavior problems. This causes an issue then when we are looking at scores from autism symptom measures without taking into account other factors and it would be same thing if we instead of looking at behavior problems, we looked at IQ. We know that children with low IQ have autism symptom scores that are higher than children with higher IQ regardless of whether they have autism and the same is true if you have behavior problems. You have higher autism symptom scores regardless of whether you have autism.

This is an even more extreme example here. This is another parent report measure. You can see that we get no separation between children with ASD who have low parent-rated behavior problems and children without ASD so children with other diagnoses who have high parent-rated behavior problems.

Back to the issue of ascertainment and in thinking about girls with ASD who may have fewer behavior problems. If we rely too much on standardized screening or diagnostic measures without taking into account these other individual factors that we know matter, it could skew samples, for example, towards girls with lower IQ who are more likely to meet cutoffs on standardized instruments and/or more behavior problems. The same is true of boys of course, but this is just one example of why we need to think about how these other individual-level factors play into scores on autism symptom measures that may be used in inclusion criteria.

Here is the opposite story. It is talking about referral bias. This is something that we saw in a group of preschoolers. When you plot the preschoolers who are identified, these are 2, 3, and 4 year olds with ASD versus those with non-ASD. The kids that we have coming to the research

study with ASD diagnoses who are girls are the kids with the highest level of behavior problems.

That is likely not a coincidence. It is probably why they got identified at 2, 3, and 4 is because they have these other behavior problems that are causing issues. They get referred and picked up with ASD. But if you are sitting down here and are very cooperative or just really do not have especially externalizing behavior problems, it is the same reason that girls with ADHD often do not get picked up. If they have an attentive type in particular, they do not get picked up until a lot later.

Another sampling issue besides the measurement issues that can affect general ascertainment into research or clinical samples. Most of the studies that I showed you where we are reporting conflicting results are based on quite small clinical samples. Some of the older studies, but even some of the newer, we are talking about 20 girls versus 20 boys. That is just not enough to

draw really firm conclusions. But it is also not enough to power our study to properly account for all the other individual differences that matter. Then we are really left trying to figure out what is a sex difference and what is a difference that could be explained by these other phenotypic variables that affect measurement.

One way to deal with that is to try to stratify our samples to figure out how we can look for fine-grained differences in particular groups of kids or adolescents or adults. These are data that come from a very large clinical database. And what I did was I just selected the school age and adolescent children who were verbally fluent. They are talking in complex sentences. They have non-verbal IQs over 80. We end up in this clinical database. We end up with 396 males and 85 females so not enormous, but not egregiously small. Still we need bigger. And there are about nine on average and they are pretty closely matched in IQ.

Although these girls have a significantly higher verbal IQ than the boys.

And what happens if you look at their scores on the autism diagnostic observation schedule, which is a direct observation instrument that is clinician rated. There should be a star. This is actually significant. It does not look at because the vast majority of both groups meet cutoffs for ASD. These are children who all received a clinical diagnosis of ASD. But whereas we only miss 5 percent of the boys, we miss 14 percent of the girls. We know that we missed them because they still got a critical diagnosis in the end so they were missed only in the sense on this measure. They did not meet cutoffs. But in the context of a comprehensive diagnostic assessment, we have room for our measures to make mistakes because clinicians should be basing their diagnosis on all the information that they obtained. But if we had made really strict rules like you can only be in our study if you meet

cutoffs, we would have missed this 15 percent of girls and this 5 percent of boys. We have to think about that when we are setting inclusion criteria for studies like this Simons or other large data gathering efforts.

Interestingly, when you look at the continuous scores and you control for verbal IQ and age, sex still significantly predicted the overall severity score, but that was driven by the scores in the repetitive behavior domain. Consistent with what other people are reporting, there are not differences on this measure that we can find in this particular sample on total social affect scores, but restricted and repetitive behavior domain scores did differ by sex controlling for verbal IQ and age.

But as I mentioned, we get to learn this because in this sample even females with lower scores including those who scored below instrument cutoffs still received best estimate clinical diagnoses of ASD.

I think that what this study highlights is that detecting meaningful differences relies on identification of appropriate comparison groups. When you lump all of the girls in the whole clinical database, which has about 4000 kids together and you just compare based on sex, you find zero differences. But when you stratify by in this case age and verbal ability and IQ, you end up finding some differences that do appear to be driven by sex.

In all of this research, we need to think about who is a relevant control. In the example that I just gave you, it is boys who are also coming for diagnostic assessment who are similar on other certain phenotypic variables to the females and we are giving them the same measure. But I think in a lot of situations, the relevant control might in fact be a typically developing female or an age match typically developing female or somebody with a different disorder who does not have ASD who is a female or in the context of the



Sisters Project that you will hear about in a little bit, it might be an unaffected sister or an unaffected brother. But we have to really think about who is our control, to whom are we comparing these kids or adults and why.

I think also we all agree at this table that there is a clear need for longitudinal data. I want to just give one example of why I think this is so important. This is work by Julie. She has looked at employment. She has sex differences in employment. In this paper, they found that competitive employment at the first point after high school exit did not differ by sex. But in fact, if you look at stability over time, the females had less stability. The men were more consistently employed than the females who showed a lot more change. The hypothesis is that they may not be - men and women may not differ in their ability to secure employment initially or post-secondary education, but maintaining that over

time is difficult. We only see that if we look at them over time.

The same thing with the discussion this morning with mortality in autism. Obviously, we only see who ends up living and who does not if we follow the same people over time. There is some research to suggest that there may be a gender gap in life expectancy in autism that is opposite of what it is in the general population where women with autism may be at increased risk for dying earlier.

Here is just another sample from Julie again where you do not see the difference at the first time point between these men and women. All of these people have intellectual disability or most of them do. But over time, the vocational index score for the women declines more rapidly than that of the men.

I think another methodological issue that we will also hear about is this should say need to move beyond existing behavioral measures. I feel a

little bit like we are beating our heads against the wall, looking at the same measures, looking for the sex differences in the same measures. They might just not be there not because they are not there, but because the measures are not picking them up. We need to be able to incorporate different measurement strategies and whether that means different behavioral measurement strategies that is great, but also combining with other sorts of neurobiological measurement strategies and experimental measurement strategies to get at this question about what might be different and how men and women present or boys and girls present and why that matters.

In conclusion, there do appear to be at least subtle sex differences in phenotype within certain groups. But the ascertainment and measurement issues that I talked about present major challenges to figuring out what is what. It makes the data that we have very difficult to interpret. I think that is frustrating for people especially

when you feel like there is something there that we are missing.

But in the end, sex is clearly one stratification variable worth considering, but it needs to be considered in the context of other behavioral and biological variables that we know are important. I think the conversation today about whether autism sometimes trumps these other contextual or cultural variables - sex may be in that category some of the time, but we know that men and women and boys and girls in the general population differ. Why wouldn't we expect there to be some differences there even if it is just in terms of life course things?

There is an article today about how it is going to take 140 years for women to catch up with the wage gap. These are real issues that face all of us. Attending to them as one important thing in autism I think is also important.

Thank you for your attention and to my collaborators on these projects and especially the

families and clinicians and researchers who collected the data.

(Applause.)

DR. PELPHREY: We will take two questions and then we will have time for questions at the end.

DR. CRANE: I was going to ask if the study tracked intersectional differences in race or culture as well as gender.

DR. BOSTON: In the cross-sectional data or the longitudinal data? Historically and in this sample as well, we have a big white problem in autism research and high SES problem at least in clinically ascertained samples. This data that I presented is no exception to that. I did not look at that in this as an additional factor.

Generally, it does not come out just because we have so few, but that does not mean that it is not there. But I know other people like David and Dan Geschwind and others are trying to help get us better samples.

DR. PELPHREY: Next up we have Donna Werling, who as we mentioned earlier, is a postdoc now in the labs of Steven Sanders and Matt State. You heard me claim her earlier and you are about to see why I was so keen to claim her as a success for my lab. But she is also proof that if you go work with Dan Geschwind and Matt State that working with me for a semester will not hurt you permanently. You are in for a treat.

DR. DONNA WIRLING: Thank you very much for that all too kind introduction and thank you all for being here for tuning in today and to the meeting organizers for inviting me to participate in this panel. I am excited to be here today to talk to you all about the role of genetics and sex-differential biology in risk for autism. On the front half of this presentation, I will be going over a few aspects of the current state of knowledge about genetics and sex and autism and then in the back half of the presentation, I will

be presenting some of our own work trying to address this question.

As we are all aware, autism prevalence according to the rates of diagnoses is sex biased. I put this plot up here to demonstrate that ASD is particularly noteworthy in this regard. This plot is showing a number of different human conditions and diseases and their sex ratio or their sex-biased prevalence. Anything above the horizontal line is a male-biased condition. Anything below is a female-biased condition. And the X-axis here is age of onset across development.

ASD is over here. It is a particularly male-biased condition, especially as compared to other neuropsychiatric conditions like depression or schizophrenia. You can see really sex-biased things include typically the reproductive organs so prostate, pregnancy-related conditions and so on.

This bias in ASD's prevalence has been the case since autism was first described as a

disorder. I always like to make this point that of the 11 cases originally described by Leo Kanner's 1943 publication, eight of them were male. And this degree of male bias has been consistent across time and across countries as Somer alluded to. And this plot now is showing you again male-to-female ratios in a number of studies, but this time for ASD only in a number of different countries across different times. You can see that every single one of these points is to the right of that equivalence line. Although the degree of male bias tends to vary by studies sometimes quite widely, every single time one of these studies are done we find a greater number of males than females with ASD diagnosis.

Why should we be interested in studying this question from a biological perspective? Clearly, sex appears to be a potent modulator of ASD risk. And what I mean by that is if you are male, your chances of having an ASD diagnosis are four times higher approximately than if you are a female.



Now if this difference is based in biology, if we were to understand the biological mechanisms by which sex modulates this risk then this might lead us to some particularly effective and particularly well-tolerated treatments. And along the way, we might also make some particularly novel or key insights about the fundamental biology of ASD, which of course in turn could again lead us to treatments.

Now one model that is frequently invoked to account for the sex bias in prevalence is something we kind of in shorthand refer to the female protective model, which really is a liability model for ASD. Under the liability model, we assume that liability or risk for autism is quantitative, meaning if we could evaluate every risk factor in an individual, we could give it a score, a numeric score. We have seen that this liability is distributed in the population perhaps following a normal distribution, as is shown here.

Then there is a threshold or a minimum level of liability beyond which individuals present with a diagnosable phenotype of ASD. Of course, given the sex bias in autism prevalence, this model is better thought of a multiple threshold by ability model where males and females have different thresholds or different minimum levels of liability beyond which they present with a diagnosed simple phenotype.

One way that we can try to evaluate whether this model accurately describes what we see in the population is to make predictions from the model and then test them. Some of the most key predictions from the model come from zooming in on this part of the curve here, which is showing individuals who have diagnoses of ASD. I will remind you that this axis here is a quantitative one. As you move to the right, liability scores if you could assign a score, go up. And one key prediction here is that among individuals who are

diagnosed with ASD, females should have greater liability than males do on average.

We can test this by looking at specific aspects of liability and of course the aspect of ASD liability that we, as a field, understand the best today is genetic liability for ASD. We can look to see whether females who have ASD diagnoses carry greater genetic risk than males who have ASD diagnoses.

What do I mean by greater risk in practical terms? This could look like in females and maybe females have a greater number of genetic risk variance than males do. Perhaps genetic variance in females is larger or more severe as compared to those in males. We can look for these.

One way this has been done particularly successfully is using the Simons Simplex Collection to look for what are called de novo genetic mutations. These are variants that are not inherited from your mom or dad, but that occur brand new in a sperm or egg cell. They are unique

to each individual. Based on looking for these types of mutations, we do see a pattern consistent with this prediction that females should have greater genetic risk than males do.

When we look at first copy number of variants, these are a type of genetic variant where entire sections of chromosomes are deleted or duplicated. We find that a greater proportion of females with ASD diagnoses carry this type of severe mutation than the males do. When we look at what are called indels, which is short for insertion or deletion when just a handful of base pairs are inserted in the genome are removed, we again see a similar pattern or a greater affection of diagnosed females have this type of variant as compared to the males. And when we look at single nucleotide variant, which is when of course a single nucleotide is changed in these individuals, we again see the same pattern where a greater proportion of females in the SSC carry this type of severe deleterious mutation as compared to the

males. This is encouraging. This suggests we are headed in the right direction with this model perhaps.

And another way that we can evaluate the same prediction is to look not just at the effects or the existence of de novo mutations that occur brand new, but to also look at the effects of genetic variants that are inherited from your parents and that are shared with siblings and family members. One key prediction from this model is that if females who have ASD diagnoses have greater genetic liability then this higher liability should be shared with their siblings, for example. This study was done - the one that I will talk about here was led by Lisa Robinson and Angelica Ronald. The way that they did this study was to take two population cohorts of children from the UK and Sweden, I believe. And these were cohorts that were ascertained for ASD status, just for the years in which the children were born. And among other measures they gave these children a

test of autism trait scores. They identified the males and the females that scored in the top 5 percent of this measure and they considered those individuals as probands, whether or not they actually had a recorded diagnosis. They are looking for the high scores.

And then they compared. They looked at autism traits in the siblings of females, in the siblings of males who are high scorers and they found exactly what we would predict, which is that the siblings of females with high scores on this measure had higher scores of autism traits as compared to the siblings of males shown in red here.

These observations together suggest that what I have laid out here as the female protective effect model. They support this model and suggest that it may be a valid way of thinking about the biology behind sex differences in ASD. The next logical research question would be to try to figure out what are the mechanisms that protect

females. What is responsible for this female protective effect?

Before I get to addressing that question directly, I would like to bring up this other question that has been brought up today, which is this big question of whether we are missing females who are affected with ASD and who are not being diagnosed. How do these misdiagnoses affect the individual's ascertainment into study samples? How does that affect the conclusions we can draw from genetic studies, from biological studies and so on? Certainly, that is happening to some degree.

But I would like to make a point that again refers to this female protective effect model and to look at this part of the distribution here. Under the model, we assume that there is some range or some level of liability that is sufficient to cause ASD in males, but not in females. This difference, I would argue, could be a quantitative one or a qualitative one. Under a

quantitative model, our interpretation of this difference, we could conclude that females are truly protected. Females with liability in this range may actually have protective biology and present with neurotypical phenotype and so on. It may also be possible, these are not mutually exclusive, that females of liability in this range simply present their symptoms differently than males do. And this different presentation allows them to escape diagnosis.

But whether this difference is a quantitative one or a qualitative one, the fact that there is such a difference I think is valid and interesting and worth understanding from a biological perspective. For the remainder of this talk, I will be focusing on this hypothesis here, which is that likely sex differential in biology contributes to male and female differences in ASD risk and/or symptom presentation. Therefore, in order to really understand sex differences in ASD either risk or presentation, we really need to



understand sex differences in neurobiology and then see how those relate to ASD.

The approach that we have been using at UCSF to try to address this question or begin to address this question is a gene expression analysis, which is a relatively unbiased way to survey as much of biology as you can in one go and then identify the aspects of that biology that are relevant to your question.

The design of the study is pretty simple. We have two main aims. The first is to identify genes with sex-differential expression levels in the human brain. We are trying to identify genes that produce different amounts of RNA in males and females. And then we would like to characterize the relationship between those sex-differential expressed genes and what we currently know about ASD biology.

We have done a study by taking advantage of the publicly available BrainSpan data set, which is a data set of gene expression data collected

from the post-mortem human brain, a number of different brain regions, and from samples across development from just a few weeks post-conception, up through adulthood. Like I mentioned, we compare gene expression levels in males and females.

Now one of the very first things that we have observed from this analysis is that as it turns out, males and females are far more alike than we are different. This plot here is showing the relative level of sex-differential expression of a number of genes. Each gene is shown as a dot. And the Y-axis is showing the level of statistical significance. You can see that Y chromosome genes are robustly sex-differentially expressed, as you would expect as is XIST, which is an X chromosome gene that performs a female-specific genetic function. But the vast majority of other genes in the genome show much smaller sex differences. I put this figure up here not to say that is it and we could not find anything, end of presentation, but to make the point that the

differences that we are looking for when we compare males and females are very subtle in nature.

With that said, using a permutation approach, we were able to identify several hundred genes and transcripts that show significant differences in expression level between males and females at certain time points in development or in certain brain regions. This plot down here is showing you an example of the raw expression levels of one of these such genes across time. Blue is the male expression and red is the female's expression. You can see that this gene, for example, is highly sexually dimorphic during prenatal development. This is the type of trajectory that we are able to identify by this method.

The next thing that we want to do is to better understand what these genes that we have identified are doing in the brain. One approach that we have taken to do this is to compare these sets of sex differentially expressed genes to gene

sets that mark the function of certain cell types in the brain. This diagram here is showing you the comparison of these sex-differentially expressed genes with sets of genes that mark neuron function. Wherever you see a blank square, that means the comparison was not statistically significant. Wherever you see a blue circle, that means that we observe a depletion or less overlap than we expect by chance between these sex-differentially expressed genes and the gene sets. You can see that there are a number of blue circles on here indicating significant depletions.

But what we really want to see in order to be able to positively interpret what these genes are doing are significant enrichments. Gene sets that overlap to a greater degree that we might expect by chance. And that would be shown in red. As you can see, there is no red up here right now. There were no significant enrichments for neuron-related genes and the sex differentially expressed genes that we identified.

However, when we compared these gene sets to genes that mark the function of other cell types in the brain particularly micro-glia and other glia including astrocytes and dendrocytes as well as endothelial cells. These are connective tissue cells are most typically interpreted as surrounding blood vessels in the brain. We do see significant enrichments. These enrichments were only evident for genes that showed higher expression in males. We are highlighting microglia, other glia, and endothelial cells.

I will skim this slide in the interest of time, but the purpose of this is to show you all that the time points at which we see the most robust sex differential expression of these microglia genes and endothelial genes is during prenatal development.

Now of course this talk is about and this whole meeting is about autism. It is great that we are implicating certain cell types potentially in sexually dimorphic biology, but we also of course

want to relate these findings to ASD. This plot here is showing you a similar analysis to what I just showed you previously, but in a slightly different format. Any of these bars that are going in the negative direction indicate depletions or less overlap than we expect by chance between our sex differentially expressed genes and these ASD gene sets. Any bar that is going in the positive direction is showing significant enrichments or greater overlap than we expect by chance.

You can see that across the board down here for these sets of genes and we find no significant arrangement or depletion. These gene sets include FMRP targets, CHD8 targets. These are two top well-known ASD genes as well as depletions for co-expression modules that were identified in the postmortem ASD brain that are associated with neuronal functions. This is consistent with what I showed from the previous slide.

But when we start to look at co-expression modules or sets of genes that show coordinated

expression levels in the ASD brain so this is from other studies, we do start to see significant enrichments or overlaps with the sex differentially expressed genes. These sets that are called expression modules are involved in microglia or astrocyte function. As you can see here, this overlap is particularly robust and particularly consistent for genes with higher expression in males. We hypothesize here that there is some convergence between male typical and ASD neurobiology.

If we apply this finding back to the female protective effect model, I would like to make the point that because we use that female protective effect name as a shorthand - refer to this model. There tends to be a focus on identifying female protective factors. But in fact there may also be an equally significant role for male differential biology and male-specific risk factors.

We have come up with this little cartoon to illustrate the way that we are thinking about this

based on these data. If this oval here represents all of neurobiology, the vast majority of which is shared between the sexes, but some of which is enriched in females and some of which is enriched in males. And then this purple oval shows the aspects of neurobiology that are impacted by ASD. Perhaps the degree of overlap between ASD neurobiology and male-enriched neurobiology in the typical human brain, perhaps this overlap is greater than that between female neurobiology and ASD neurobiology. It is this greater degree of overlap with male biology that leads to male sensitization. We could talk about the female protective effect model or the male sensitization effect model that are roughly equivalent. Therefore in order to understand ASD sex bias, we can make the case that we really need to characterize this intersection between typical male neurobiology and ASD neurobiology. To summarize, the work we have done I think shows that one way or one approach to begin to



understand the mechanisms involved in sex bias in ASD from a biological perspective is to look for the intersection between ASD neurobiology and sex-differential neurobiology.

Results from this analysis have shown that genes involved in microglial function as well as collagen genes and endothelial cells show higher expression in males at least in this data set and that there is an overlap in genes involving glial function and that they showed dysregulation in the ASD brain from previous studies that I referenced and they show higher expression in males.

Of course, these results are based on the analysis of a single data set. Validation in independent samples is required. We are working on that now.

But I do not have the results to show you today. Looking forward, like I mentioned, we need to validate the findings that we found in additional data sets. There are data sets available, but what we are doing for the most part is repurposing data sets that were generated to

answer different questions. They may not be particularly well powered to address this question of sex differences in biology. There may not be equal numbers in males and females. They are almost certainly not age matched, which is a problem. It would really be crucial to better understand sexually dimorphic neurobiology. To do this we need well-powered foundational data sets to be able to make this comparison.

These data sets could involve data types like I talked about today. Gene expression from RNA sequencing. They could also involve better understanding of sex differential regulatory mechanisms so where do estrogen receptors bind in the genome in the brain. Where do androgen receptors bind in the genome in the brain? Ideally, these data sets would include enough samples to use a two-by-two design so enough males and females and enough cases and controls to be able to distinguish which effects are due to sex and which are due to ASD. But well-powered

comparisons of either type, the horizontal or vertical, would also be very useful.

Of course, ASD is a developmental condition so as many stages of development as we can tackle and understand in detail, the better. Of course, we need to look at different cell types as the results that I have just shown you suggest that different cell types may be involved, different brain regions.

And of course, the last point is that in a perfect world, we will be able to run all these studies in human tissue, but for obvious reasons, human brain tissue is difficult to come by as it should be. Model systems will really be critical for understanding this. And these model systems could include common genetic models such as mouse and also potentially more human-relevant models such as primate. There is a lot of work to be done to better understand this question.

With that, I would like to thank you all for your attention. Thanks, my mentors at UCSF,

Stephan Sanders in that state, as well as Nenad Sestan and the BrainSpan Consortium, who we have been working with on this analysis and of course funding from Simons and the Autism Science Foundation. Thank you.

(Applause.)

DR. GORDON: Can you take a stab at putting together the phenotypic and genotypic data? You have increased risk, increased genetic liability in females and from the phenotype data that is not clear necessarily does look like there might decreased symptomatology.

DR. WIRLING: That is not something that I have spent a whole lot of time thinking about.

DR. BISHOP: I think we are saying the same thing actually. That because females require higher genetic load to manifest the disorder, in the absence of that, they would not surpass that diagnostic threshold. Since the variants that Donna is talking about are rare, we would expect that it would take you more to get over that hump

so to speak into the autism diagnosis. They are converging models.

DR. WIRLING: I think so. The genetic results that I was showing, the comparisons between males and females - we can only make those types of comparisons in the top of the most affected individuals who have these very severe mutations.

As we better understand the full scope of genetic risk of ASD, getting into variants with smaller effect sizes or polygenic risk and so on, I think we will better be able to start comparing males and females who are not at that very tip of the distribution. That might be more informative for some of the differences that we see.

DR. RING: Is that loading based on exome data? Because a lot of the whole genome data that is just emerging suggests that there is loading of de novo mutations in a different manner than what we seen through the lens of an exome.

DR. WIRLING: Between males and females?

DR. RING: Yes.

DR. WIRLING: I am not familiar with that difference. I have not seen those data. We are analyzing some of the whole genome sequencing data and I have not seen results to that effect, but we can chat afterwards.

DR. RING: -- paper that was published last year in the Genomic Medicine paper published this year looking at 200 trios so looking at multiplex families through the whole genome data through the missing project. There is some interesting loading of risk outside the exome that may have gender differences that were not predicted by the exome.

DR. WIRLING: Certainly, we need more samples than 200 families, but it would be interesting to see how that shakes out as we look at the non-coding genome.

DR. PELPHREY: My turn. I am going to try to make up a little bit of time as we go as well. I mentioned earlier that I spent a better portion of the first few years of my career laying out brain systems that support social cognition and

understanding other people. That has turned into a value in terms of understanding autism, which of course features such profound social impairments. That is what we have focused on, by and large.

As we have discovered different components of the brain and in particular, regions of the brain that allow you to understand when you are watching another person versus when you are watching a non-person move, we have found that that very simple perceptual exercise reveals a lot about how the brain is organized and in particular, how it is organized differentially to process things that are socially meaningful versus that which is not. Make that fundamental distinction to start out with and I will talk about biological motion and the shorthand for that. That is the movements of people versus nonbiological motion or scrambled motion. That is the movements of something else. We have done various experiments, something like 20, of these at this point that have laid that out both in terms of typical adults as well as the

developmental trajectory of that from infancy to adulthood. We are even starting to do studies of biological motion perception in fetal imagine now, using another form of biological motion, which is sounds that human beings make versus those that do not. It is really illustrating the point that I hope you will get at the end, which is that basic science, basic cognitive neuroscience in this case can inform the study of autism I think in meaningful ways.

All of that to say, we wanted to get to the point where we would have a biomarker for autism. We spent half of a decade laying that out in different individual imaging studies. We recently published a paper where we looked at an early finding that we had in comparing groups. Most imaging studies compared groups. We cannot really say anything about an individual. In order to have a biomarker, we need something that we will be able to say - something regarding an individual's status. The best way to do that and a way that had



not been done until we did it was to first look at a discovery sample, find something, call your shots, and look at a replication sample. We did that. Not only did we replicate finding an imaging, which is something that is not done very often at all, but we were able to look at the individual level. We were able to draw out exactly what parts of the brain during social perception best differentiate a group with autism that meet gold standard diagnostic criteria versus a group without autism, still not doing the critical thing. Don't let anybody trick you when they present imaging data, which is why autism versus schizophrenia. What differentiates autism versus an ADHD sample? This was an easy thing to do, which was autism versus typical, using functional magnetic resonance imaging.

At first, our results were quite disappointing because we had in this study a fairly large number of girls. When we lumped boys and girls together on machine learning techniques were doing a

horrible job. When we separated them out, it was sort of like the parting of the seas. This works really well for boys. And everything that we have spent the last ten years discovering only applies to boys because we somewhat broke math when we calculated our sensitivity and specificity for girls. The point in fact the social brain almost anti-predicts autism in girls. This was coming out just as we were beginning our network where we were trying to follow up that observation.

I like to present it as though somehow we knew what we were doing, but it was one of those situations where we had a failed experiment and then we decided to break it down according to sex. In my training as a cognitive neuroscientist, my mentor would like to say that they were lies, individual differences and then sex differences. We were only interested in that which was universal. For me, it was a hard knock. But we were just ramping up with this Autism Center of Excellence network that included the

University of Washington, University of California San Francisco, University of Southern California, UCLA, and then Harvard, Yale, and now George Washington University and Children's National Medical Centers, the lead site. We have collected 125 - we set out to collect 125 boys with autism, 75 well-matched typically developing boys, 125 girls with autism, 75 typically developing girls and then critically unaffected siblings.

Another study we had done using this biological motion paradigm had suggested to us that much could be learned by studying these Simons Simplex unaffected siblings, which is important to say because they were given the \$5 million work up to make sure they did not have the broad autism phenotype. We were able for the first time to separate out cause and effect in terms of what is a reflection of having autism for several years brain imaging studies versus what might be an endophenotype for autism. I am going to put

that in your mind and have you hold it for a moment.

The renewals are coming up. I will take this opportunity to say that we have hit our target recruitment in the fourth year or five years in a way of 121 percent. We are well over our recruitment goals particularly when it comes to minority recruitment and different ethnic groups. We have performed I think really well. This is now a national treasure because we have genetics, gene expression and gene structure and incredible phenotypic data because all these sites are leading autism centers.

Comprehensive imaging data and comprehensive EEG data. We are able to look at the integration and you are seeing the fruits of that in the talks that have been presented. And people like Stephan Sanders, Donna, and Somer, have developed as young investigators through this and taken on their first faculty positions. I calculated that we placed eight assistant professors in tenured track

positions over the past four years that worked on this project.

Obviously, we are very interested in this female protective effect. The first thing we went after was to utilize our biological motion paradigm to compare our different groups on biological motion perception. This is a complex slide to tell you essentially two things. First, the social brain is not broken in girls with autism even though they are showing a phenotype of autism and have made it through the ADOS and the ADI as well as expert clinical judgment.

What we have called the social brain in terms of amygdala function, superior temporal sulcus, ventral medial prefrontal cortex, all functioning normally when it comes to processing biological emotion. And in the unaffected girls, there is a strong over performance of that system and over connectivity as there it is compensating for something as well as in those unaffected girls, a tendency to recruit much higher order social

cognition systems when processing low-level biological emotion. I am painting for you a picture of the female protective effect in terms of systems in this case that are functioning normally some hyper functioning in the girls who have a genetic liability for autism, but have avoided it, the unaffected siblings.

And then when we do look at other components of the brain that are involved in processing biological emotion, we actually see increased dysfunction in the girls with autism versus the boys with autism. A complex picture of a simultaneously preserved system, but ancillary systems that are involved in processing biological emotion are more affected in the girls so evidence in two different ways for the female protective effect.

I am often criticized as being - you are that biological emotion guy. That is all you care about. We took another approach to this, which involves resting state data. And resting state

data has really been embraced by psychiatry for good or ill as a fundamentally important methodology. Essentially what you do is just put the person in the magnet and you ask them to keep their eyes closed or to fixate on a cross hair. There is a debate about what is the best way to do that. More or less you get the same answer either way.

It is very challenging with kids. I should have said that these are fairly middle school aged children, at this point when we were doing the study, but we were able to get most of them through the procedure.

And then we utilized a method that allowed us to determine which networks were broken and predicted autism in boys with autism versus typically developing boys and girls with autism versus typically developing girls. This was the important comparison for us to make. Again, no task here. There is no preconceived judgment.

Then we took that data. Imagine that we have these networks by parcellating the brain. We take that data and we look at the - we go to the records and we say of all the imaging studies that have been done that are archived, looking at all these maps in a program that is available online called Neurosynth, you feed it all in what you have found, your map of differences. It tells you what psychological constructs and concepts, what functions underlie or are most correlated with those networks. We did that separately for boys and girls.

And then because everybody loves Wordle, we took those constructs and I am showing you the Wordle for girls. For example, comprehension. That means that we found a network that when fed to this unbiased representative set of studies, a different data set, many thousands of different data sets, it fed back to us. That is probably a network for comprehension. That is probably a network for emotion regulation. I think you get



the point. I am using the size of the font to represent the size of the correlation.

And what I am showing you is that based on resting state data, the networks of brain systems that are tied to the underlying genetics are completely different in girls and boys. There is very little overlap and most of the overlap is in terms of language functioning. But otherwise, the ones that stand out most are what I have been preaching about for many years in boys. Person perception, social perception, this idea of autism is a fundamentally a social motivation disorder, social expertise. That looks to be true in boys, but not in girls where anxiety, emotion regulation, attention meaning. Very different neural systems are implicated. This is about the most unbiased way we can go about doing this in terms of parsing it up because we are not making judgments based on looking at individual tasks that we pick a priori. I am a little uncomfortable with that because I like hypothesis-driven work.

But we wanted to allow the brains of the individuals with autism, male and female, to speak for themselves during resting state and tell us what networks were engaged.

Can we use this? This is to the point of John's point earlier. What good is all this stuff? Yes, we can. I love this slide. This is the imprecision medicine slide. I have always had great envy of areas of medicine, but it turns out that after billions of dollars are spent developing drugs and they get FDA approval, this is the number of people - I believe the scale is times either 10 or 100, 10, I think, that you have to give it to before you get one person for whom it works. These are blockbuster drugs. Although a shout out to Abilify. That surprised me given that it is psychiatric medication. This gives you a sense of the problem. You can measure cholesterol and see if Crestor works. Try measuring something equivalent in autism. That is what we want to do

is to provide a biomarker that is quantitative that can be measured in a treatment study.

This is my colleague Pam Ventola, who for now, is at Yale University and is just an incredibly talented clinician and researcher. She and I have teamed up to use these imaging techniques that I have shown you to figure out which kids will benefit most from evidence-based behavioral interventions. For example, pivotal response training, which is one of the few evidence-based methods out there that has been shown to work. But even on its best day, it works for about half the kids. In our experience as well as the broad experience, nobody can tell you for whom it will work. Unlike Crestor, which is a few bucks a pill, it is \$200 an hour and you do it for 20 hours a week for 16 weeks. It is an incredible investment. It would be very important to know ahead of time if it is going to work.

We asked the question. Given in our hands, PRT shows a nice decrease after 16 weeks of PRT versus

weightless control in the SRS score, which was our primary clinical measure. For good or ill, that was our primary behavioral measure. And of course, this is the mean, but this is the spread. That is the problem. For half the people, it does not work at all. That is consistent. But it works pretty well for some. You get on average a mean effect. It is a behavioral intervention and it is evidence based.

I think excitedly Daniel Yang, who is now an assistant professor with me and this is a paper where Pam Ventola is the senior author. She and Daniel were able to show that you could take a set of brain regions and using a classification analysis where you first developed a model and then applied it to its gold standard in terms of applying it to the set that is getting the treatment. You are able to predict with almost perfect certainty which kids will benefit and how much they will benefit from this behavioral intervention ahead of time. I think that that

might be a useful lead in terms of figuring out how to stratify intervention studies, but also more practically we know a lot about these neural systems. Several of the people in the room are world leading experts on these neural systems. They are systems engaged in social reward, in emotion regulation, my favorite, social perception area, and distribution of social attention. These are regions that predict very beautifully.

But most importantly because we used fMRI where we could get a location as opposed to say Scalp EEG where you can just say there is some difference. We know exactly what parts of the brain and we know gene expression in those parts of the brain and timing. We know what the functions of those brain areas are, which means we have targets as opposed to just a signature from the EEG. Now we can say can we actually change those targets using different techniques. I will come to that in just a moment.

Now of course the topic is sex differences. You are wondering does this work differently for boys or girls. In general, for boys and girls, you have a set of brain legions that respond and change when you utilize something like PRT and it works for the kids. They are different and this is an important clinical point than the regions that predict success. Different mechanism of change. Two different sets of targets. I think that is important.

In girls and boys, there are subtle differences. Girls tend to show more change over this middle childhood period. In behavioral measures that we want to use of improvement even when they are in the wait list. They are much more mobile. Even after we control for that, there are sets of brain region that will show differentiation in terms of the mechanism of change. But by and large, the predictors of response are very similar for boys and girls in this case.

I mentioned something about targets. If we have a target in the brain and it is a location, can we affect it perhaps with a drug? Going back to a study of intranasal oxytocin that we did, you might notice that when we publish this, this was a double blind placebo controlled study of intranasal oxytocin. When we did that with a single administration, we did not care about behavioral change. I was not foolish enough to believe that a single dose of intranasal oxytocin would change behavior especially in the absence of an accompanying context because everything we know about oxytocin is that it is incredibly context dependent. For example, you give oxytocin and present somebody with their outgroup. It increases their hatred of the outgroup. It is not clear who the outgroup and the ingroup are for children with autism.

But if you present it in the context of a setting that encourages collaboration like pivotal response training, it might well have an impact on

behavioral change. What I am trying to illustrate here is the opportunity to do something like target the very neural systems that predict improvement with PRT and turn a non-responder into a responder and again I think that that is an incredibly useful tool or useful concept especially when you are suffering from - we in the imaging world are always suffering from being irrelevant. We love these tools, but can we ever do anything that is actually going to help anybody? Here, I think, we are getting on the verge of something that could be potentially and clinically useful.

And then I am reminded of course that autism is a developmental disorder. We are simultaneously doing two things. One is trying to downward extend this. We have introduced a model where we take optical imagine and EEG on every baby that is born in the GW Hospital in Washington, DC, which is most of the babies that are born in Washington, DC so an incredibly diverse sample and not study baby



sibs because I do not want to develop a diagnostic technique that works in baby sibs because that is not very useful. By epidemiology, we will work only the base rate is 20 percent as opposed to 1 percent. If we are developing something that works on all babies to give us these early markers and it links up to the imaging data then we can begin to look at something where we can alter development trajectory. We are working on that.

But then simultaneously just a shout out for the study of adults. I think that it was a wonderful policy win that we as a country have emphasized early childhood development, infancy and early diagnosis. I remember getting into the field running as fast as I can towards the baby studies because that is the sexy stuff. It is this provision of services to adults. I do not know about that. That seems really hard.

Now though as cognitive neuroscience has matured and started studying development, it looks like the most interesting developmental periods

are that late adolescent period to young adulthood. Beautiful neuro-economic studies like Sarah-Jayne Blakemore's and Jennifer Pfeifer's, looking at how adolescents process risk. The take home message from those studies is that adolescents are a real wakening period for plasticity and an incredible opportunity for intervention. No wonder we developed colleges basically not to just house adults, but to take them at a period of time and shape them. It is an argument for doing the same thing and putting resources towards those longitudinal studies that involve an intervention component so we can do experiments in humans, not experiments with random assignment per se, but experiments where we are working on an intervention that we have every reason to think will work and then using cognitive neuroscience and genetics and careful phenotyping to begin to understand the mechanisms by which they work.

I will stop there and I will take one question while Alison sets up.

(Applause.)

DR. AMARAL: Kevin, wonderful and exciting work. I wonder how you deal with the issue that when you are looking at the brains of kids who are in middle childhood, they have already had years and years of plasticity. What you may be looking at is more an adapted brain than a brain that shows signs of autism. How do you think about that?

DR. PELPHREY: It is a great question. I think that there the siblings are best shot and even more ideally in twin studies to look at what is an endophenotype and what we think of as a group difference may just be an adaptive response. That is still very relevant for our clinical understanding of autism. But if we want to understand mechanism of etiology, we have to be able to pull that apart. I think that is our best shot at pulling it apart.

And then of course the longitudinal nature of the data is very important. I sort of beat up on the baby sib studies. You know as well as anyone how interested I am in them and your own work with baby sibs and imaging is using it to understand etiology, which is very different than trying to develop a diagnostic technique that you can sell. That is a very different approach. You are trying to understand mechanism, which should allow you to develop diagnostic technique. In that case, I think the baby sib design is incredible and the only one that will let you do that.

MS. SINGER: I am going to speak briefly about a new project that the Autism Science Foundation is creating that grew directly out of the wonderful research that we heard about from Donna and Somer and Kevin, today. It is called the Autism Sisters Project. At its heart, it is focused on resilience. So much of our research is looking at why do certain people have autism. What are the causes? What are the genetic causes? What

are the environmental causes? But this project is looking at why some people do not have autism. It really grew out of the genetics research that I think Donna beautifully explained, which is over the last five years, we have learned that the genes that confer risk for autism are equally distributed in males and females despite the fact that males are four times more likely to be diagnosed with autism.

For many years, we looked at this and we said there must be something about being male that confers extra risk. Now, we are saying maybe there is something about being female that confers protection. This project is really trying to get at that piece of the graph that Donna showed where - as I said, the girls are equally likely to have the genes that cause autism, but they are showing no clinical symptoms. We think that if we can build a database, a resource, we can start to use it to look for this female protective effect. What is it that is protecting this cohort of girls from

developing the clinical symptoms of autism? If we can understand what that female protective factor is, we can use that to protect both boys and girls.

As I said, we are in the process of building a database of DNA of unaffected female sisters. We are looking at female sisters because we believe this is an enriched cohort. Just like with the baby siblings, we looked at the younger siblings because they would be more likely to go on to be diagnosed with autism. We think in the unaffected female siblings, we are more likely to find girls who have the genes that cause autism in boys, but these girls again have no clinical symptoms.

We are building this database in three ways. The first is we are trying to collect data that is already out there that many of you in this room have collected where you collected quad data, DNA from parents, an affected child, and then an unaffected sibling. In some cases, there is already exome data from the unaffected sibling and

in some cases, not, but we are trying to gather up that existing data and move it into the autism sequencing consortium database.

Secondly, we are trying to re-contact families who participated in studies as trios where we have DNA from the parents and the affected child with autism and we are going to go back and ask those families if there is an unaffected sibling and try to collect DNA from those siblings, again, because that is economical. We already have data from three of the four members of the family.

And then finally, the key piece of the autism Sisters Project is to go out to new families and try to reach families who in many cases are now super excited to be able to participate in autism research particularly the unaffected siblings who are, as you will see in the video, so eager to participate and try to help find answers for their sibling with autism.

But we are now actively recruiting families to go to Mount Sinai Hospital. Right now, we are only

recruiting in New York, but hopefully over the next few months, we will add two and three additional sites. But we are inviting families to come to Mount Sinai Hospital to, as we say, give a spit for autism because the DNA is collected through saliva samples. That is our hashtag.

We are very honored to be working on this project with Joe Buxbaum at Mount Sinai Hospital, and Paige Siper at Mount Sinai Hospital, who are the principal investigators. And also with Somer and with Donna and with Elise Robinson at the Broad and Ed Cook at the University of Illinois and Chicago, as well as with the Hillenbrand Foundation, which is our funding partner for this project.

This is a three-minute video that I think really helps to explain why so many of the sisters are excited to participate in this project.

(Video Shown.)

MS. SINGER: The IRB at Mount Sinai would not let us put this on the fliers that I passed



around, but if anyone is interested and I encourage everyone who is a sibling, a female sibling, and as Dr. Buxbaum likes to remind me, we also need brothers as controls. We need siblings of both genders to participate. Right now, it is at Mount Sinai Hospital. The person to contact is Kristin Mering(phonetic). There is her number on the screen. 212-241-0961. I hope everyone who is watching this via the web will flood her phone with messages.

As I said, we need as many families as possible to participate to build a database that will enable us to really start to answer the questions that we heard raised earlier today. Thank you.

(Applause.)

DR. WEXLER: Alison, I just wanted to say while we cannot do anything direct, my shop funds 110 parent centers throughout the country, and a bunch in New York too. I am sure that we could arrange for you to contact them. That is their job. They

are connected to families with children with disabilities, not exclusively autism, but certainly plenty --

MS. SINGER: That would be great. You will be hearing from me tomorrow.

DR. PARNELL: Alison, how far off is the iteration of the survey where the testing can be done by computer? I have children who I would love to participate in this, and I am sure they would love it too, but traveling to Mount Sinai is a bit of a barrier.

MS. SINGER: The reason we wanted to develop the online assessment is for exactly that reason because we want to be able to involve children who live all over the country. Actually, Somer Bishop is involved in creating the online tool. She is probably in the best position to say how long it will take her.

DR. BISHOP: We are piloting right now. We hope to have at least some data within a year's time. It is complicated because we have to do everything

online and then do everything in person. And then just make sure that the online data collection is as valid as we want it to be. But I would say we would have some preliminary data and then we might be able to roll it out hopefully in a year.

DR. GORDON: We can open up questions to the panel. We have a few minutes. If there are questions for any of the panel, it would be great.

DR. ROBISON: I am not sure which of you is best to answer this. In your video, there was an obvious difference between the autistic and non-autistic sibling. I would agree that the boy looked autistic and the girl did not. In all of your presentations, you kept suggesting that there were these female protective factors, but you also suggested that the females were affected in different ways and were therefore under recognized on diagnostic tests. But you really did not talk much about that. You mostly talked about the protection. Do you have a comment to offer on the under recognition of the females?

DR. PELPHREY: For that question, that is the question that keeps me up at night since the funding of this network. I knew when I wrote the network if I did not say gold standard diagnostic, ADI/ADOS and they would meet on all the criteria and essentially the Simons Simplex Collection battery, it was not going to get funded.

Now with the emphasis on RDoC and the interest in quantitative distributions of traits, it is a much more open field there. Still within autism, there is an unwritten rejection criterion for JAD or kind of key journals where if they do not have ADOS and ADI on all the patients, it is not getting accepted. It will not even get sent out for review.

That is simultaneously an incredible thing that was created to allow us all to talk about a common disorder, a well-characterized disorder. But if you think about all the results we have presented, everyone went through other than Somer's study with a more clinic sample. In the

genetic studies and imaging, they are all going through an incredible filter to induce homogeneity. The fact that we found any sex differences at all is sort of incredible, let alone these huge sex differences. Donald Trump has ruined the word huge. Large sex differences. I think Somer wanted to - did you have a comment on that same point?

DR. BISHOP: I think it is a really important point and it is an important question about how to put all of these findings in the context of each other. I am a clinician. I will just be on my clinical soapbox for a second. I think the minute that any of us becomes slaves to any of these tools, we have not done our jobs anymore. If we are going to understand individual differences in autism or anything else, we have to be able to understand what works for whom and when it does not and why it does not. At least in clinical assessment context when people are good at what they do, they try to take all of the information.

The hard thing is getting those anecdotes into data. I think that is what Kevin is talking about. We have to balance high-quality stringent inclusion criteria with also the ability to survey people who might fly under the radar.

When people were talking about the registries and other things this morning, I think these are opportunities where if we have people coming from different roads, all to contribute to this, then we can understand who we are missing and where. I think it is absolutely a really important question that I do not know exactly how we are going to contend with.

DR. CRANE: I am going to agree with John here and also say that I do not see how sex differences are necessarily inconsistent with the theory that girls on the autism spectrum are being under diagnosed. In fact, that would explain why some girls on the autism spectrum are being under diagnosed. If you have incredibly homogeneous samples where the boys and girls outwardly look

exactly the same, but even then there are a lot of different things going on in their brains then we can imagine that a lot of girls on the autism spectrum because they are doing a lot of processing, a lot of extra effort to process social cues, might not have the same clear differences in ability to process certain social cues because they are over compensating or something along those lines. I just want to emphasize that we cannot necessarily - we still cannot discount that possibility.

DR. PELPHREY: I think all of us completely agree with you. That is the interesting science. How does that work? And then we know there is no free lunch in nature. If you avoid autism and you have a genetic liability that we now - I think it is still the case that every candidate gene that we have for autism also causes any one of another neurodevelopmental or neuropsychiatric disorder or it causes nothing recognizable as a disorder. There is incredibly developmental heterogeneity.

We do not understand those developmental paths to those different outcomes. There is no free lunch. If you are a girl and we take a snapshot of you in time in middle childhood or early adolescence or infancy and we say there are some sex differences. This is kind of a characterization. That does not mean that at age 20 they are going to be the girl who emerges with an eating disorder or profound depression even later in time. The underlying phenomenon is the difference in brain function. The over behavior is simply the last step in that process and not the one that you necessarily want to treat although when they show up in the clinic, if you want to understand how to intervene early, you have to understand every step of that developmental process. But it will not be completely unique. It will be lumpy.

I think all of us are saying that even if you account for real sex differences in biology that kind of real and uninteresting that protect women from almost all neuropsychiatric disorders and you



account for the 14 versus 5 percent missed and a few other things and you kind of look at it all in three-dimensional space, there is an absence of a group where there ought to be a group. That absence of something is what is interesting. Who are they? I think those are the girls who are extremely good at what some are calling camouflaging, but what is the cost to that?

DR. CRANE: It actually rang very true to me. If you talk to a lot of girls on the autism spectrum, you will find that, for example, they are devoting so many cognitive resources to processing social cues because they could not survive without it. They just devoted every single thing, parts of their brain that normally would not even be devoted to social cues. They are brute forcing it.

And then you see massive issues with anxiety and executive functioning even language processing because there is a cost to everything that you divert brain resources to compensating for. You

are going to have some other issue. It would be really interesting if you are going to look at - for example, even supposedly unaffected siblings. Are they different in some way even if they are not necessarily meeting all of the criteria for autism? Are we seeing differences in anxiety levels in these girls? Are we seeing differences in executive functioning or attention? It would be really interesting.

DR. ROBISON: I want to say that listening to this presentation that Kevin and all of you, I really want to support what you want to do because I think that the questions you are seeking to answer are important questions and they do deserve answering.

But I have to say at some level, it makes me deeply sad to listen to your presentation to hear parts of it because what I hear from you is the ultimate goal that you could find this female protective factor and inject it into baby boys. I think, what does that mean? That means that my

kinds future is limited in a world where that comes to pass. But the thing is I still even though I feel that, I still support your pursuit of the science because I know it could have many outcomes other than that.

What it really also makes me just keenly aware of, and even though I am sure I sound like a damn broken record to some of you, but it makes me aware that if you went out into the community of autistic people who could talk or communicate at some level, and when we talk about adults, that is most of us. If you said to us, what would you want most. Would you want this protective factor to maybe help children you do or do not have? Would you want the quality of life research, research into older people? It shows that we need more research that actually addresses the issues people like me live with at the same time that we need to go after the basic questions that you are trying to ask here. It really troubles me because I do not want to be seen as an opponent of what a team

like you is doing because I believe in it. I just so wish that we had a level of commitment to the research that would keep me from getting sick and dying in five years that would keep people from wandering that would help us communicate when we cannot. We have so many of those problems. I just so wish we could balance it differently.

DR. PELPHREY: I do not think we are that separate in our views. I understand the characterization injected in a boy to prevent the emergence of autism. I realize that that is a logical extension of what we are trying to do. But what I am more interested in is to say to an adult who under their own free will comes and says I am having a hard time with autism. I have this diagnosis or more likely I have a hard time with these four or five things. If I understand how women naturally live longer, live healthier, all the things you mentioned speak more effectively. If I can understand those processes and study it over time at some point and not too far away by

combining those different levels of analysis and focusing it on a thing that looks real and is definable, I can then offer a full plate of things for the person who comes into the office to try.

Ultimately, you know my political convictions are nothing would be forced on somebody, but rather an informed choice where you have something to choose from as opposed to choosing from different versions of snake oil that are out there. That is what we are in for.

I think that this particular question has a lot of meat to it because of all of the stuff you see spinning around the focus on the female protective effect, for example.

DR. ROBISON: I think that that is a noble goal and it is a good one, but it is in an ethical minefield and we just have to be really mindful of that. That is all. But I support you.

DR. GORDON: I think we should thank the panel for a great presentation and the discussion along the way. John, it is great that you can live with

the cognitive dissonance of really wanting to see what science can bring to us, but the watchful concern that that science be used in a way that benefits patients and individuals suffering from the disorders that we study as opposed to being used in some other more nefarious ways.

Now, we are going to move on from the panel discussion to a round robin. We reserve this session each time at the end so I have been told for the opportunity for members of the committee to share updates about how their agency or organization has taken the advice of the committee or worked on issues of relevance to the committee.

We also have already heard of a fantastic example of that from Alison. We have at least two of us, myself and Cindy Lawler, who have already told us they want to share things. We will start with Cindy. And then we will certainly open it up after I finish.

DR. LAWLER: Thank you. I wanted to share some information about the latest round of grants that

we funded as part of what has been a three-year NIH initiative that is targeted on environmental contributors to autism spectrum disorders. This was led by NIEHS, but also co-sponsored by the Institute of Mental Health and Child Health as well. This initiative overall was aimed at stimulating and accelerating research to identify environmental contributors to risk and expression of autism as well as understand how these factors impact the underlying biology that may be implicated in autism.

We were interested in applications, using a range of approaches from basic mechanistic work in cellular and in vivo and in vitro models and also studies, clinical and epidemiology studies that added new data collection activities and took advantage of existing data and biospecimens. We were particularly interested in studies that were going to look at exposures in the context of genetic susceptibility.

Collectively, the three institutes funded eight applications the first year of this initiative. That was fiscal year 2018 and another nine grants were funded the second round. Those were grants that were rewarded late summer this year. The applications that we funded so far really reflect a mix of basic mechanistic work as well as human studies, the kinds of exposures that our investigators are looking at, range from things like air pollution to heavy metals to chemicals that are known endocrine active compounds as well as maternal risks such as metabolic conditions. And some of the grants that we funded are indeed looking at how exposures interact with genetic susceptibility.

We have applications that were submitted to the third and final year of this initiative in August. They will be reviewed this spring. We will be able to report this time next year hopefully another round of applications that were funded.



Long term, I think this really has been a great example of inter-institute cooperation and what we have done is really funded a good base of projects and what we consider to be a high priority area that needed that extra boost. We really hope that with that investment, there will be additional data that are generated that can be explored more in future studies.

DR. GORDON: Thank you, Cindy. Before I go into our updates from the NIMHS, I just wanted to mention that we heard this morning of NINDS and some of the fantastic grants that they have going around those single gene syndromes that also contribute risk to autism. I see that Walter has left and I think his representative has also left. But I did want to give an update into the NIMH. I think it is particularly relevant given the topics we have covered today. In response to the need identified in our strategic plan, for improved access and effectiveness and services, in 2014, we awarded 12 research grants through three different

calls, three different requests for proposals. One focused on early childhood. Another one on adolescence and the transition to adulthood. And another one on adults.

At that time, we funded 12 grants. They are fantastic grants. But most of them are focused on the early time period. We did not get a whole lot of applications for the transition and for the adults. Last October, we re-issued the adolescent and adult calls. I am really pleased to say that clearly it takes some time to build momentum in the research world. But over that year or so from 2014 to 2015, the signal that we sent out in 2014 generated a response, just a little bit delayed.

We have 34 applications for these two calls, one for the transition-aged youth and the other for adults. Those are being reviewed now. We expect to give awards early in 2017. We are very excited about the opportunity to really see some good science come along in these areas that I know

are crucial for patients today. That is our update.

Are there any other updates?

UNKNOWN FEMALE SPEAKER: I am Lisa from the Child Health Institute. I just wanted to mention, and I think somebody next to me has already alluded to this, but the ACE program, the Autism Centers of Excellence program, is up for renewal, a batch of them anyway. We have a request for applications out, which closes on November 18. I have started to receive letters of intent from PIs who have told us they would like to apply. It was a very healthy response. That is all I will say. We look forward to reviewing this.

DR. SHAPIRA: Stuart Shapira from CDC. It has been very well recognized that the earlier a child is identified with development delays and enrolled in early intervention services, the more likely the child will be able to achieve his or her full potential. To that end, I would like to give an update on CDC's Learn the Signs Act Early Program,

which I had mentioned earlier. It focuses on the age of enrollment of first evaluation and getting children into early intervention services as early as possible. The program works by education and providing resources on early child development to parents and to daycare and preschool providers and to physicians.

The program recently completed a pilot study that integrating Learn the Signs Act Early into WIC clinics in selected locales in Missouri. And because the pilot was so successful at identifying young children with developmental concerns and getting them into the services that they need that this program is being expanded to all the WIC clinics in the entire State of Missouri with plans to expand to other sites.

Learn the Signs Act Early also has some exciting resources that are now available or soon to become available. One of them is the Milestones in Action image library. That was recently launched online. It is a photo or a video of every

developmental milestone covered by Learn the Signs Act Early comprehensive checklist from age 2 months to 5 years.

And then there are two items coming soon. One is *Where is Bear*, a terrific tale for 2 year olds. This is a new children's book that is entertaining and an interactive story of 2 year olds. It introduces the concept of developmental milestones to parents and other care providers. It includes complete 2-year-old checklists and GUIDance for how to act early if there are concerns.

Finally, coming soon will be a milestone's tracker app. This interactive app will give parents and other caregivers the ability to track and store their child's developmental milestones on their Smart Phones.

DR. GORDON: That is fantastic. Thanks. Are there other updates from other committee members? Any questions for any committee members about the updates that we just had?

DR. DANIELS: I have an update for you from the Interagency Committee on Disability Research, which is managed by ACL and I am a member of that committee so that I can help be a liaison between our sister committee and this committee.

They have recently posted a draft of a government-wide strategic plan for FY17 to 2020. It is posted up on the website for public comment. They just recently extended the public comment period to November 4. I wanted to make sure that all the committee members knew about this and members of the listening audience and the webcast audience. Feel free to go in and put in your input. They really want to get a wide variety of comments from the public on this. We will try to do our best to interface with them and provide information from our side towards this although it is for the broad disability group and bring information back to us as well. Thanks.

DR. GORDON: One more chance for questions. I guess I will begin to close the meeting. First of

all, I want to say that this was really an educational experience for me, learning more about the committee and hearing from all of you today. Thank you very much for all the participants, particularly our speakers who really were fantastic in terms of updating us about science and also about efforts in the UK that are directly relevant to our own efforts here.

I want to just highlight a couple of issues that were raised throughout the day that I think we are going to need to revisit over time. One of them of course being the issue of "budget recommendations" that we are going to include in the strategic report update. That is going to be something we are going to have to come back to. I know that David Mandell is going to try to work on baseline numbers, but we are going to have to come up with some way of reporting the budget requirements for our recommendations.

And then the second one is about the rigor around the scientific advances that we report.

Just because we did not want to adopt a more formalized rigorous process to approve or not, it does not mean we do not have the responsibility to ensure that the reports - the activities that we want to go into Congress are not - we want to make sure that they are not misunderstood and that we are only putting forth genuine advances. I think the best way for that to happen is for us to get lots and lots of recommendations and then each of us take it upon ourselves to think seriously about our own individual areas and make sure that the ones that - we are going to basically make sure that the only ones that go through are rock solid stuff that we can all agree upon.

With that, I will turn it over to Susan who has some remarks about what has to happen before the next meeting.

DR. DANIELS: Sure. I will be in touch with all of the working groups about your next calls. I know that you have received schedules for most of those calls. There are a few that are still being



scheduled and we will be providing you with outlines and information about that. We are aiming to come to the January meeting with the drafts of the different chapters. I will be working with the chairs. If anyone has questions in the meantime, feel free to reach out.

DR. GORDON: I note that the next meeting is on Friday the 13<sup>th</sup> of January, 2017. Plan your travel accordingly. Thanks a lot, again for participating.

(Whereupon, at 4:46 p.m., the Committee adjourned.)