U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

FULL COMMITTEE MEETING

TUESDAY, JANUARY 19, 2010

The Committee met in Conference Rooms E1/E2 of the William H. Natcher Conference Center, 45 Center Drive, National Institutes of Health, in Bethesda, Maryland, at 9:00 a.m., Thomas Insel, Chair, presiding.

PRESENT:

THOMAS R. INSEL, M.D., IACC Chair, National Institute of Mental Health

DELLA HANN, Ph.D., IACC Executive Secretary, Office of Autism Research Coordination, National Institute of Mental Health

SUSAN DANIELS, Ph.D., Office of Autism Research Coordination, National Institute of Mental Health

JAMES F. BATTEY, M.D., Ph.D., National Institute on Deafness and Other Communication Disorders

LINDA BIRNBAUM, Ph.D., National Institute of Environmental Health Services

ELLEN W. BLACKWELL, M.S.W., Center for Medicare and Medicaid Services

JOSEPHINE BRIGGS, M.D., Director, National Center for Complementary and Alternative Medicine (For Dr. Francis Collins)

HENRY CLAYPOOL, Health and Human Services Office on Disability

LEE GROSSMAN, Autism Society

PRESENT (continued):

ALAN GUTTMACHER, M.D., *Eunice Kennedy Shriver* National Institute of Child Health & Human Development

GAIL R. HOULE, Ph.D., U.S. Department of Education

YVETTE M. JANVIER, M.D., Children's Specialized Hospital

WALTER KOROSHETZ, M.D., National Institute of Neurological Disorders & Stroke

CHRISTINE M. McKEE, J.D.

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

CATHERINE RICE, Ph.D., Centers for Disease Control and Prevention (For Dr. Edwin Trevathan)

STEPHEN M. SHORE, Ed.D., Autism Spectrum Consulting (via telephone)

ALISON SINGER, M.B.A., Autism Science Foundation

PETER VAN DYCK, M.D., M.P.H., Maternal & Child Health Resources & Services Administration

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PROCEEDINGS

9:03 a.m.

Dr. Insel: Okay, I think we're ready to get started. We've got most of us around the table. Stephen is going to join us by phone. Happy new year to all and welcome to the first 2010 meeting of the Interagency Autism Coordinating Committee. We were just going back over 2009 and realized we had somewhere between 16 and 17 meetings last year so it's been a very busy period over the last 12 months. Going forward we have a fairly busy day today. We're going to divide this up by having public comment first instead of at the end of the day and we're also going to focus on some of the scientific presentations that you asked for in November and December and use most of the morning to talk about scientific opportunities and some of the advances that are going on both globally and here locally.

One procedural detail in terms of the makeup of the committee. I think we mentioned

last time that Dr. Francis Collins was then new, now not quite as new Director of the NIH, serves on this committee but like his predecessor he had difficulty making it to most of the meetings. He does intend to attend in April but for today and for some of the meetings where he cannot attend he's appointed a proxy in his place, Dr. Josephine Briggs, who I think you have met at an earlier meeting.

She talked from her regular position as the Director of the National Center for Complementary and Alternative Medicine. So Dr. Briggs will be with us later in the morning. She was only informed about this last week and she had already made some other commitments for today, but she will be able to join us. And as you can see from the name tag she'll be starting - she'll be sitting over here on this side of the room.

For those who are joining us by phone it's sometimes helpful to know who's in the meeting and so I'd ask for us to do a quick

round of introductions, then I'll make a few introductory comments thereafter. So we'll start with myself. Tom Insel, the Chair of the IACC and otherwise Director of the National Institute of Mental Health.

Ms. Redwood: Hi, Lyn Redwood. I represent the Coalition for SafeMinds.

Dr. van Dyck: Good morning. Peter van Dyck, Director of MCH in HRSA.

Dr. Guttmacher: Alan Guttmacher, Acting Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Mr. Grossman: Lee Grossman with the Autism Society and the dad of a 22-year-old with autism.

Dr. Birnbaum: Linda Birnbaum, Director of the National Institute of Environmental Health Sciences.

Ms. Blackwell: Ellen Blackwell, Centers for Medicare and Medicaid Services. Also the parent of an adult son with autism.

Dr. Battey: Jim Battey, Director of the National Institute on Deafness and Other Communication Disorders.

Dr. Janvier: Yvette Janvier. I'm a developmental pediatrician with Children's Specialized Hospital in New Jersey.

Dr. Trevathan: Ed Trevathan, Director of the National Center on Birth Defects and Developmental Disabilities at CDC.

Ms. Singer: Alison Singer. I'm the president of the Autism Science Foundation. I have a daughter with autism and also an older brother diagnosed with autism.

Dr. Koroshetz: I'm Walter Koroshetz. I'm the Deputy Director of the National Institute of Neurological Disorders and Stroke at NIH.

Dr. Daniels: Susan Daniels, Office of Autism Research Coordination at NIH.

Dr. Hann: Della Hann, Office of Autism Research Coordination and also serving as a designated federal official for this committee.

Dr. Insel: And Stephen?

Mr. Shore: Yes, Stephen Shore, Professor of Special Education at Adelphi University.

Dr. Insel: Great. We can hear you just fine and don't be shy about interrupting as the day goes on. Because we can't see you raise your hand you'll just have to speak up.

Mr. Shore: Okay.

Dr. Insel: Thanks to all of you for joining us this morning. I wanted to take just a few minutes at the outset to get us all on the same page. There have been a number of recent scientific papers that I thought would be helpful for you to know about and just to make sure we're all starting at the same point as we think about research status right now. Many of these actually fit right in with the Strategic Plan. The first, as you can see on the screen, has to do with epidemiology. So this is really out of the first objective of the plan. You all know I think about the *MMWR* report that came out

on December 18 that looked at the prevalence of autism spectrum disorder. This is of course the ADDM network and you're going to hear much more about this later in the morning or later this afternoon from Cathy Rice who was the principal investigator in the ADDM network. The key thing here is just the new numbers need to be looked at very carefully. We've got numbers that span from 4.2 in Florida up to 12.1 in Arizona and in Missouri. And if you put all of this together as I think all of you know the current prevalence according to CDC is 1 in 110. That's an increase of 57 percent from the 2002 numbers. The ADDM network looks at 8-year-olds in these 11 sites so this is a way of maintaining the surveillance network. The 2006 data that they're looking at here involves children who were in a 1998 birth cohort. The 2002 data then of course would be 1994.

This is a very rich data set and that's why we thought it was important for you to hear much more about this which Cathy will

take us through later. I know the focus has been largely on this number 1 in 110 but in fact there's a lot more in the data that looks at ethnic differences in diagnosis and prevalence. Also, one of the things that's quite striking is this fact that in this epidemiological survey the age of diagnosis is still really late. It's anywhere from 41 to 60 months and that's a point that hasn't been made often enough. It just tells us that we still have a lot of work to do here in thinking about how to move the dial.

Certainly these are numbers that none of us should be happy with because it suggests, if anything, that we're going in the wrong direction from where we were in 2002. We would much rather come here to tell you that there's a 57 percent decrease relative to 2002. But more about all of this later and a chance to discuss the details of what is really a very rich data set. In addition to these numbers from CDC there are other reports coming out just in the last week about spatial or geographic clusters,

one in the Journal of Autism Research released early last week and then Health in Place which has a paper coming out. It was supposed to be out on Friday. I think it is going to be posted this morning. And both of these are using the California DDS, the Developmental Disabilities - or the Department of Disability Services data to look at where the cases are in the State of California. In this case, in both of these efforts looking at these as birth cohorts. So where were the children born. And you can see from this graph which is taken from the Autism Research paper by Karla Van Meter that there really is a huge difference in the way that cases have been identified across the State of California, and at least in one area. The "RC" here means Regional Centers. In the regional centers of L.A. County shown in this insert. There do appear to be areas where there are significant increases relative to other areas. That's what we mean by geographic cluster. Overall the clusters show about a four-fold

increase in prevalence which is actually equal to the sex difference in autism, they seem to be stable over time, but the meaning of this is still not clear and how much of this is just due to demographics and how much to potential environmental influences is a big question. As Peter Bearman says in the *Health in Place* article cluster research should be used to disprove rather than confirm causality and I think that's where this sits at the current moment, but it's worth all of us taking a look at these kinds of reports to get a sense of what may be feeding into these geographic differences.

One other piece that has been out in the last couple of months that deserves your attention are the two papers in December in *Pediatrics* on ASD and gastrointestinal issues. The piece on the left is really this very important consensus report and I just want to - we can distribute this if people are interested. I think most of you have seen it. It's really

a very nuanced effort to look carefully at questions around what do we know about GI distress and autism spectrum disorder. They point out that GI symptoms are common in ASD, they're also common in children without ASD and from what they can in this consensus report there doesn't seem to be a unique syndrome either at a pathological level, that is at a cellular level, or at a symptomatic level of gastrointestinal distress in autism. That is, there hasn't been a syndrome found here that hasn't been described elsewhere. But they do point out just the critical need for understanding much more about this and the difficulty often with diagnosis because most often gastrointestinal problems in kids with ASD are going to present as behavioral problems, not necessarily as a complaint about a specific GI symptom. So particularly the report on the left, the consensus report as well as the recommendations go over and over again this need for more research and the need for evidence-

based practices, both for diagnosis and for intervention. And so I think as we think about the Strategic Planning effort these documents should be very helpful to us in pointing where the need is for more information for the field, particularly for clinicians as well as for families.

Just a couple of other points to make sure we're all up to date. A very important study that came out in terms of interventions published last month in Pediatrics as well by Geri Dawson, Sally Rogers and their colleagues. This is looking at really the first double-blind randomized controlled trial for toddlers on the ASD spectrum and in this case comparing this early stage Denver model which was essentially ABA that's been modified for toddlers around a control group that was monitored over a 2-year period. And it's quite striking actually. The results if anything are better than what had been reported earlier and somewhat much better than what we heard from

Tony Charman two or three months ago when he came to this meeting and talked about a review of early stage interventions for children with ASD. Twenty-four kids went into this modified Early Stage Denver Model intervention, 24 in the assess and monitor group, and overall over the 2-year period there was a 17 point increase in IQ measured by MSEL here on the left in the kids on this experimental treatment. Also, a significant improvement in adaptive behavior whereas the control group actually showed some deterioration and almost 30 percent of the kids receiving this early stage intervention lost the diagnosis of autism. Jim?

Dr. Battey: Was a comparable amount of clinician exposure time present in both groups, or was that a confounding variable?

Dr. Insel: It's clearly a confounding variable in any of these kinds of studies and it's also not clear necessarily what the active ingredient is. And as we've talked about before here, one of the things we really

need in the research base is both moderators and mediators of treatment response.

Dr. Battey: Because we did a clinical trial and studied this in language disorders and the conclusion that that study came to was that it was a function of exposure time to a clinician, and it didn't really matter what they did it was just a function of the time.

Dr. Insel: Well, so the mechanism of improvement is not really laid out in this study, but I think what they do establish is the magnitude of improvement that you can see if you move early. And so it is an argument for early detection, early intervention. I'll just finish by saying that this is sort of really tracking our Strategic Plan so if we go to the latter part of the plan, particularly Aims 5 and 6, there was a supplement to Pediatrics that came out last month that was based on this national survey for children with special health care needs and I think Peter van Dyck who's here may

know much more about this as much of this was done with HRSA's support. But again, I would recommend this series of papers. I've only listed four of about seven or eight that came out in the supplement that looked very carefully at where are we in terms of services to this broad group of children, including many - not all, but many on the autism spectrum and the news is not good. I think it's very much in line with what we've been hearing and what we've been talking about especially for the sixth aim of the Strategic Plan. But this is a place that I think we can go back to in terms of this set of articles and this recent survey to get a sense of the numbers that we might be able to look at as a baseline in the hope that we can move the dial on many of the measures that this survey was going after.

So that's a real quick rundown. I don't want to take a lot more time. We're going to get back to some of these issues later in the day, but I wanted to just make sure everybody

was up to date with some of the recent papers coming out, and these are really just in the last month. This isn't comprehensive. There's lots more that we could be talking about here, but this is at least a good start. And I intend for future meetings to also try to just keep you up to date with things that people need to know about.

We've got a pretty big agenda here. We'll start with public comment and then we'll have a chance to hear from the two Andy's, Andrew Shih who's going to talk about global autism, Andy Feinberg who will be with us soon to talk about epigenetics. As I said, Cathy Rice is going to then get us deeper into the CDC data and Dr. Linda Birnbaum who's here on the committee is also going to do an update for the National Institute of Environmental Health Sciences. Okay. We're ready to get started.

The first order of business then is to have public comment and we have two people who are going to join us for that. The first is

Paula Durbin-Westby. And Della, where would you like to have people sit for public comment?

Dr. Hann: Actually we have a standing microphone this time.

Dr. Insel: Okay.

Dr. Hann: Right there.

Ms. Durbin-Westby: Hi, I'm Paula Durbin-Westby. Thank you for this opportunity to comment on updating the IACC Strategic Plan. I'm representing the Autistic Self-Advocacy Network.

Dr. Insel: I don't think this microphone's on so let's see if we can get this - just a moment. Paula, try again.

Ms. Durbin-Westby: Okay. Now can you hear?

Dr. Insel: You're on.

Ms. Durbin-Westby: All right. I'm Paula Durbin-Westby. Thank you for this opportunity to comment on updating the IACC Strategic Plan. I'm representing the Autistic Self-Advocacy Network. Much good work has been

done to update the Strategic Plan for 2010. In fact I like a lot of the changes. Among the positive changes to the plan is the aspirational goal for Question 3 with the addition of services and supports as a goal and the improvement of quality of life rather than the language of prevention and preemption that was there before. Because of some of the reversions to language and concepts found in the 2009 Strategic Plan as opposed to some of the things we talked about in the scientific workshop I need to reiterate several concerns from ASAN's past commentary.

The aspirational goal that was generated by the recent scientific workshop's Panel 1 for Question 1, "When should I be concerned?" has been replaced with the original language. Although adults are mentioned elsewhere in the text of the plan this aspirational goal should at least reflect some concern about the diagnosis and assessment of adults on the autism spectrum. The long-

term objective to develop measures of behavioral and biological heterogeneity in children or adults with ASD with the recommended funding level of $71 million over five years was deleted. This was one of the few places in the 2009 Strategic Plan that addressed adults with ASD at the level of diagnosis and assessment and the line edits that I have say it was deleted and not moved elsewhere in the plan, so I think that's just been dropped. The sections in the plan that address the ethics of communicating genetic risk should be amended to read, "Genetic and other risk" in light of current developments in maternal autoantibody research and other research. Under Research Opportunities in Question 2, research on individuals with ASD who are non-verbal or cognitively impaired should be qualified in some way to indicate that non-verbal is sometimes a contested concept depending on how it's used. For example, some people on the autism spectrum communicate other than with spoken language and so it needs to be

distinguished whether or not the person uses another communication system or like PECs or AAC because everybody communicates in some way. In Questions 5 and 6 there's a stated goal to investigate the use of medications to control challenging behaviors in people with ASD, particularly adults. I wrote do not assume that we all know what that means. Challenging behaviors, depending on who is getting to do the defining could mean anything from hand-flapping to serious threats to the self and others. Adults on the autism spectrum should be consulted as to the ethics of using medications to control harmless but socially stigmatizing behaviors. Another research goal in this section brings up the same concern: conduct a study to evaluate current practices leading to the use of psychopharmaceutical medications and their effectiveness in the treatment of comorbid of co-occurring conditions or specific behavioral issues with adults across the autism spectrum. Without careful attention to ethical

concerns this research goal could lead to what is in essence chemical restraint which is one of the prohibited categories in the Preventing Harmful Restraint and Seclusion in Schools Act recently introduced by Representatives George Miller and Cathy McMorris-Rodgers and supported by organizations such as the Autistic Self-Advocacy Network, the major teachers' associations, the Association of University Centers on Disabilities and many others.

The new proposed Question 7 needs to also be addressed carefully. We want to avoid autism registries or databases that use personally identifying information without the person on the autism spectrum's consent. If a person cannot or cannot at that time give informed consent, or a child who cannot or cannot yet give informed consent every precaution should be taken to make sure that personally identifying information is not included. People who have been added to a registry or a database during childhood should

have the right to remove themselves from the registry upon attaining legal adulthood should they choose to do so. All participation in autism registries and databases should be on a voluntary basis. To the statement, "As more professionals become involved in autism research there is a need for organized input from established scientists who provide guidance and expertise" should be added the need for organized input from adults on the autism spectrum in order to assist researchers in making sure research is relevant to the needs of people on the autism spectrum as well as family members and the community.

And on a personal level I want to say that I prefer moving the public comments section to a bit later in the meeting and this is because I - as IACC members know, I change my comments. If something has changed during the course of the discussion I can toss out things that I don't think are relevant anymore or I can add comments that are relevant to the current

discussion that day. And finally, I would like to close by repeating the call for additional members on the IACC drawn from the community of autistic adults who have a perspective that focuses away from questionable cures and elimination of autism, and should be given a seat on the Interagency Autism Coordinating Committee. Nothing about us without us. Thank you.

Dr. Insel: Thank you. I'll remind the committee that all of the public comments are also available to you in written form in the packets that you received. We have five minutes for an additional comment from Ms. Caroline Rodgers.

Ms. Rogers: Hi. My name is Caroline Rodgers and I am a writer. I'm the author of "Questions About Prenatal Ultrasound and the Alarming Increase in Autism." It was published in *Midwifery Today* in 2006 and reprinted in *Pathways to Family Wellness* last summer. What is causing autism and how can it be prevented?

That's Section 3 of the Strategic Plan which you revised in November. I am here to discuss results of three investigations published since then that implicate some aspect of prenatal care in causing autism. The first study is the CDC's prevalence report that Dr. Insel mentioned. It showed that the overall increase in autism was 57 percent, but when you look closely at the breakdown Hispanics in Alabama actually dropped 68 percent. What could have caused such a big difference? Was there a change in public health policy? Yes there was, but not what you might expect. From 1993 to 2002 Alabama was one of three states to decrease Medicaid for prenatal care according to a CDC multi-state surveillance report. The other states were Florida and West Virginia. The new autism figures show that the two states, Alabama and Florida, that reduced their prenatal care - their aid to prenatal care at that time had the lowest autism rates. The December prevalence figures also show significant overall ethnic differences. White

non-Hispanic women had 101 autistic children per 10,000 versus 76 black women and children of - thank you. Let me start again. The December prevalence figures also showed significant overall ethnic differences. There were 101 autistic white children born per 10,000 versus 76 black children and 61 Hispanic children. Well, 101 versus 61 is a very large difference. And then when you look at another CDC report, "Entry into Prenatal Care" it showed that fewer black and Hispanic women had first trimester care than did white women. Taken together these three CDC reports tell a disturbing story as more women across all ethnic groups received early prenatal care the autism rate among their children increased, with greater increases among the groups that had more early care. While these studies do not prove causation or even correlation they raise the question could some aspect of prenatal care be bad for babies. Let's go to California for some answers.

The UC-Davis study published this

month identified 10 autism clusters that showed highly educated white women were much more likely to have children diagnosed with autism than parents who did not finish high school. This seems counter-intuitive. Don't highly educated white women get the best health care money can buy? The higher autism rate could be due to various factors, but one thing that has to be considered is their access to the best prenatal care. Prenatal care hasn't changed much in the last few decades. A pregnant woman is weighed, her vital signs are taken, her rising belly is measured, she is prescribed prenatal vitamins, you know the drill. What has changed is the addition of prenatal ultrasound and it has changed a lot in terms of technology, applications, prevalence and gestational windows of exposure. One industry trend has been an increase in scans per pregnancy. A Canadian study published this month found that in the 10-year period ending in 2006 the number of prenatal ultrasound scans per pregnancy

increased 55 percent with the largest increase among low-risk pregnancies that had no medical need. To summarize the three studies the first one showed that ethnic groups with the least access to early prenatal care had the fewest autistic children, the second showed that white women who had educational advantages had a much higher rate of autistic children and the third showed that at least in Canada the number of ultrasound scans per pregnancy has increased dramatically. Taken together they raise new questions that should involve everyone currently working hard to understand what is causing autism. Questions such as do some people have genetic predispositions that make them more susceptible to ultrasound-induced damage that results in autism. Early studies show that ultrasound can damage mitochondria. Could ultrasound be causing non-inherited mitochondrial disorders that lead to autism? Ultrasound heats tissue. Could this damage heat-shock proteins, hampering their ability to

protect newly vaccinated children experiencing prolonged high fevers who then regress into autism. Could the thermal effects of ultrasound be causing changes in gene expression that result in autism? The good news is if prenatal ultrasound is contributing to the autism crisis we can quickly start driving the autism numbers down again just by unplugging it in routine pregnancies and severely restricting its medically indicated use. Specifically, I am asking the IACC to consider making the following changes in Section 3 of the Strategic Plan.

Dr. Insel: We'll need to go through this quickly because we're over time.

Ms. Rogers: Just five points. Thank you. On Page 1, what caused this to happen and can this be prevented, I suggest adding the bullet, "What aspect of prenatal care may be increasing the risk of ASD." On Page 5, Line 17, after the sentence ending in the word "risk" I recommend adding, quote, "New studies regarding ethnic differences in autism rates

combined with previous studies regarding entry into prenatal care indicate that some aspect of current prenatal care may contribute to causing autism." On Page 5, Line 21, after the sentence ending in "EPA" I recommend adding, "Wherever possible in the previously cited studies efforts should be made to record data regarding ultrasound exposure, including the output power, type and length of examination as well as information regarding optional keepsake ultrasound sessions." On Page 9, Line 18, I recommend a new paragraph as follows: "Since prenatal ultrasound exposure may prove to be a factor in causing autism, we need to provide all ultrasound operators with a standard format for recording the power output, type and length of examination along with any other factors recommended by experts who specialize in fetal ultrasound safety. This format must be required so that accurate data in a standard format are available for future analysis." The last one I recommend is on Page 10. Remove the word

"ultrasound" from the seventh bullet listing potential environmental factors. Instead, add the following bullet: "Changes in prenatal care, specifically changes in the application technology including but not limited to increases in potential acoustic output, harmonic imaging, Doppler imaging both spectral and color, 3-dimensional imaging and ultrasound contrast agents and gestational window of exposure for prenatal ultrasound."

Dr. Insel: We'll need to wrap up.

Ms. Rogers: Thank you. If you incorporate the above suggestions then additions will also need to be made to both the short-term and long-term objective sections. Thank you very much.

Dr. Insel: Thank you. And again, these comments as well as written comments that were submitted from the public are in your packets and I encourage you to look at those carefully. We had a discussion, I think it was in December at our last meeting about how to

respond best to public comment and we'll get back to that later today when we get into more of the business of the committee and we'd like your thoughts about how best we should do this going forward.

Moving on with the agenda, the next thing to do for us is to look at the minutes and see whether there are any corrections or edits for the minutes from the last meeting which was in December.

Ms. Redwood: Tom, the only edit I saw was regarding the date for the IMFAR meeting is in May and not March.

Dr. Insel: Right, so we can make that change to the minutes, Susan, to make sure it says May 2010. Anything else? With that change I move to accept the minutes as written. All in favor?

(Show of hands)

Dr. Insel: Any opposed?

(Show of hands)

Dr. Insel: We have minutes accepted

and we'll move on now to the first of the presentations for this morning from Dr. Andy Shih who's going to talk to us about global perspective on autism. Andy, it's great to have you here. You probably know but some around the table may not that a global perspective is becoming higher priority at NIH. The new NIH director has listed this as one of his five specific areas for focus. We had a meeting about 10 days ago with almost all of the leaders in global health and one of the things that's becoming very clear is a shift from a focus on global health meaning tropical disease or infectious disease to increasingly meaning chronic disease and often non-communicable diseases. So there's great interest in thinking about cardiovascular disease, but also neuropsychiatric and developmental disorders in the sense that "global" no longer means foreign but global means international including what we do at home. So with that as introduction, terrific to have you here.

Dr. Shih: Thank you very much, Tom. I want to thank Dr. Insel and the members of the IACC committee for having me here to share some of our current thinking about international scientific development relative to autism as well as some of the progress that's already being made. So most frequently when I talk to families - affected families about doing international scientific development in autism disorder the first question is usually why. Why do we do that when there's so many needs here at home that we need to address. And I think this is an obviously very important and legitimate question. An answer actually is fairly straightforward. I think the reason we want to do work internationally is for the same reason we do work here in the United States, is to deliver answers to affected individuals and families. And working internationally there's actually some exciting opportunities which we can exploit that can help us arrive at some of these answers much more quickly. We believe

there are key opportunities in areas of causes, diagnosis and treatment, and dissemination that are also relevant to the priorities in the U.S., specifically IACC.

So what are some of these opportunities? As Dr. Insel mentioned, epidemiology has been getting a lot of attention in scientific literature recently. What can we learn about autism risk factors by comparing prevalence incidence around the world? The idea is that if there are territories that have significantly higher or lower incidence of prevalence rate that should give us an important clue about maybe there's something going on in the population that deserves a closer scrutiny. And obviously, relative to that is environmental sciences priorities. Can we identify environmental risk factors, for example toxic and diet, infectious agents, et cetera by comparing exposures across large countries. And this obviously follows up on the first point is that if we do see differences in public health

statistics looking at environmental factors that may be in play is certainly one of the approaches we can take to help us find some of the answers there.

Certainly in genetics there are opportunities as well. As we know from medical literature that genetic risk in one population doesn't necessarily always translate to other populations. So for example do Europeans and Africans have the same genetic risk factors for autism? That's an answer that we can find out hopefully, and obviously other populations for example in the Middle East because of culture and tradition they offer a unique opportunity for discovering autism risk genes as the work done by Chris Walsh and others have demonstrated recently.

In diagnosis/treatment, how do culture and social norm impact recognition, diagnosis and treatment? An example of that is that for example some cultures seem to frame successful child development in terms of

academic achievement, so in those cultures such as one I grew up with how does that impact recognition of autism in a community and obviously diagnosis? And finally, and this is certainly a major unmet need relative to our autism portfolio in the IACC Strategic Plan: dissemination. We know a lot of solutions already that are efficacious, behavior intervention is certainly one of them and Dr. Insel highlighted the paper in Pediatrics, but what is the best way to influence sustained best practices even in places where there are limited resources and capacity? I would suggest that the answer to this question not only has application globally but also is important on the population in the United States.

So thinking about the global autism public health challenge let's put that in perspective in terms of how to measure it. According to WHO, the burden of diseases or disability-adjusted life year daily is really predicated on several factors: the prevalence,

functional impairment, chronicity, age of onset and cost. As you can imagine, when you put all those things together autism's DALY is higher than Type I diabetes, childhood leukemia and cystic fibrosis combined. We know that the cost to society in the U.S. is $35 billion per year. We don't know what that is globally, but I can imagine it's comparable if not more. And of course, last but certainly not the least, the cost to families are immeasurable.

From talking to a lot of professionals and families around the world and experts we understand the following are the major challenges across the globe for progress in autism spectrum disorder research. Certainly the lack of public health statistics. Many ministries of health and ministries of education are - would need information like prevalence and incidence in order to inform proper policy planning. Lack of public and professional awareness, I think we know very well what that can do in terms of competing progress. The lack

of training and expertise. In many of these territories there's no individuals who are skilled in diagnosing autism and more importantly even delivering basic intervention and treatment services. And of course when you put all this together that leaves a tremendous amount of stigma for the community at large. So in thinking about how to address these public health challenges there's several strategies that have surfaced. Certainly - and all these strategies are from the Global Autism Public Health (GAPH) Initiative Strategic Plan that was developed recently. Certainly we want to increase public and professional awareness of autism spectrum disorders, want to implement efforts that facilitate collaborative research and research training, and we want to address immediate needs by enhancing service delivery via training and diagnosis intervention. The way we implement these strategies practically is through some of these approaches. We want to prioritize and coordinate activities in

awareness research and service development because we believe that integrating these activities are important for the success of any one component. It's important that there's local ownership of the effort. Outside experts really serve as advice and facilitator. The priorities need to be set by local stakeholders. For example, some countries may see service development as top priority rather than awareness, whereas others may see epidemiology as the most important effort as opposed to genetics. Driven by - and all these efforts need to be driven by collaboration with local government, professionals and families. We believe by working together then we'll be able to develop solutions that are meaningful and impactful, and that the sustainability of these solutions are - the opportunity for creating sustainability of these solutions are much more enhanced. And finally, we want to adapt evidence-based solutions to accommodate cultural and social factors and available resources and

infrastructure. As we said earlier, the solution we have here in the States, develop medical centers, even community clinics, may not translate well outside this country.

So we have made some progress in terms of collaborating with various territories and these are some of the countries where awareness research services collaboration has really seen some progress. In Qatar we partner with the Shafallah Center for Children with Special Needs. In Mexico we partner with Carso Health Institute, Telmex Foundation, CLIMA which is a network of community clinics in Mexico and the Ministry of Health. In Albania we're looking at Albanian Children's Foundation, Ministry of Health, Ministry of Education. In Ireland we're working with the largest autism advocacy group there Irish Autism Action. In Philippines we're working with Autism Hearts Foundation, First Gentleman's Foundation, Autism Society Philippines. And in Chile we're working with Ministry of Health. So together we're

actually looking at - we've been making - looking at some of these challenges and making some progress.

In the area of epidemiology, the goal obviously is to enable epidemiological studies to allow comparison of statistics across countries and in doing so hopefully to help identify potential environmental risk factors. And obviously these public health statistics can also generate public health to inform policy development. The barriers that we see are limited availability of translated adapted gold standard diagnostic instruments such as ADI, ADOS and of course a lack of clinical expertise. Progress has been made in this area. Screening and diagnostic instruments have been now adapted in languages spoken by 1.75 billion people, mostly funded by Autism Speaks. And the standardized international training program for use of screening and diagnostic instruments launched by UMACC, WPS and Autism Speaks and a good example of this and predecessor of this

model is actually the collaboration we did with NIMH in India. The table shows some of the territories where we have supported translation of the instruments, everything from Mandarin Chinese to Zulu in South Africa. With the CDC we have also put together the International Autism Epidemiology Network - currently just over a hundred members from 30 countries involved - to facilitate sharing, collaboration. A good example of this is the iCARE project which is a registry project put together of many registries from around the world to look at issues like environmental factors and trends in diagnosis and of course mentoring. And this is important to train interested researcher on the latest methodology and best practices in research. We have epidemiology studies ongoing in South Korea, many the first in the country. South Korea, India, Taiwan, South Africa which is actually an interesting study because it's an add-on to an existing NIH HIV/AIDS project, an idea to see if

there's - the endemic infection of HIV/AIDS has an impact on autism prevalence. Of course in Ireland we're sponsoring - we're helping the Irish Autism Action to sponsor a study with support from the CDC. And studies are also in development in Mexico, Albania and the Philippines.

In genetic, the goal is to enhance identification, understanding of genetic risk factors in different populations around the world. The main barriers like in epidemiology is lack of adapted "gold standard" screening and diagnostic instruments in case ascertainment and limited capacity, especially in molecular and statistical genetics. The progress we've made in this area, Autism Genome Project for instance, a successful international research consortium involving participants from 19 different countries and it's sponsored by a consortium of funders. And this consortium has already made significant progress in autism genetic research and it is one of the models for

psychiatric genetic research going forward. Diagnostic instrument adaptation and clinical/research training. A good model of this is the MENA ADI-R translation and adaptation effort that was facilitated to bring together countries such as Egypt, Saudi Arabia and Qatar to develop an instrument that is broadly applicable across a region, across cultures and regional language differences.

Research collaboration, for example, NIMH and Autism Speaks hosted an Autism Genetics in Special Populations meeting a few years ago to look at these opportunities and we also facilitated a partnership between the Qatar Shafallah Foundation with Autism Genome Project. In diagnosis and treatment the goal is to enable early diagnosis and intervention worldwide, and certainly these are the same here in the United States. The main barriers again is a lack of adapted "gold standard" screening and diagnostic instruments, limited capacity and expertise, especially in behavioral

intervention, the lack of low-cost, community-based treatment solutions to maximize coverage and impact. As I mentioned earlier, this last point is particularly important, especially in low- and middle-income countries where they do not have the benefit of trained professionals or even medical centers dedicated to autism so to find a solution that can be effective on a community level is a top priority. Progress is being made in this area. For example, in service - in infant siblings research in the U.S. co-funded by NICHD and Autism Speaks and UK funded by MRC and others, and we are planning an expansion into Europe and other territories. The Pan-American Autism Awareness and Training Initiative or PAAATI is a collaboration among Carso Health Institute in Mexico, NICHD/NIH, CIHR Canada, American Academy of Pediatrics, Autism Speaks and the CDC. The development of screening and diagnosis research, for example, I've been invited to participate in a MENA newborn screening meeting at Shafallah Center,

Hamad Medical Center and the NIH/NICHD. And finally with WHO we're now exploring partnership effort aimed at disseminating evidence-based information implementing cost-effective and feasible solutions to the global autism community in the context of WHO's mhGAP Action Program where child mental health is a priority and autism is certainly a part of that. Furthermore, we're conducting diagnosis training in Qatar, Saudi Arabia, Albania. We're conducting intervention and service training and as well developing pilots and community-based and cost-effective training programs in Albania and Mexico. We're exploring distance learning technology professionals and parent training in Mexico. And finally, facilitate and implement the DG Sanco-funded - that's a European Commission-funded project to establish diagnosis and intervention standards in Europe. We're doing this in collaboration with Irish Autism Action.

So in conclusion, international

development in autism research presents a unique opportunity to address key scientific questions in multiple IACC priority areas. Outcome from these international efforts will benefit both the international and domestic autism communities. While each country has its own priorities, common themes such as adaptation of screening and diagnostic instruments and capacity-building in both research and services provide a robust foundation for future development and collaborative activities. Investing in awareness, training and service development help build trust with partner communities and enhances the overall quality of research. It is also just the right thing and the ethical thing to do. Progress is already being made in collaboration with NIH, CDC and various IACC members. Additional investment and collaboration in international research and development by the NIH and CDC are needed to accelerate progress and enhance impact on the global autism community. Obviously I want to

thank the friends, families and stakeholders from around the world who informed our thinking in this area, NIH and CDC, and of course the list of advisors. I include members of this committee who guide us in our effort. Thank you very much.

(Applause)

Dr. Insel: Thanks very much, Andy. I neglected to mention at the beginning that you're the Vice President of Scientific Affairs at Autism Speaks in case anyone hadn't recognized that and to note that Autism Speaks really has taken the lead in this area which I think is important for all of us to appreciate. They've even created I think a World Autism Day through the United Nations which is something that doesn't exist as far as I know for any other disease category. If you'll stay up by the microphone let's open this up to discussion and questions and see whether there's issues from the committee that they want to explore with anything that you've talked about. Yvette?

Dr. Janvier: I was just curious about your choice of countries. Albania struck me as somewhat, you know, unusual.

Dr. Shih: Right. So some of these territories were developed through strategic partnerships. Other were - others through our existing partnership. For example, Albania, the First Lady of Albania Dr. Liri Berisha who heads Albania's Children Foundation - often speaks at one of the disability forums in Qatar, Doha.

Dr. Insel: Jim?

Dr. Battey: To follow up on that point that Yvette made, you would expect in a country like Albania which is a third world country that there would be far fewer neonatal ultrasound screening done and if in fact that was a major driver of the etiology of autism you might predict then that an epidemiological study done in that country would reveal that the rate of autism is lower. Is that the case?

Dr. Shih: Well, we don't know that yet because such a statistic doesn't exist in

Albania, but what you say is absolutely correct. A situation like that does represent n opportunity for us to look at these issues. Another concern I often hear in Albania is that as a country that is rapidly industrializing at this point and obviously environmental pollution is becoming a concern for many of the population, so it also represents an opportunity for looking at environmental factors potentially contributing to not just autism but general issues of public health.

Dr. Insel: Walter?

Dr. Koroshetz: Just a narrow question, sorry about it, but have you had any discussions with groups in Norway? Because we're running this very interesting population study of maternal-fetal environmental factors and we're having a lot of trouble in getting patients who were kids to come back for follow-up. So if there's any organizations with ties to autism organizations in Norway I'd certainly like to discuss how we might be able to improve

that case ascertainment issue. Because we have this amazing database of mothers, perinatal care, cord blood samples but it's only valuable if we can get the cases to come back in and that's actually been a problem for us.

Dr. Battey: And if I could add to that, Norway represents an extraordinary opportunity because the - as I'm sure you know the genetic heterogeneity is reduced to a level far below that found in say the United States and so it might be easier to tease out environmental issues.

Dr. Shih: I think both of you are absolutely right. I mean I think looking at cohorts and registries that are available internationally is certainly a significant opportunity for environmental science research internationally. We have been in contact with Norway. The Norwegians were involved and actually they are part of our iCARE project at this point to look at information collected from across registries for multiple countries. We

have also been in discussion with some of the principals about how we can be helpful in that territory. And certainly this would be one of the issues that we'd be thinking about and discussing.

Dr. Koroshetz: I'd like to talk offline about how to kind of help that study.

Dr. Shih: Okay.

Dr. Insel: Linda?

Dr. Birnbaum: Yes, I'd like to respond to that a little bit, Walter, in terms of NIHS is also working with that MoBa study and I think the issue of getting appropriate samples or getting the follow-up on those kids is really important because there's a wealth of environmental data and health data on those populations.

Dr. Insel: On this topic, Andy, can we draw you out a little bit further about sort of a more general issue which is the strategy in this area? It sounds like a lot of what's happened up until now has been driven by the

serendipity of a personal connection with someone whose family member, you know, a prime minister or someone who's very important in the country has a family connection to autism which sounds like it's getting more and more common. But as you think about it from the Autism Speaks perspective and you look out at the whole range of what's there on the planet, where do you see the most important scientific opportunities? What are the - what's out there that would make a particularly critical area for us to partner with you and try to get certain kinds of data? We heard the need for screening and diagnostic instruments that are in many languages and that are culturally and ethnically adequate or even optimal, but what about the opportunities? What are you looking for? What's the likelihood of finding something that will tell us what we can never find if we just stay within the 50 states?

Dr. Shih: Right. So, I mean I think first of all as organizations driven by a mission to bring solutions and hope to the

families I think certainly a priority for us is trying to inform the public, to increase capacity for diagnosis and most important services. I think by doing that you allow us to build a foundation to add on other type of research such as genetics, environmental sciences and so on. But even within the capacity-building activities I think they help us - we can certainly integrate research questions into those activities. The idea of what is an effective dissemination model, for instance. How do you encourage best practices? I think these are challenges not only - they're coming challenges that are not only for international community but also for community here in the United States. I think if you look at some of the hard sciences, whether environmental sciences or genetics certainly there are plenty of opportunities there. I think the way we're thinking about this is that it needs really to be a package approach, right? Because different territories have different

priorities and different opportunities. I think you're right, up to this point I think the development of this international opportunity has been sometimes through personal contacts, but if you notice the countries in which we are working right now does represent a nice breadth in terms of available resources, infrastructure, potential different environments than what we found here. I think it is the kind of comparison of information across countries, across territories that would be hugely important for us to inform our thinking in terms of areas of opportunities and interests to pursue.

Dr. Insel: So let me just follow up on this. Linda may be helpful here as well. We hear an awful lot here about prenatal factors and the interest in finding - and you heard the fora comment about ultrasound - but we've heard similar comments about folic acid, about nutrition, about all kinds of environmental exposures some of which are part of optimal care

in the United States and some, like folic acid, something that we've added in that we think is probably really important and has been shown to be critical for preventing spina bifida. The question is whether, as you look around, are there places that one could go where some pieces of this just haven't been implemented and you could do a specific comparative study where the variable of interest would be most evident. Is that something that you've looked at or is there an opportunity there particularly for prenatal care?

Dr. Shih: I think the idea - for example, I mentioned the project, looking at the add-on in South Africa. The idea of looking at a population where HIV infection is endemic. If we're interested in exploring through relative immunoactivation, maternal immunoactivation for instance as a possible risk factor for autism I think that's a potentially helpful environment to do something like that. Another possibility obviously is looking at malaria infection and

how does that - and maternal immunoactivation in malaria infection, does it have an impact on autism prevalence for instance, or autism risk in general. So I think these are some of the things that can be looked at in that context.

Dr. Insel: Linda, is there anything you can share with us about specifics, particularly around prenatal exposures?

Dr. Birnbaum: Well, there are many studies that are going on in different parts of the world that are really focusing on the environmental exposures that are occurring prenatally by taking, for example, maternal blood at various times. There are studies, you know, the National Children's Study eventually may provide us some information there as far as what exposures are in our part of the world, but in many developing countries. There are a number of collaborative studies going on where prenatal samples, you know, mom samples are being taken. I mean I think one thing, and maybe Andy Feinberg's talk will help elucidate

some of this is there are possibilities that things may have occurred to mom long before she ever became pregnant which have in fact resulted in epigenetic changes which will affect her developing child.

Dr. Insel: Alison?

Ms. Singer: Andy, when you were talking about service delivery you talked about doing things because they were the right things to do and so I was wondering if the international group has made any efforts to reach out to families in Haiti or whether there's been any talk about resurrecting the Autism Cares group as a way to try to reach families raising children with autism or individuals with autism who are affected by the earthquake?

Dr. Shih: Yes, well I mean that's certainly - thank you for that question, Alison. I mean, we have not specifically reached out to families in Haiti yet, but certainly as an organization we have. Obviously the - you know,

Haiti is probably one example where the needs would be just overwhelming for the families there. In addition to the day-to-day struggles and obviously when you're dealing with poverty and the kind of natural disaster like that I think the scale of needs is really unimaginable in some sense. I think that our focus and certainly interest in low- and middle-income countries help us think about these things in - and develop solutions in a more systematic way so that going forward in the future when communities in need such as ones in Haiti will be able to formulate a more evidence-based response and more impactful response for this kind of work.

Dr. Insel: Ed?

Dr. Trevathan: Just great presentation, Andy. Just a comment and then a question. One of Tom's comments I thought was really important and illustrates that some of the comparative studies across countries don't have to be developing countries. So for example

the folic acid question, most of the - or many of the European countries don't have wheat flour fortification with folic acid like the Netherlands, for example, and have higher rates of neural tube defects but not different rates really for autism. So we really do have already data that we can use to compare some of these countries.

One of the issues that I know we've discussed in some of our conversations and I think you've alluded to but others may be interested in hearing is that, just as an example, an African country that we're involved in offering technical assistance in this area, when we go to these countries of course there has to be something that's of importance to them and addresses needs that they have, not just our own scientific questions. So that for example some of the comments we've heard have been we're really interested in autism, we have children with autism, we don't know how many, we're concerned about services, but we're more

concerned, a bigger priority for us is cerebral malaria or epilepsy diagnosis and treatment or one I heard recently, services embracing for people with cerebral palsy. That's sort of a more urgent issue for us. So very often we - in order to address some of our autism scientific questions we also need in the same system to address some of the concerns and the needs of that particular country. So how are you all looking at - at Autism Speaks of addressing the needs of the home country even when they go outside the technical autism boundary but are in sort of a general developmental disability framework.

Dr. Shih: Right, I think you're - well first of all, I think there are many learning opportunities in the scenarios that you have described. I know in our conversation for instance we talk about how for example socio-communication deficits is not unique to autism and identifying a solution for socio-communication problems in autism may have

implication for socio-communication challenges in other diagnoses as well. That's certainly one way to think about this. And I think the other thing is that - that's why it's important for us when we work internationally for the local communities to set the priorities and we provide technical assistance where it's relevant, where it's meaningful, where it will have an impact on the community.

So an example is that if you're thinking about diagnosis, now obviously developmental disability as a broad category have many challenges and some of them are obviously shared by autism, but we also know that autism requires a special kind of intervention that could be effective. So the idea of looking at differential diagnosis in developmental disability is probably important and the earlier we can do that in life probably the better outcome it is for not only children with autism but children with other intellectual disabilities as well.

Ms. Blackwell: Andy, I'm sorry, I'm facing the wrong way. I've heard you talk a lot about and services and how they relate to children, but I wondered if you had at all assessed what's happening on an international level in terms of adults with autism.

Dr. Shih: We haven't had time to do that in a systematic fashion, but I can tell you anecdotally, you know, some of the interaction I had with families, especially families with older children, older children with autism has been absolutely gut-wrenching and is certainly a major motivation for me, you know, in thinking about this work. And I know there's a lot of needs in the United States and Western Europe and so on and the families are struggling here, but when you talk to parents in their seventies in southern Taiwan who worry about what's going to happen to their 40-year-old son when they're gone, you know, there is no answer to that and the desperation is palpable. And I think that, you know, we're just starting to look at the

global challenges and I think that in the context of developing solutions that are community-based that could be cost-effective, you know, if we can think not only in terms of early diagnosis but also the needs of young adults and adults on the spectrum I think there could be lessons learned there for us as well.

Dr. Insel: Any other questions or comments? Yvette?

Dr. Janvier: It just came to mind when you were talking about maybe collaborating in other parts of the world that Kiwanis International for years had a project to promote iodine usage to prevent iodine deficiency causing cognitive impairments, and there's certain pockets of that throughout certain parts of the world, but it kind of - I wonder if there isn't some sort of collaborative approach through United Nations, UNICEF and - that micro-nutrient iodine project kind of reminded me of some of the things that Andy was talking about. Just an off-the-wall thought.

Dr. Insel: So Andy, in the process of doing this, have there been specific either very dense clusters like we had with Huntington's or with Parkinson's with manganese, or have there been areas where there have been a very, very sparse presentation of autism that have popped out in any of the environments that Autism Speaks has been working with?

Dr. Shih: Nothing that I can verify right now, but certainly anecdotally. For instance, in Saudi Arabia we've heard from multiple sources that eastern provinces in the mountains. For instance, there haven't been that many autism cases reported. But of course, without having a sense of the baseline to the national prevalence in autism it's difficult to say that and I think you know, we're making progress there by making standardized instruments available so we can actually make meaningful comparisons. And by working collaboratively with the research stakeholders in Saudi Arabia maybe we can find the answer and

inform the rest of the global community as well.

Dr. Insel: Lee? Stephen, can you hear us? But you can't - do you want to ask Stephen's comment? We cannot hear you, Stephen, so we could do this by augmented communication if you want to send a note to Lee. We can pass that along. If you can hear us well enough. Let's wait a minute and see if something comes through. Any other comments in the meantime, or other questions? Lyn?

Ms. Redwood: I was just going to follow up on the comment you made about clusters and I think there's opportunities here in the United States that we haven't taken advantage of too to look at areas that have very high or low incidence like the Somali population, and also there's been reports of very low incidence of autism in Amish populations. So I think we should also look here at our own country for those type of opportunities for research.

Dr. Insel: Let's just wait another minute and we'll get Stephen's comment and then

we'll move on from there. It's a great example of the value of technology when you can't communicate.

Mr. Grossman: Or its inefficiencies as well.

Dr. Insel: That's right.

Mr. Grossman: I guess I can comment a little bit in the meantime on some of the international efforts. We have actually quite a rigorous effort going on on the adult issues or adult services issues. We have, as Andy has so well pointed out, it is a plight that's not only in the U.S. but around the world. We have identified that there are some areas such as in Scotland and Wales that have actually fairly - and England that have fairly good adult services relative to the U.S. Also there are areas such as - in a much more limited fashion, but the Autism Society of the Philippines, for example, has a very good residential program for their adults. So there are some pockets and obviously some models and we've had these people over the

years present at our conference for us.

Okay. Stephen has said, quoting Stephen Shore, "I've traveled extensively and finding a growing number of adults with autism eager to contribute to the well-being of our peers with autism." I'm not sure if that's the end of his comment or he used all of his characters, but that's Stephen's comment I guess.

Dr. Insel: Well Stephen we're working on getting you back into the meeting and we're going to have to move on with the agenda, but there will be an opportunity I think to capture Dr. Shih through the course of the morning. Andy, are you going to be able to stay with us? So either later on when you join us or we can do this by texting, whatever works best for you. Lee, anything else?

Mr. Grossman: This just in. "For example, in Singapore, Poland" - let's see, let me go back - "I've traveled extensively and finding a growing number of adults with autism

eager to contribute to the well-being of our peers with autism, for example, in Singapore, Poland, et cetera. What is being done to work with those of us with autism in the global efforts?"

Dr. Insel: Did you get that?

Dr. Shih: Yes. So I think, you know, to - I mean, I think what Stephen said is exactly the point I was trying to make. It's that you know certainly traveling around the world you meet many communities and even though there are differences in priorities I think they all want - all the members of the community want one thing, better lives for their children and better lives for the families. And the only way we can make that happen is by working with them and partnering with them and to tap into the talent, the motivation, the dedication that's within all of these communities to make things happen and sustainable in their own countries. So yes, I completely support Stephen's comment about that and that the only way we can make

this a successful enterprise is by collaborating broadly and widely with not only the scientific community but also the advocacy community and autism community around the world.

Dr. Insel: Okay. Andy, thanks so much for this run-through and thanks for your leadership on this important problem.

(Applause)

Dr. Insel: We're going to move on with the agenda. The next presentation is from another Andy, Dr. Andy Feinberg, who's the head of the Center for Epigenetics at Johns Hopkins School of Medicine. And we've talked a little bit about this topic but in a just a very introductory way. One of the things we discussed at the last meeting was the importance for the IACC hearing about where this field is moving because it's moving very, very quickly, a lot of this happened just in the last eight weeks, and it's now beginning to move from its focus largely in the world of cancer research to now being able to inform what we think about in

neurodevelopment as well. So with that introduction, Dr. Feinberg, great to have you here.

Dr. Feinberg: Well thanks. I'm honored to come and talk to such a highly motivated and engaged group of families and professionals and tell a little bit about this new area. I hope it's - we certainly think it's important, but I'm hoping that you find this helpful. So I'm going to be talking about epigenetic approaches to neurodevelopmental disorders and I'll define what I mean by "epigenetics." We actually have a center named for epigenetic now at Johns Hopkins and I'm going to explain a little bit about what that means and how we organize. It's a new way of doing scientific research - I mean, not totally new, but it's a little bit new in the epigenetics field in terms of integrating lots of different disciplines together. So what I'd like to do is have - I'll stay within the time limit but I want to cover three topics,

basically. The first is I'd like to present to you a Gedanken experiment, and I'll explain what that is in just a minute, but it's meant to put in a simple way, a straightforward way, why epigenetics must be important in neurodevelopment. Second I'm going to talk about a method for assessing normal and abnormal DNA methylation which I'm also going to define that we call CHARM. It's a new method. It enables us to ask questions about the hidden genome that we haven't been able to ask about before. We depend heavily on the wonderful results of the Human Genome Project that have made available the DNA sequence for investigation, but there's a lot of information that's in the DNA that isn't the sequence itself and this is one way to get at that. And then finally I'm going to talk a little bit about how you apply high-throughput epigenetics, some of these new technologies and this sort of new structure that we've created at Hopkins to ask questions about the epidemiology of

neurodevelopmental disorders, including autism.

So first is the Gedanken experiment. So what does that mean? It's a somewhat pompous scientific word for thought experiment, it's a German word, and there are some famous examples and my thought experiment is going to be to explain to you why epigenetics and DNA methylation must be important. So other Gedanken experiments are Schroedinger's cat. So Schroedinger's cat is about a hundred years old and this was a cat that was put into a box that was radioactive and according to quantum theory sometimes it gets a little bit more radiation than other times, but that both are true at the same time so the cat is alive and dead at the same moment. And I don't mean anything disrespectful towards cats, but this was Schroedinger's idea and it was a brilliant insight that led to a whole revolution in physics. Another Gedanken experiment was Maxwell's demon which illustrated the third law

of thermodynamics and there was a little monster inside of a box that would let a little atom get through or not through and open the door or not open the door and violate thermodynamic principles and again, that led us to understanding entropy. So what's my Gedanken experiment that's going to explain epigenetics? The United States Congress. So I thought I'd explain them today. So what makes them different? I mean, here they are, 535 people, and you know, they're very different from one another as we read in the newspaper from minute to minute, very difficult to get them to agree on anything. So, well let's see. They have 3 billion base pairs of DNA, every one of them, and there's 300,000 to a million depending on how you count differences in DNA sequence, I count more than 300,000 actually, and that's it. So those 300,000 DNA sequence differences are enough to explain the differences among 535 individual people. But ask yourself the following thing: what if you were to take a

person and look inside using one of these Transportation Security Administration devices, I don't really know what they do, but see inside their brain, their liver, the stomach, the eye, the kidney and so forth of the person who's sitting next to you. Now, those are more different - those tissues in that person from each other than the United States Congress members are from each other. They all have 3 billion base pairs of DNA, but there are no differences in the DNA sequence. It's exactly the same sequence. Now, you can argue that there are some differences, like telomeres, the lengths of telomeres and a few little things like that, but they're not going to explain the major differences among the different parts of the body. So that's a big deal. I mean, they have the same DNA and yet you can't explain that using conventional DNA sequence. So how do you explain that? Well, that's what epigenetics is. So epigenetics is formally defined as modifications of the DNA, like chemical changes

in the DNA or factors that are associated with the DNA, and I'll give you a cartoon in just a second to show you what those are, that have information content just like the DNA does, but are not the DNA and they are replicated, that information is copied during cell division. That's critical for it to count as epigenetic information. And another way of saying that is epigenetics has a life cycle while the DNA sequence does not. And so when you start out, the sperm and egg are very different epigenetically and then there's a wave of reprogramming that occurs shortly after fertilization, and then a reprogramming in a tissue-specific manner that takes place early in development around the time of implantation that leads to tissue-specific differences and we even think that those change during age. Actually, we have data that was published a couple of years ago in JAMA showing just that, but I'm not going to have time to talk about those results.

So here's this source of plasticity in development that carries information content that's critical to the development process that isn't the DNA at all. It's dependent in the DNA in the sense that it occurs at certain locations, but that carry information and can distinguish one tissue from another, and perhaps developmental disorders from normal development. So we think that epigenetic marks distinguish stem cells, tissue types from one another, aging, and cancer. Actually, the strongest evidence is for cancer so I'm going to talk about that in just a moment.

So what are the types of epigenetic information? So if you start with the chromosome which you're all familiar with and then go to higher and higher levels of resolution there are - the chromosomes themselves are organized into very dense regions and less dense regions that we refer to as bands, then there's a level of organization that involves loop structures, higher order

chromatin, with hundreds of thousands of bases of DNA that are wrapped into these large super-coiled domains, "super-coiled" meaning like a rubber band, and then are anchored by certain critical proteins. And then if you zoom in further onto that you find that the DNA is actually curled around these balls of proteins called nucleosomes that are eight peptides that themselves undergo chemical modification, covalent modifications, for example, methyl groups, acetyl groups attached to these, and then there are proteins that recognize those factors as well. And then you finally zoom on down to the double helix and the double helix itself has a modification that we call DNA methylation which is a methyl group, a methyl group of CH3 that's added to the DNA and is maintained during DNA replication. So how does that actually happen? So here's the double helix and let's say that we have one of these methyl groups. Now, the methyl groups that are remembered during DNA division - this is sort of

like the fifth base. So it's important for me to cover this, it's sort of - you have your A, G, C and T, then you have this methyl C, so that's what I'm going over right now. So the information is copied whenever there is a methyl group on the cytosine that is followed by guanine, and the reason has to do with the Watson-Crick base parent. So opposite to the CG is a CG going in the other direction. So when you have a methyl group here you have one there as well. Now, the great insight of Watson and Crick was that when DNA replication takes place you have a parent strand and a daughter strand. That's called semi-conservative replication. So one of the methyl groups goes with each daughter cell. The other newly synthesized site is unmethylated and there is an enzyme called DNA methyl transferase 1 that looks for this hemi-methylated DNA, looks for the CG that's methylated over here but that C is not methylated and puts a new methyl group on there. And that is a way that the information is

copied during cell division. So it fulfills the definition of epigenetic memory.

Now, I came to this view about three years ago when I was asked to write a review in *Nature*, the journal *Nature*, on epigenetics of developmental processes in human and also in human disease such as cancer and so forth. And they only gave me about 2,000 words and I had to sort of come up with a unifying theme for everything. When I thought about it I realized that a common feature of any disruption in epigenetic information would be that there would be an alteration in phenotypic plasticity. So I think that's the common element to developmental disorders that involve epigenetics is that they're going to change the normal developmental program and change the way the phenotype or the characteristics fold out during normal development. And the classic example of this, and I think that shows that epigenetics must be important in developmental disorders is Rett syndrome. So Rett syndrome, the gene was cloned

a few years ago and was identified as something called MECP2. This is a protein that recognized methylated DNA and silences genes when it sees it. So for example, you might have in early development a gene that is here. Here's the nucleosome, here are a variety of modifications, and that RNA is getting transcribed, so that is an active gene, and then during development it might be necessary for that gene to shut down. And what happens is that it becomes methylated as shown by these brown circles that are on the double helix and this MECP2 recognizes that and leads to silencing of that gene shown by that X. In Rett syndrome you get the normal DNA methylation, but the protein MECP2 that recognizes the methylated DNA is not functioning normally and now that gene is leaky and you get this abnormal expression. And shown up here - I'm not going to read it - is the definition from the NIH of Rett syndrome, but note the critical feature that's shown in green, that you have normal early development followed by loss

of developmental milestones. And I think that's also an aspect that we often see in autism as well where you have perfectly normal development and then you have neural developmental changes that occur at some point during early childhood. And of course autistic features are one characteristic of Rett syndrome as well.

So, why do I think DNA methylation is a key thing for us to study when we're studying the human condition? And that is that first of all, it's a stable mark so it's practical for human genetics studies. So bear in mind the NIH has spent a lot of money over time collecting cohorts of patient samples as have private groups as well for genetic analyses. And insofar as one can go back and relate the important genetic information that's been collected on those samples and connect that up with the epigenome that would save a lot of resources and also add to a wealth of information. And DNA methylation is the only epigenetic mark that one can study in those

sorts of studies, in other words from markable samples because it's stable for at least decades in the DNA where other types of epigenetic changes I mentioned are not. Second, there's a known mechanism for its propagation. And for the computer types, I understand there are quite a few of them actually in the audience, DNA methyl transferase 1 that I mentioned is a Turing machine. In other words, it's something that's able to both read and write information and therefore preserve that information content, and we don't yet have any other Turing machines identified for other sorts of epigenetic information. I think we'll find them, but we don't know them now so we don't know what would be the critical mark to focus on except for methylation. But having reached that decision it's critical to assess DNA methylation genome-wide cheaply and with high precision. Now, we have not been able to do that previously using conventional methods and in addition, I think that there's been a bit of a blind spot in

epigenetics research and that has to do with something called CpG islands. So people refer to the CG dinucleotide sequence, they put the "P" in between because there's a phosphate - phosphodiester bond. Sorry about that. I don't really think it's necessary to do that, but that's what people do. So anyway, where you have CpG's is where the methylation can occur and there are very dense regions of CG that are called CG islands, or CpG islands. Again, it's not a very good term but it's the accepted one in the literature, and almost all epigenetics research has been focused on that, at least in disorders such as cancer. But I questioned about a year and a half ago whether or not that's even right because systematically it hadn't been - the genome, the epigenome hadn't been examined outside of those regions. So, but first let me just mention that we think that DNA methylation is very important in neural development because in a fairly straightforward study focused on these CG islands actually using

a commercial array we were able to show that the pattern of DNA methylation even in 1,500 randomly selected regions across the genome that we could examine on a commercial chip were able to discriminate between the various brain regions from one another, like the cerebrum and the cerebellum, sort out in this cluster map. What's shown here is each of these is a different sample that's examined, each of these is a different CG island that's examined and red is more methylated and blue is less methylated, and this you can see by the colors clearly can distinguish these tissue types as I was suggesting in that earlier picture about the epigenome having a life cycle. But that's important because it means that the epigenetic information is as good as microscopy, as anatomical examination in distinguishing one brain region from another. And I mentioned Ramon y Cajal because that's the great scientist of 80 years ago who first did the identification of brain regions using conventional microscopy.

In my case it's much better than microscopy because I nearly failed my histology and pathology courses in medical school and I was charitably allowed to graduate given my visual deficiencies. But at the level of DNA methylation we can distinguish those tissues from each other.

So what is this new method that we developed for analyzing the methylome, or in other words, the DNA methylation across the genome in a comprehensive way and in an unbiased way that might collect new information other than what the focus has been earlier on these relatively small number of so-called CG islands. So we call this CHARM. Now, it's an acronym and I spell out the definition of the acronym, but this is a little PR for Baltimore, quite frankly. We came up with the word CHARM because the Baltimore City mothers and fathers call it Charm City and I do like the place, but it does have a bad reputation on television, so this was meant to improve its image a little bit. And

what the method involves is first of all a chemical fractionation of methylated from unmethylated DNA. I'm not going to go through that on the left because it's not necessary, but also there are several other ways of fractionating the genome so that you can separate methylated from unmethylated DNA. The critical part is what's shown on the right and this was done, and I think it illustrates one of the key elements of our center. I'm going to talk a little bit more about that because I think this is a model when you think about funding, when you think about grants, especially you philanthropic foundations about how to approach autism research. But this is a method that was equally developed by statisticians along with molecular biologists. It's not like the statisticians are consulted. We don't do an experiment until it's been co-designed by statisticians, molecular biologists and clinical investigators all working together. And there was a great insight by the statisticians which

was that what we should do is represent - these are on glass slides, custom designed arrays - but what we should do is put these CG sites for examination across the genome, but they should be selected based upon the density of the regions, regardless of what anybody says about where DNA methylation should be. Now, the densest regions of CG are the islands, so all of the islands are on the array. And then we go down from there though, 70 or 80 percent of the array does not have islands on it, it has other material. So we didn't know what we were going to find, we didn't make any assumptions about where the differences in methylation should be, but we decided let's just go look and see.

And here's the first result. It's kind of a complicated figure so bear with me for a moment but I think it's important. Shown on the left is a representation of the CG island space and on the right the non-CG island space, and what we're asking is where are the differences in DNA methylation in cancer. So

I'm going to be talking about that now for a little bit because that's the disorder that we're coming from that we understand the most about at an epigenetic level. And shown here on the X axis is the level of methylation using the parameter that we use in the laboratory, the more to the right to the more methylated it is. And this is the variance. This is how much that varies from one individual to another, or from cancer to normal, and actually we get the very same tissue result if we compare tissues to one another as well. And how dark blue that is is how many points that are there. If we made this black it would just all look black. So what you can see is that the range of methylation is much greater outside of the CG islands and as well, the variation is much greater outside the CG islands. There's some variation in them, but most of the action in terms of epigenetic variation is outside the islands.

Now, if we look close up where the

DNA methylation differences are in tissues this is what we see. So we're looking now at the brain, the liver and the spleen of a series of autopsy specimens that we were given permission to examine, and what you can see is that the methylation is the same - this is about 2,000 bases of DNA. Here's a gene. This is the promoter of the gene where normally people look for methylation. Here's the island, so that's the CG density map and the orange shows the island. That's where everyone always looks, that's where the commercial arrays are, but the methylation is the same until you get out to about 1,500 bases away and then the liver and the brain and the spleen diverge. So we didn't know what to call that, we saw that all the time, and we came up with this word "shore" just because shore is next to an island. And again, this is a bit of a Baltimore thing. We're in sort of our cubicle in Baltimore and it evokes a little bit of kind of a tropical kind of pleasant feeling about it. So I mean, that

really is why we came up with the word. And it fits the idea, what I was saying, about epigenetic disease disrupting - or disorders disrupting phenotypic plasticity, specifically focused on cancer. So let me say something about cancer and what people have found at the level of DNA methylation previous to our applying this CHARM approach to it. So one simple way of looking at what cancer is you have genes that maybe should be on and maybe should be off and in a certain tissue Gene A is supposed to be turned off and in another tissue Gene B is supposed to be turned on. And what happens in cancer is the genes that are off, are supposed to be off are abnormally turned on. And if they contribute to the cancer process we call those oncogenes; that's what that means. And then you have other genes that are supposed to be on but are abnormally turned off, and if that contributes to tumor growth we call those tumor suppressor genes. So you have this disrupted plasticity of going from this

potentiality to a pattern of on and off to the reverse pattern where genes are not behaving the way they're supposed to. And we've already known for decades that there's hypomethylation in many oncogenes, hypermethylation in many tumor suppressor genes, but this was a paradigm test of CHARM. In other words, where is the normal DNA methylation and abnormal methylation in cancer if we use that unbiased genome scale approach that the statisticians designed for us? And here's the result.

So I've shown the same sort of graph with the same sort of meaning for those tissues as I did before, but I added one more tissue. I added the normal colon, and the normal colon is methylated normally in this particular gene in the shore, but look what happens in the colon cancer. The colon cancer is this orange line right here. The colon cancer is acquiring a hypomethylated pattern that's similar to the normal liver. And so what you're getting in cancer is you're getting methylation changes at

the CpG island shores, the same ones that are involved in tissue, normal tissue variation, but it's an aberrant pattern of tissue methylation. In other words, the mutations - I don't want you to get the idea because I work on methylation that genetics is not important. Of course it is, and there are defining critical mutations necessary for cancer to develop, but I think that equally important are these epigenetic changes and I think that what happens in cancer is that the tumors are acquiring a kind of hybrid methylation pattern that you would expect to see in several different normal tissues, the colon included. But that I think explains a lot of abnormal tumor behavior because the colon cancer sort of thinks that it is not just a colon, but a kind of a liver and kind of a brain as well and therefore is expressing those properties that it's simply not supposed to express and that can explain an awful lot of properties that seem mysterious until you know that, like they're not growing in

the normal place for example, or they're not responding to drugs that would normally target rapidly dividing colon cells but that wouldn't have an effect, say, on brain cells and yet the colon's acquired that sort of epigenetic pattern.

This is just a graph to show the relationship between these varying methylated regions, we call them DMRs or differential methylated regions in cancers and the differential methylated regions in tissues. Now the array - I told you this - the array is enriched in islands, so 35 percent of the array is on islands, but these are the shores then broken out in 500 base increments and then there's the stuff that's outside the islands and shores altogether that's on the arrays. And in the cancers you can see that the islands - despite the literature, the islands are heavily under-represented for differential methylation in cancer; most of the differences are in the shores, as are the differences among tissues.

Dr. Insel: Andy, can you take us through what those different rows are?

Dr. Feinberg: Yes, absolutely. So this is the array itself, okay, so this is the distribution. This is sort of the control because that's what's present on the array. This is the differences in methylation where they occur in different tissues, like comparing the spleen, the liver, the brain, the normal colon, and so while 40 percent of the CGs that are on the array are - lie within islands, only 5 percent of the differences between say the liver and the spleen lie within the islands. Most of those differences lie within the shores and we've simply broken that out instead of giving just a single peek. This is overlapping the islands, then 500 bases away, 1,000, 1,500 and 2,000 bases away and then very, very far away. This is the same thing for the differential methylation in the cancers so that, again, most of the methylation differences are in the shores and even though 40 percent of the

arrays has islands on them, only 9 percent of the differences between cancer and normal are in those islands. Most of them are in the shores. And then this breaks it down by the hypermethylation and the hypomethylation, and there's a little bit more of the hypomethylation farther away from the islands, a little bit more of the increased methylation a little closer to the islands, but they're still under-represented.

And this is another independent method because our CHARM method is a new technique. This is a quantitative DNA sequencing method in which you use a chemical that can distinguish methylated from unmethylated DNA. And rather than go through all those numbers I just want to call your attention to this. Here's the shore, the island, the shore, the island for a series of different genes where we're comparing either different tissues or normal and cancer, and these are p values under there. And you can see

that the significant differences are in the shore and not in the islands, and that's true in each of these cases. Another thing that we have to do to be sure that our results are right is we have to validate these studies. So we originally did these experiments on 13 paired normal colon and colon cancer pairs, but then - on the CHARM array, so we went back and looked at 50 completely independent tumor-normal pairs and found that in every case where we had observed hypermethylation in a shore we found the same thing true in independent samples in the same region using that sequencing method. So here's the normal. This is called a box and whiskers plot. That's where the mean is and this is a representation of the variance, and you can see that there's increased methylation in the tumors, increased methylation in the tumors, and where we saw hypomethylation on the CHARM arrays there's decreased methylation in the validation set and decreased methylation in the validation set. We always see this.

This is another sort of complicated graph courtesy of the statisticians and what it's showing is a graph between the degree of methylation, the difference in methylation between tumor and normal and the difference in gene expression. And you can see that down here is increasing methylation as it becomes more methylated it becomes less expressed. As it becomes less methylated it becomes more expressed, so it's not just an incidental observation. It seems to be regulating these genes and responsible for this phenotype that we see.

And here's a fairly - oh, it's not really projecting very well on the projector, sorry, the words. I'll just explain them, what they mean. But this is another heat map similar to the one that I showed you, but this one derived from the CHARM data. And what we've done here is we said all right, we've asked the computer tell us the 500 sites across the genome, the differentially methylated regions

that most clearly distinguish the colon normal from the colon cancer. And so this is what's called a supervised clustering analysis. Again, red is more methylated, blue is less methylated. Each of the columns is a different sample. So there's a colon and there's the colon cancer from the same individual. There are 13 of these normal colons, 13 of these colon tumors. Each of these rows is a different differentially methylated region and there are 500 of these, and this is how they cluster. And you can see that clearly they're very different, the tumors from the normal, and you can also see, this is quite striking, look at the great degree of variation even among the normals. We think this is a very important source of variation in the general population even with an identical genotype, and I'm going to come back to that when I show some data from autistic twins. But we think that the epigenome can show marked differences even in a very similar genetic background. But again, this is supervised. Now

what we do is we take those 500 sites and we ask the computer, all right, now what I want you to do is at those 500 sites look up what the DNA methylation. You see how that drawing on the left here looks the same because it's the same genes. Now we're saying at those genes how well do the sites that distinguish colon cancer from colon normal distinguish the spleen from the liver from the brain - the colon's not even on this picture - and they completely discriminate those three tissue types from one another. And what that means is that the sites that are involved in the epigenetic basis of cancer are exactly the same sites - well, they largely overlap I should say to a statistically significant level - they largely overlap the sites that are involved in normal differentiation and normal phenotypic plasticity generally. And I think that's a really important observation and we're seeing this in a number of other studies as well that Tom asked me not to go into because it would just take

forever, but where we're seeing the very same sites involved generally in disorders generally, but also in, say, stem cell reprogramming and so forth. It's very similar targets for epigenetic programming.

And there's a hopeful thing about this, and that is I started out with this, you know, very complicated approach to looking across the landscape of the epigenome to identify sites without knowing where they might be that are involved in normal development or disease and now I'm saying that at the end of the day those sites might not be as complicated as one would think, that there might be a relatively manageable subset of genes that seem to be critical in a variety of processes involving development. And I want to show you one such process. This is unpublished data, I don't know where this gets copied and whatever, but I'd ask that this particular slide at least not be distributed because it's from some unpublished data with collaborators, but here

we're looking at neural development itself and what you're seeing here is these are cells that come from Rusty Gage's lab where we've looked at stem cells and then neural progenitor cells and then neural stem cells, and you can see these marked differences in DNA methylation at each of these stages of development again occurring in the shores of the CpG islands. And this is this method that we use for this quantitative sequencing of methylation differences again showing differences among these different lineages. Again, it's at the very same site, similar sites that we saw involved in cancer and involved in tissue differentiation. So we think it's relevant to neural development as well. Here's just another example, again showing differences. The grey are ES cells, the pinkish color are neural progenitor cells, the green color are neural stem cells and finally neurons are shown by the purple and again, there are these very dramatic differences that occur at each of these stages of development again in

this region that people hadn't thought to look at before.

So how do we approach epigenetic epidemiology? What do we do? This is the third part of the presentation. Disorders in general or normal development in general, how do we do that? Well, here's a list of the major studies that we're pursuing right now in our center. We're trying to understand the epigenetic basis for autism, bipolar disorder, major depression and schizophrenia. We're interested in the nature of the newborn epigenome. I mean, what is a baby epigenetically when it's born? How is that related to its underlying genome sequence, and how is that related to its exposures during development? Nutritional exposures which we're identifying through questionnaires as well as possible toxin exposures that we're identifying through samples that were obtained from the mothers. And in the cohort of individuals that we're tracking this includes the early cohort, so we're collaborating with the early studies.

So half of these children that we're following are sibs of autistic children, and so they have about a 10 percent risk of developing autistic features sometime in their first year of life and that's being assessed, and so we'll be able to relate that to the presence or absence of the development of autistic features in development.

So how do we do those things? So what we do is we bring together - this is what I promised to tell you. I don't think you can do that unless you bring together as co-equals skilled investigators in a variety of disciplines. And I think I understand why that is now. I didn't realize that when I was younger, but it takes 10 years to learn how to do something well and 10 years of insanely hard work to learn how to do it really well, and you just don't have that many decades to sort of combine all those different things, so unless you collaborate you really can't do anything that involves different disciplines coming together. So we involve a group of

investigators both in the School of Medicine, the School of Public Health including biostatisticians and epidemiologists, neural developmental experts such as Walter Kaufmann at the Kennedy-Krieger Institute and then clinical consortia, and we're working with superb investigators who are leading major national studies for these sorts of problems. And then we also have a component - I'm just going to mention it briefly - it's not really exactly germane to the talk, but we have a program - the Genome Institute requires for large grants that you have a program for promoting education for minority students so we actually paired up with the Center for Talented Youth at Johns Hopkins which identifies brilliant high school kids and gives them special training, but they have a minority component, outreach program. So we've had 32 minority students in our centers taking special classes and working with us and actually some of the data I showed, two of the students were on those papers.

So I'm going to give you an example of some data, it's very preliminary, in which we've been looking at monozygotic twins who were discordant I shouldn't say exactly for autism, but for autism features. So it's not that unusual. About one-third, 25 percent to 33 percent, something like that, of monozygotic twins where one of them has strict autism and the other one has some form of broad spectrum disorder is how Walter explains the terminology to me. And here's data from a series of MZ twins where you can see a methylation difference in the more severely affected twin than in the sib. And I don't show the gene name, not for secrecy reasons but because we have only done this on a handful of specimens showed by the numbers of those dots and we're recently going - got access to some samples so we can extend that about tenfold. I need to have this data before I feel confident -

Dr. Battey: Andy, is the coding region of the gene shown on the green block at

the bottom?

Dr. Feinberg: Yes. So this is the first exon, that's the second exon. The promoter region is here. There's an island, it's a typical story where the differences are found in a region that you wouldn't have looked at using a commercial array.

Dr. Battey: And an intronic region.

Dr. Feinberg: It is actually and that's pretty typical. About half the shores go inside the gene, half go the other direction. We have some theories about what that's really doing that involve alternative transcriptional start sites.

Dr. Insel: Can you just make sure we all understand what we're looking at here? This is one pair, right?

Dr. Feinberg: It's a series actually. So these are statistically significant differences among a set. It's altogether I think six twin pairs and this is - the red are the strict autism, the black are the

broad spectrum half of that twin set, and this is where you're seeing consistent difference. And you can see the actual data are shown by these little numbers in black or red, and they track along - I think it's probably right because whenever - sort of in the analysis of biological data over some function, in this case the function is the DNA length, when you see this ramping up and then ramping down it usually turns out to be right. I mean, noise doesn't normally appear like that, and so I think that's probably going to be right but I really hate the idea of publishing or describing something that could be wrong. So we're going to do a few more experiments before we let that out.

Dr. Insel: But just so we understand what we're looking at. What do the numbers represent?

Dr. Feinberg: The numbers are just the number of that patient sample. So like the 8 means twin set number 8 and that's just a way of distinguishing them. You could just use dots

for the individual people. And then each of these sites along here is where we measure. So you can see it's not continuous, there's actually a column and then a tiny space in another column, tiny space in another column. That's how the experiment works. We assay - we have probes on the arrays. They're pretty tensely spaced, actually, but they're still not everything. It's not a complete tiling array. So that's about 2kb of genome and here's a start site of transcription, and it's occurring right around the first - the second exon, the second intron boundaries where that difference is.

Dr. Battey: Andy, what tissue is being assayed here?

Dr. Feinberg: Lymphocytes. These are non-immortalized cells from lymphocytes.

Dr. Insel: And these findings would be in the context of how many comparisons would we be doing with CHARM? What's the rough number?

Dr. Feinberg: Well, I mean this is

only from six or seven -

Dr. Insel: How many sites are you looking at?

Dr. Feinberg: Oh. It's - let me think. It's 4 million CpG's. Now there's a number of CpG's that are across here. There's several hundred thousand regions of the genome and we're seeing these differences in a relatively small number too, you know, half a dozen regions.

Dr. Insel: So what's the - statistically out of 4 million questions that you ask the likelihood that you're going to get the same area -

Dr. Feinberg: So - right. So the way we do this is by doing permutation. So there's no way to solve this Bonferroni thing on data like this so what we do is the statisticians simply permute the data a thousand times. So we kill the mainframe computer when we do these things. I mean, we get this hate mail from the sysadmin, but we're buying more

storage and so forth to keep more notes to keep them happy. But we basically permute all the data a thousand times and we ask how often would we see differences of this magnitude, and you know, we set a false discovery rate of 5 percent. So there's a 5 percent chance that these are false based on the statistics.

Dr. Insel: Linda?

Dr. Birnbaum: Yes, so Andy I guess I just have one question back to what Tom was asking before about the individuals here, the individual pairs. If you look at them just as individual pairs, does the pattern look similar or do you have any of your - I realize you only have six pairs - that you just don't have the number to see if you have outliers within that inner six?

Dr. Feinberg: Yes, so I mean we validate the experiments by doing this it's called bisulfite sequencing technique. So I mean the data that we're seeing here hold up when we do this other method. The real question

is whether or not this would hold up in a much larger number of individuals. I mean, that really comes down to numbers. I mean, this six or eight is just too small a number so I mean you have to do an experiment on dozens or of individuals.

Dr. Battey: Well, another big question is whether or not this is causal or whether or not this is simply a marker.

Dr. Feinberg: Yes, well that's the same question that's been brought to bear for, you know, epigenetic studies in cancer too, and the answer to that will come from functional studies. So it'll come from showing that your targets actually are playing a meaningful role in development. It just so happens though that the targets that we see are targets that are involved in neurodevelopment. So then you know it'll turn to animal models and so forth to really nail that down. I will say the following thing though because I did the first experiment showing altered DNA methylation in cancer and

for 10 years I mean I sort of faced the same question. It's a perfectly valid question. But I would say the same thing is true for mutations. So you can't tell when you see a mutation whether or not that's playing a causal role just because it's a mutation.

Dr. Battey: Unless you can recapitulate it in an animal model or somehow validate -

Dr. Feinberg: Correct, absolutely right. That's exactly right.

Dr. Insel: We should let you finish and then we'll come back to all this.

Dr. Feinberg: Okay. And here's just another example and there's about six of these that we found so far. But you see the similar sorts of difference in methylation, in the red line versus the black line, again relatively small number of individuals.

So how do we put all this together and where do we go in the future? So we've suggested a model for how common disease such as

cancer, we think it isn't just things like cancer. We think that things like schizophrenia, neurodevelopmental issues such as autism, things like rheumatic disease, diabetes even. We think that most common disorders or developmental differences are in some way related to a combination of genetics and epigenetics. And so there's a controversy. You know, are the genes involved in human differences, or are - is the environment involved in human differences? And I think it's both and I think that the environment acts on the genes through this epigenetic mechanism. And we've referred to this model as the common disease genetic and epigenetic hypothesis. So what does it mean? You have DNA sequences, and of course you have changes in the DNA sequence that can lead to altered proteins ultimately and altered developmental processes, but you also have a number of environmental factors. I've just shown in a cartoon radiation, growth factors, hormones or dietary factors. So for

example methionine which is the amino acid that you need to make methylated DNA, you can't synthesize it, you have to eat it. I'm not saying that you should go out and have, you know, a methionine sandwich, but it is certainly sensitive to the environmental world that we live in. And that's been shown experimentally in animal studies as well, that it can have an effect upon phenotype. And so those also impact upon what really comes out in terms of the final product. And the other thing that really matters I think as well is that there are genes that encode the epigenetic modifiers. So MECP2 is encoded by a gene. DNA methyl transferase is encoded by a gene, and all of these modifiers are encoded by genes. So variants in the DNA sequence of genes themselves or of the genes that are targets for epigenetic modification could affect the plasticity of, for example, methylation differences at those locations. And so in order to address human genetics and epigenetics in a comprehensive way you need to

do in addition to the genome-wide studies, and again, I said it before, I'm going to say it one more time so it's really indelibly etched into the memory of this talk. Not only is genetics important to do epigenetics, but the epigenetic studies are utterly dependent upon what we know from human genome analysis. The two really go hand in hand. But in addition we're doing these genome-wide methylation scans, that's basically what CHARM is an example of. We also examine the behavior of genes on the two chromosomes. I mean, you have - you know, epigenetically you have a maternal and a paternal genome that come from the two parents, and you can distinguish them using molecular tools in the laboratory to see which of them is working, and it's known that there are modifications that occur in a parent of origin-specific way that affect gene expression. And of course it's important to look at chromatin, but that is actually very difficult I think to relate to epidemiology.

It's very important to look at a

population of individuals over time, and I mentioned one example in which we're looking at that newborn study. I think we often forget to do that and I think it's terribly important to do. This is a general issue I think for studies, even the conventional genetic studies that are being done at the NIH, large-scale studies of populations have to look at not just presence or absence of disease in phenotypes, but when they occur and whether or not they're contributing say to mortality as opposed to just morbidity. So those are time-dependent issues. With epigenetic studies there's a subtlety of a phenotype genome relationship that we can examine because not only do we have case control status, but we have quantitative data on what are called endophenotypes. So for example, developmental methods like ADI scores for example are a number, so you can relate that quantitative number to quantitative levels of methylation which gives you additional statistical power but also creates a need for

novel statistical development, new kinds of research. And of course, it's important to embed within this studies of environmental exposures.

So that's basically the message that I had. I want to mention the people that did the work that I'm talking about, in particular Rafael Irizarry the statistician, Christine Ladd-Acosta who was my award-winning graduate student, has now graduated, and I mentioned our collaborator for that unpublished data, and very important Dani Fallin who is critical to the whole model and approach to everything that we're doing. She's a world-class epidemiologist at Johns Hopkins and Walter Kaufmann has been working very closely with. He's really the pioneer of these differences in twins and autism, published the first paper in that area and so he's been a very close partner in these studies. Thank you very much.

(Applause)

Dr. Insel: Okay, we have about 10

minutes or so for discussion.

Dr. Feinberg: Can I ask a favor of the AV people? Can I just get some water?

Dr. Insel: We can do that. I think we can do that. Andy, can you hear while - if we ask questions while you drink? Jim.

Dr. Battey: I just want to provide a point of clarification. On the Rett syndrome definition that you provided which was very nice by the way, from the Neurology Institute, it was pointed out that Rett syndrome occurs essentially exclusively in women or girls and not in boys. And the reason for that I believe is that homozygous deficiency in MECP2 is lethal, right?

Dr. Feinberg: Yes, that's right.

Dr. Battey: So basically the girls have one copy of the defective MECP gene.

Dr. Feinberg: That's correct. Yes, that's right.

Dr. Birnbaum: So it's X-linked.

Dr. Battey: Yes.

Dr. Insel: Linda?

Dr. Birnbaum: I was just making sure I was interpreting it right.

Dr. Insel: Okay. Other questions, comments, issues? Walter?

Dr. Koroshetz: Well, I guess I'd just ask your opinion about the issue of the tissue specificity. So you're studying a developmental brain problem, you know that there's tremendous tissue differences even within the brain there's tremendous differences. So how do you think about a methylation abnormality in the lymphocytes reflecting what's going on in brain? Do you think it's a - do you think - are there ways to think about how abnormalities in a certain gene may be occurring at both sites, or has anything like that actually ever been shown?

Dr. Feinberg: So, we think this is okay to do and there's several reasons. First of all, we are also looking at the brain. I mean, in autism this is not as practical to do

obviously, but in other problems that we're examining we are looking at brain tissue very heavily and relating that to differences in lymphocytes. But we think it's okay to look at lymphocytes and one reason is that there are a number of studies in animal models and in human studies that show that differences in gene expression are - that you see in brain tissue, the differences actually, are - that are associated with disease are also found in lymphocytes, that they closely follow each other. There's studies from Steve Warren that go back 15 years showing this and animal models for fragile X for example, but there are other studies for example in Alzheimer's disorder comparing gene expression patterns in the brain to gene expression patterns in lymphocytes. So it's not that the patterns of methylation or gene expression are the same, but where there are alterations that are disease-specific or disorder-specific those are reflected in what - or looked at in lymphocytes.

We ourselves have data like this for epigenetic change that we identified that's very frequently associated with colorectal cancer risk called loss of imprinting of the IGF2 gene that was reported in a couple of Science papers about five years ago. And we find similar differences in lymphocytes as we find in the target tissue in the colon. Now, a clue to why this occurs and this got me thinking about the mechanism a lot more recently is that we find this in cases in which there is a hereditary component. And so it's as if there's some genetic variation that's increasing the risk for this epigenetic change and therefore, when you have that genetic variant it's going to be present in all of your cells and therefore the altered or abnormal pattern of DNA methylation is more likely to occur. But very recently I think we figured out why this is and it has to do with how we inherit differences generally. We have a paper that just came out yesterday I think. No, it's coming out online officially on

the 26th or something, but it's been advanced online at PNAS and if anybody emails me I'm happy to send that, but in which we're able to show that there are genetic variants that increase the frequency of epigenetic variation in the population. So we've come to a view that what may be very important in the heritability of disease may have to do with the heritability of the potential for epigenetic variation as opposed to the hereditary of the methylation difference. In other words, there are sites in the genome that predispose you to having a highly variable methylation pattern. If you inherit them, you're going to get those differences in methylation and they're just as likely to occur in one tissue as they are in another. So I'm happy to provide more information, but it's now - that idea is published and we have some experimental data in - it's actually in mice, but experimental data to support it. I think that one should use the mic so that the people outside can hear your

question.

Dr. Dar: So you're suggesting that autism and cancer share some immune phenomena? But what I wanted to know is if methionine is deficient and hinders the methylation process, this is something that has been found to be occurring frequently in autism. And if it's supplied through the GI wouldn't more GI research perhaps offer some insight to not only autism and cancer and Alzheimer's and many other immune phenomena? And that would also link to what you just mentioned about the colon which is integral to a lot of this - many of these events and also to the immune system overall.

Dr. Feinberg: So I thank you for the question. It's a multi-part question. I'm going to try and answer it the best as I can. I think my main answer is that one thing I've learned as a scientist has been doing molecular research for decades. It's like 25 years I've been doing this sort of thing. I'm humbled as we get data. So as we get information, as we

learn something new that opens a new pathway to understanding I've been humbled by how little I know. I feel like each time I discover something in some ways I know less. So while we have a better idea of the tools and the questions, I think that we have some leads towards understanding differences in autism that involve epigenetics. Exactly how - it raises many questions that I don't have answers to, that I hadn't thought about before. So for example, might there be some, you know, shared effect of environment? Might there be - that might be affecting these targets. Could there be similar genes that are involved in different disorders that would give a clue to common forms of disease generation? I don't really have the answers to those questions yet. They're going to take more time and more research to do, so I think, you know, I just don't know I mean how to answer those questions. We don't have any - all we're asking right now is can we tell the differences in more severely affected twins

epigenetically in autistic patients, you know, in autistic twins, and we think that we can. So we think that there's an epigenetic component, but we need to do a lot more work to identify where all those changes are and then start to put together the pieces of the puzzle to ask why might those have arisen. I just don't know.

Dr. Insel: Andy, one last question. We'll kind of push you a little bit into the future. The Strategic Plan that we've all worked on has a big focus on biomarkers and it sounds from what you're saying that this might be a promising area. In fact, there's a paper that I think you know about, we've talked about it, just submitted to Nature from Steve Warren's group showing that there is, when you compare children with autism with their sibs, male sibs, there's a consistent difference and that the kids like the ones that you're showing us are hypomethylated, not on any consistent genomic regions, but grossly across the genome, and that gives you about a 70 percent predictability as a

diagnostic. So we're not there yet, but it's moving in the right direction, there's lots of other people working on the same question.

So let's say this does work and going back to Jim's question we don't know whether this is cause and effect, we don't know how much this is involved with the mechanism of disease, but let's say that it is. Is there a therapeutic that will come out of this area?

Dr. Feinberg: I think that the potential for therapeutics in the epigenetic arena are very high, and the reason is that we've done - it comes from some of the work that we've done on cancer. And my view of this is a little different than, again, some of my cancer epigenetic colleagues. So there's a lot of research that's being done right now on drugs that would modify the epigenome in a gross way. So like DNA de-methylating drugs in the treatment of cancer. And they haven't so far borne great fruit, but one thing that we observed in the studies that I just mentioned a

little while ago and our study of loss of imprinting of IGF2 and colon cancer. So that, we have an animal model that clearly increases the risk of developing colon cancers in mice that have this epigenetic change. What we've found is that there are specific targets and those targets can be attacked using drugs in the conventional way. So the IGF2 signaling pathway can be attacked using conventional drug analogues that are designed by the pharmaceutical industry that they're very good at doing that, even using existing compounds. And if you block this IGF2 signaling pathway in the mice that have this IGF2 defect with this over-production of IGF2 their incidence of cancer falls below that of the control group. So it's sort of like - in the one example, I realize it's just one example, of an epigenetic disorder that increases cancer risk, but if you target the pathway the individuals with the abnormal epigenetic pattern are hypersensitive to the effect of the drug as an inhibitory

factor. And we call that a therapeutic ratio. So the therapeutic ratio I think is unusually high for conventional drugs if you know where to attack the problem and if you have an epigenetic disorder. So I'm thinking that as we identify, say, validated epigenetic targets, gene targets in autism, that it may be that those individuals who have an epigenetic abnormality in those pathways might be - might have - be particularly sensitive to the therapeutic effects of drugs that ameliorate or block those pathways. So I think that's a promising approach. I'm not knocking the other methods, but I think that you have both possibilities and you know, quite frankly I see this as in some ways potentially an easier issue than conventional mutations to deal with, at least for cancer. I mean you know, someone's missing a gene or the gene's been mutated, it's very difficult to figure out a drug that's going to change that, but if you have a difference in activity it's not quite as extreme.

Dr. Insel: Okay, well thank you very, very much. This is really enlightening, gives us a lot to think about going forward.

Dr. Feinberg: Thank you very much.

Dr. Insel: And let's give Andy one more round of -

(Applause)

Dr. Feinberg: Thanks.

Dr. Insel: We're going to take a 10-minute break. We'll reconvene at 11:25.

(Whereupon, the foregoing matter went off the record at 11:17 a.m. resumed at 11:27 a.m.)

Dr. Insel: It is my pleasure to introduce Dr. Cathy Rice, who is well known to this group. From the National Center on Birth Defects and Developmental Disabilities, Cathy was the lead author on the recent Autism and Developmental Disabilities Monitoring Network Report that was published as we talked about earlier, the *MMWR* on December 18th. And she's graciously agreed to take us through the major

findings because as I mentioned before, this is a very rich data set and I think we've heard only about a few aspects of it thus far. Cathy, it's all yours.

Dr. Rice: All right. Thank you, Tom, for allowing the opportunity to do this and to go a little bit deeper into the data. We have a short time so I'm going to try to get through as much as we possibly can and certainly encourage you to read further into the paper and hopefully we can have time for further discussions over lunch or other times. I'm Catherine Rice from the National Center on Birth Defects and Developmental Disabilities at CDC. And I'm mainly going to be providing an update from the ADDM network that Tom mentioned.

One of the reasons we're here and talking about prevalence and talking about autism in general has been the concerns over increases in autism that particularly started during the 1990s where since that time it's become very clear that there are more children

receiving services and more children being diagnosed in a medical or clinical setting. And I'm saying children because that's where we have most data from. And this little teeny graph that you can't really see the details, but you can see the main point of the increases in numbers of children identified. This is from the California Department of Developmental Disabilities Services System. They were one of the first places to really be reporting these increases in children being identified. But what we want to do is certainly take those increases seriously, but we also need to understand does that really tell us what's happening in the underlying population because it's very different in terms of who's identified for services as opposed to those individuals that may be in the community that have those same features of autism or have the condition that have not been diagnosed or have not made their way to a service system. So one of the questions we ask at CDC is mainly who else may

have an autism spectrum disorder, and the prevalence studies that have been done try to look at the population-based features of autism, whether it's diagnoses in addition to actively going out and screening the population to identify other individuals. So some studies have used a direct screening and that's occurred particularly in countries in Europe that have systematic screening programs in place where they're able to have more full access and follow-up at particular ages. We find that somewhat more challenging here in this country, although we have recommendations, new recommendations for ongoing developmental screening in particular for autism. We really don't have a systematic routine way of screening individuals and getting access to the entire population to look for the features of autism.

So another method of doing that would be looking at records-based information. So of children that come to the attention for some sort of developmental concern, whether it's

autism, language, development, ADHD, obsessive-compulsive, a wide variety of issues that may affect a child's health and development. Those individuals as they get evaluated have that information documented in records. So what we use at CDC is a records-based screening method where we're not just relying on the diagnoses as it's documented, but are going through and looking for descriptions of symptoms that could be related to autism and I'll talk a little bit more about that in a minute.

So just a very basic summary of what we know in terms of the prevalence estimates. The first epidemiologic study looking at prevalence was done in the `60s in England, and since that time through the `80s the findings were relatively consistent, finding about 0.5 per 1,000 children, or about 1 in every 2,000 children. Often it's been quoted 4 to 5 per 10,000 children. We heard that for many, many years that that's the standard of autism so I just tried to translate it into the per 1,000 to

get into modern times.

Now, a challenge here is we know that this was focused much more on autistic disorder and what we now call the more classic form of autism, and since that time, particularly since 1980 we've had quite a sea change in what's happened in autism. Before 1980 autism was considered a form of schizophrenia. We now have a very different outlook in terms of what autism is and I think in some ways our numbers recognize the spectrum of the condition and the successes we've had at identifying individuals and recognizing the heterogeneity of autism, but at the same time present a very sobering picture of how many people are affected with the conditions. So over the last decade or so studies that have been using the most recent criteria, the DSM-IV and the ICD-10 criteria that have really looked at more of the spectrum of conditions have been converging around an average about 6 to 7 per 1,000 children, but we've always had in some of those studies

outliers. For instance, in the last ADDM network report we had one site that was closer to 10 per 1,000 children. We've started to see reports from Scandinavia and from Europe and Japan showing about 10 per 1,000 children. And so we really need to see what's happening here, is this a new trend where we're now starting to really converge around this 10 per 1,000 children. Also there was a study in the UK indicating about 1 percent of adults with an autism spectrum disorder, again another interesting convergence here. So what we need to do is have some updated information in the U.S. to see where we are.

So our primary way of looking at problems of autism is the Autism and Developmental Disabilities Monitoring Network. Now, it's important to remember that the purpose of this is to estimate prevalence and provide descriptive data. It can also help us in terms of informing hypotheses for potential risk factors, but in and of themselves those are more

association studies. They give us sort of the springboard to give us an idea of where should we look deeper. And also, what we do in the ADDM network is not just try to provide a single snapshot of prevalence, but to build this infrastructure that we've been working on for the past 10 years to have an ongoing way of evaluating prevalence over time. So that's where we are now. This came out of some community investigations in Brick Township, New Jersey, and in metropolitan Atlanta, and now we have multiple areas across the United States using these similar methods to track autism on an ongoing basis.

So the ADDM network in late 2000 and we've had two main phases. These are just the current sites are in the sort of teal blue and these are the ones we'll be talking about in a minute. So the basic methods of the ADDM network. I mentioned a little bit that it's an active case-finding so we're not just dependent on reported diagnoses. We're going a little bit

further to not only say who has a diagnosis on record, but also who has the symptom profile documented in their record that may not have a documented diagnosis. It's also important to recognize that this is a retrospective records-based screening. So certainly a question we get is it's 2009 when we publish these data. Why are you publishing data from the year 2006? And what we've needed to do is to go back in time, particularly over the crucial period in the `90s and build a data set that accesses children who are born over that time period so we can go forward and look at changes and trends over time. It's also important to know that also from records-based perspective we need that information to be documented and available. So if we're looking at the study year 2006 technically we can't really start to investigate all those records until they exist. So in the year 2007 we actively started going and looking through those records to identify the individuals. In the case of the year 2006 that

was over 50,000 records that had to be reviewed across the sites. And I'll show you a little bit in a minute how that kind of plays out in terms of the number of people that we identified. That process took about two years and so as soon as those data were available the active analysis and publication efforts were underway with the publication in December.

Another aspect of the ADDM network is that we look at children at age 8, and this comes from earlier work from other studies, but also from metro Atlanta that showed that we identified the peak prevalence; that if we went younger we were missing many children with autism because they haven't come to the attention of a service provider yet. So we focus on age 8 because that's really the youngest age that we can get the highest prevalence estimate to give us what is the most - the peak concern over time, and we use that as an index. But as I'll mention, as we go forward we certainly want to figure out how we can do

that at a younger age.

We also use multiple sources of information so it's not just a single reporting source. We collect detailed descriptive and testing information and I think a key point is that we have these multiple sites, but we have ongoing quality control up front in terms of initial and ongoing both within and across sites. So we're doing our best to sort of understand what we can about the methodology effects of what we're finding so we can measure variation in that way. And then another aspect is that we have an independent clinician confirmation of case status based on the DSM-IV text revision criteria. So each record goes through an independent review by a clinician who determines if the criteria are met.

So the first report of the ADDM network was published in February 2007. And just as a very brief summary, it was found between 1 in 100 and 1 in 300 children with an average of 1 in 150 children affected with an

autism spectrum disorder. Now, I know our tendency is to always boil it down to the one single number, and the challenge that we are talking about within autism because it is a behaviorally defined set of conditions, we're always going to have some variation. But I think for ease and understanding and trying to really get a grasp on who's affected we tend to focus on that single number. But always remember there is some variation.

So this updated report, as I mentioned, was published last month. It looked at the 2006 surveillance year for 11 sites and also was the first time we were able to say we had earlier data from these same sites, 10 of the sites, to compare from 2002 to 2006. The report - I'm not going to talk about it in detail, but it's in the report. There was also an additional surveillance year included. This was optional for sites that were able to collect this data basically for free to some degree in between grant cycles. The folks that collect

these data are highly motivated to understand what's going on, so the sites that participated in 2004 went above and beyond to get an additional data point.

So for the 2006 surveillance year we have the states represented, but they're really varying geographic areas, but overall represents areas covering over 300,000 8-year-old children which is about 8 percent of the U.S. population of 8-year-olds. So that was the population we started with. And then going into educational, health, medical, diagnostic centers, identifying children who had been evaluated who were at age 8 for a range of developmental concerns, going through and looking for either a diagnosis or a suspicion or what we call behavioral triggers, one behavior that could be associated with the social symptoms of autism. So for instance, if in a record it said, "Child has difficulties with eye contact," that would be enough to flag that child as a potential case of autism, and then all information that we can gather on that

child is compiled and goes through the review process.

So as I mentioned, we started with this larger population of over 300,000 children. We had about 50,000 records that had to be reviewed. From that 50,000 records there were over 5,000 children who either had a diagnosis, a suspicion or one of these behaviors that gave us some indication we should look closer. And from there, we identified close to 3,000 children who met the criteria for an autism spectrum disorder. And when I'm saying autism spectrum disorder, I'm meaning autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified. So that sort of gives you the idea of the process here.

So this is just summarizing the main findings from the ADDM network so far. So starting in the year 2000 - so these were children born in 1992, then we have 2002 born in `94, and then the more recent report 2004 born

in `96, 2006 born in 1998. So here we see that for the first two years we had a pretty consistent finding in terms of the average prevalence across the sites, although we did see a range. So this isn't a confidence interval here, this is the range. So we had a low of 4.5 per 1,000 and a high of 9.9, and then again a range as well. Although that range seems quite wide, most of the sites - there were two outliers here, and most sites were actually very close and not statistically different from each other. We found a very similar thing in terms of the range for these study years, but we had a higher average prevalence of 8 per 1,000 and then 9 per 1,000 in these surveillance years, and I'll go into more detail about that. We're currently in process collecting data for 2008, children born in the year 2000. In addition, going back a little bit further from our metro Atlanta site we have data from 1996 children born in 1988 and there's some more detail coming out in an upcoming publication in the Disability

and Health Journal on those data.

So the overall prevalence estimates as I mentioned for 2006 varies from 4.2 to 12.1, translated into about 1 in 80 to 1 in 240 children. The average across all the sites was about 1 in 110 children, or about 1 percent. I'm saying "about" because we've rounded to even numbers. Here you see the different sites that were involved and the red is the average. Now, we do have two sites that have a lower prevalence, Alabama and Florida, and two sites that have a higher prevalence, Arizona and Missouri. But most sites, seven of the sites were in a much tighter range here and that - those sites were in about between 1 in 95 to 1 in 130.

We also looked at differences in terms of sex and race and ethnicity. So we found what has often been found in epidemiologic studies: 4.5 boys - again, sorry for saying half boys - 4.5 boys to every girl identified, translating into 1 in 70 boys and 1 in 315

girls. Certainly we need to be concerned about anybody that has autism, but it's particularly concerning that we're now here with 1 in 70 boys affected. We did see differences by race and ethnicity, with white non-Hispanic children having the highest prevalence, but there was variability across the sites. And this gives us some idea as we look at the patterns that we see across the sites and the changes over time that some of the race/ethnicity differences do appear to be more about ascertainment in terms of who gets evaluated, what gets documented for those children. So as we monitor over time hopefully we'll have a better understanding of how much of this is ascertainment versus a true difference in risk.

Some of the other features. There is more detail, but just a few highlights in that we did find that the majority of the children, between 70 to 95 percent, somebody was concerned about their development enough to bring them to a provider, or the provider themselves was

concerned enough to document in a record that they had a concern about this child's development before the age of 2 years. But unfortunately the average age of diagnosis was still quite late, between about average of 4.5 years. We did see a range, but still from a concern being documented from 2 years to an actual diagnosis of over 2.5 years later is quite a gap. Now, although these data are still a little bit back in time - these are children born in 1998 so they would have been being identified in around 2000 to 2002 - hopefully in future years we'll see this go down. But even this gap is quite surprising at that time. We also found between 13 and 30 percent of the children had a reported developmental regression so somebody noted a concern about a loss of skills, whether it was in language, social skills, by 2 years of age. This is just to show in terms of some of the other things that we identified. So most of the children were receiving public special education services,

between 76 to 96 percent depending on the site. But 34 to 76 percent of those children had a documented autism eligibility. So although our public schools are doing quite a job in terms of providing a range of services in terms of autism needs, if you're going to look at autism prevalence changes it's going to underestimate what's happening in autism because although a child may have autism, they may or may not have special education eligibility under the autism classification. And so we see that here, and we also see a lot of variability across the sites, from 34 percent in Colorado to 76 percent in Maryland. So here, if you just looked at education data you might think that Colorado has a much lower prevalence than Maryland and that's not necessarily the case.

So next I want to talk a little bit about changes in prevalence estimates from the year 2002 to 2006, over this 4-year period. So these were children born 1994 to 1998. Some of the overall findings is that we certainly saw

consistent and concerning trends overall towards significant increases, but there was variation again by site. So overall we had an increase in identified prevalence estimates of 57 percent, for boys it was 60 percent increase, girls 48 percent, white children 55, black children 41 and Hispanic 91 percent. So again, this is sort of playing into that we think some of the issue in terms of the increase here is a catch-up effect in doing a better job of identifying Hispanic children, but overall a concerning trend.

This is just showing again total prevalence, and so I wanted you to see some of the variations. So here the most consistent finding we had was the increase in overall prevalence estimates across all the sites. It was significant in all sites but Colorado. So the average increase was 57 percent. This varies from a low in Colorado of 27 percent although still quite a big increase to a high increase of 95 percent in Arizona.

The second most consistent pattern was the increase among boys. So overall there was an increase of 60 percent among boys. So this is actually absolute change in prevalence. So this is say for instance in Alabama prevalence in boys increased 4 per 1,000 over this time period. And you can see the blue in boys and the red in girls. So within boys we see significant prevalence increases among boys in 9 of the 10 sites. Among girls we see a lot more variability with some sites showing slight decreases or minimal change at all where other sites show significant increases. So 4 of the 10 sites had significant increases among girls. Again looking by race and ethnicity we see the overall trends towards large increases, but again it varies greatly by site in terms of what subgroup that those increases were among. We had some decreases, in particular really only in Alabama in Hispanic children and in Wisconsin among black children.

Another aspect we look at is

cognitive functioning level. And although this is a very gross estimate in terms of cognitive functioning and so hopefully people will forgive being so basic about this, but one of the things that we can look at is the documented IQ scores that the children have on various testing. So we looked at how we could divide up the group in terms of those that scored within the cognitive impairment range of an IQ less than or equal to 70, those in what's called the borderline range which is just above or above the cognitive impairment level and in between average, so between 71 to 85, and then the average to above which is an IQ of over 85. So we found increases among all three groups, 35 percent among cognitive impairment, with the greater increase among the borderline group and then among the average to above average. So although we're seeing increases across the board most of the increases are in the borderline to the average to above average.

Overall, across the population the

average cognitive impairment as 41 percent. So for many, many years the statistics indicated that about 75 percent of people with autism had intellectual impairment or cognitive impairment, intellectual disability. We're finding a much lower range which is consistent with other studies. So here you have 59 percent, so the majority of children identified with an autism spectrum disorder do not have a co-occurring intellectual disability. This is a very different - you know, some people use the term "higher functioning." I know that's offensive to some people, but for lack of a better word, a higher functioning group than what we've had in the past. Although this was not wildly different from what we saw in 2002. In 2002 the - 46 percent of the children had cognitive impairment. Again, showing the variability among the sites in terms of which subgroup increased.

One other aspect I want to point out is looking at ASD subtype. So one of the

challenges we have when we're looking at records is, one, there's a lot of challenges in subtyping even when you're doing a direct clinical evaluation with a child. So we tend to not reassign a subtype, but we can look at how did community professionals - so those that did the original evaluation assign subtype, and then how is that changing over time. One theory is that we're seeing a shift from autistic disorder to more of spectrum over time, and we're not really finding that in our data. We're seeing a pretty consistent with the average autistic disorder diagnosis being given ever at 45 percent in 2002 and 47 percent in 2006. But again, we see variability in sites. So the red is autistic disorder. You see it actually increasing - the use of autistic disorder increasing in a few sites, increasing greatly in Missouri and decreasing in some other sites, and the same with other spectrum. And the yellow are those children that didn't have a documented ASD diagnosis. So we're actually seeing that

some improvement in that more children are having a documented diagnosis, but it's not a huge amount. It actually parallels the increase for overall prevalence. So in this case we're not seeing that community identification shifting towards the MILA forms is explaining the increase in prevalence.

So what's going on here? This was the basic look at the descriptive statistics, but we also did want to start at least to go through the methodology to say well what can we measure? Going through the scientific process we always start with, well you know, is there something in our methods, is there something in ascertainment that can help us explain this increase? We did find that there were small aspects of the ascertainment that did explain some of the increase. So for instance, we found that there were more evaluation records per child, there was better quality of documentation. Early on it would be very rare to see a description of something like joint

attention, a very key social behavior, but as we move forward in time we see that coming up more and more often, again representing changes in community awareness for the better. We did see that some sites were able to locate more records, had a more stable population, had some decreases in age of diagnosis but not huge, better identification among some subgroups like Hispanic children and children without cognitive impairment. So these were small incremental issues that I think added up to some of the increase. And this is my very simplistic sort of picture to leave you with in terms of I think when we're trying to say what's causing this increase, I think we all want to have the jar of sand that's very clear and we have a single explanation, but I think what we're learning and what is also reflected in the IACC plan is that autism is very heterogeneous and that we are talking about multiple causes for multiple forms of autism and that's likely reflected in the population data here. We have multiple

ascertainment issues as well as the potential of multiple risk issues going on here as well. And so we have to be a little bit more complex in how we go forward in looking at what is the cause. It's more of what are the causes and how do they work together.

So just some of the basic strengths of the ADDM network methodology. It is collaborative, it's multi-site. It is the first system to provide the population data at this level within the U.S. It does allow application to a large population, also confirming the documented symptoms with the DSM criteria, ongoing quality control. Some of the ADDM sites have also expanded to look at other disabilities so we can look in context of intellectual disabilities, cerebral palsy, ASD and epilepsy. And now as we've gone back in time and constructed this data set we're really at the cusp of being able to delve deeper, and I'm very excited about this from a nerdy statistical standpoint, but really from a community

standpoint of hoping that this provides us some very important information to give us clues of where to look further. So we've got this data set and we're next going further to divide out how can we better quantify the ascertainment issues that we can measure in ADDM, how can we look at things that were happening in the community and what are some clues of risk that are going on? We know that some things have changed in our population and may be contributing slightly to the increased risk. For instance, we know there's association between autism and pre-term birth, older parental age, those are some aspects. Certainly there's been some interesting studies looking at hazardous air pollutants. Those are all association and ecologic studies, but if we can apply that here that may give us some indication of how these fit together to form some of these layers as we go forward.

Some of the challenges we've had is the maintenance of the network of sites.

Certainly the first several years take quite a bit of time and effort to build the infrastructure, to get the permissions in place, to form all the collaborations needed, but we also need to be a fair and open process where we have typical grant cycles and people have to reapply. So unfortunately we've added and gained sites and that causes some infrastructure challenges. Also, as much as we try to standardize things there's always some site-specific differences in methodology. One of the main differences is access to education records which we find to be a very rich source of information, but that's really a state by state decision in terms of who is able to access those records for public health purposes. We know that contributes to underestimates in sites like Alabama and Florida, for instance, and unfortunately there's - you know, we have to do the best we can in terms of moving forward, but we also then are able to establish baseline given the same methodology in those sites, and

each of the sites have had pretty consistent sources over time. Another challenge is timeliness. We would love to be able to provide you with 2009 estimates in 2009. Unfortunately in terms of a behaviorally defined condition, that takes quite a bit to go out and verify the symptoms. We're not quite there yet, but we're certainly always working to push forward to be able to be as timely as possible. It's a collaborative process and we have this retrospective review. Again, some of the challenges, but also some of the strengths of the network.

So just in sum, the overall findings. Autism is affecting about 1 percent of 8-year-old children, translating to 1 in 110, ranging from 1 in 80 to 1 in 240, 1 in 70 boys to 1 in 315 girls. This is similar to other studies in Europe, Asia and North America. Prevalence increased 57 percent from this time period. And although methodological factors can't completely account for changes in ASD prevalence estimates

they were able to account for some based on better identification through records. Another big challenge as we saw, although there were slight improvements in age of diagnosis the delays persisted. So one thing we do know for sure is that more children are affected, meaning more families. More communities are struggling particularly in the challenging service times with budgets happening - being cut left and right with the reality of what's going on. We know more people want answers and hopefully these data will be part of reinforcing the importance of what this committee is doing. Certainly the prevalence estimates can be used to plan for policy and service needs for persons with ASDs, but they also do highlight the need for the coordinated, collaborative and multi-pronged approach, intensifying the search for risk, improving early identification and access to intervention, addressing some of the disparity issues that we potentially saw, also understanding how to better intervene to reduce

the debilitating symptoms and improve quality of life and long-term outcomes. I think these are things that the committee has talked a great deal about in the revision of the Strategic Plan and hopefully we'll keep those in mind this afternoon as we have that discussion.

So one of the main aspects of the plan that's new that we're going to be talking about this afternoon is Question 7 and some of the things that have been proposed in there are to build on the ADDM infrastructure, to continue to estimate prevalence in the same populations over time, also to go forward in evaluating the measurable identification and risk factors, but also expanding the scope of surveillance to increase the types of data collected, look at other neurodevelopmental disorders, looking at different age groups, younger and older groups, providing technical assistance and going - working within international settings and partners. Certainly from a CDC perspective these are things that we consider important

future priorities and certainly may not have all the resources to implement that right now but are putting that on the table in terms of future planning and where we go forward.

So I definitely - although I'm honored to represent the team we have over a hundred people across the country that have worked to provide these data. It's quite a time-intensive effort. These are the principal investigators and the project coordinators, and I appreciate all that they have done and the hard work that they do every day. There are a few copies of the report over by Tom Insel and Lyn Redwood over there as well as a community report version that's a little bit more friendly to get through. If you - if we run out of copies there you can download them on the website and also get more information on the CDC website. So I appreciate your time. I'm sure I went way over. Thank you for your patience.

(Applause)

Dr. Insel: Thank you, Cathy. That

was a great summary of a fairly complicated data set and we are way over time, but there's so much interest in this I think we need to take maybe five minutes max to allow for questions. Josie?

Dr. Briggs: Yes, I really enjoyed your presentation. This is terrific. It sounds like one of your hypotheses for the low-prevalence states is the absence of access to school records or diminished access to school records. Can you actually quantify that and how many of the children are ascertained through mention in educational records? And do you have hypotheses for the other states that are different from the middle group?

Dr. Rice: Yes, we can go back and say where did we identify children. And again, I'm talking - although we had individual data, nothing is ever reported for the individual child level, but we are able to go back and say where did we identify children. So that's what gives us an idea. For instance, in Alabama and

Florida we know from the numbers there that the lack of education data is playing into that. Where we have another site, Missouri, which is one of the highest prevalence sites and they also do not have access to the education data. However, they have it through a different source. Their statewide developmental disabilities services system provides a lot of that information in terms of the records that they keep so we see it in an alternative way. So the easy answer is why is it lower in some states. The hard answer is why is it higher in other sites and to be honest we don't know at this point. It's really describing and seeing. At this point we don't see that there are any trends that stick out a great deal. Some are that we see - like for instance, the biggest increases happened in Arizona and Missouri over that time. I know in Arizona in particular this also overlaps a time period when the SARRC center has really started getting established and is a really big resource within the metro

Phoenix area. So people may be gravitating for that. Although then we can look at our migration patterns and it doesn't play out that that explains a great deal of it. So not a sufficient answer to say. We have some small inklings, but not a clear explanation.

Dr. Insel: This is such an important question, Cathy. If you go to the 2002 there's also a 3:1 ratio between the high and the low. You went from 300 - 1:300, 1:100 to 1:240 to 1:80, so both cases. Is it possible to do some sort of a modeling exercise so you could determine how much of that threefold difference can be explained strictly by ascertainment?

Dr. Rice: That's something we're certainly trying to explore. We have a group working on this in terms of really dividing out all the aspects of ascertainment and how we can better quantify it, and that's certainly something we want to do. I know some sites like for instance the North Carolina site has done some analyses where they've looked at, similar

to what California just reported, about prevalence variation based on proximity to a service center. So you can tell some of those things by ascertainment, but we have a lot more work to do to do that and that's where we want to go. Ms. Singer: Cathy, you talked about using the prevalence estimates for developing service plans. I was wondering why then you don't separate the data into prevalence by classic autism, PDD, OSS and Asperger's because the service needs of those different populations are very different.

Dr. Rice: I sort of explained super quickly, but one of the challenges is because we are based on a record review methodology and so subtyping is very challenging. We could come up with an estimate but how true it is to reality, we're not quite certain about that. We use other ways to subtype in terms of mild, moderate to severe and we have some other ratings that we could provide some additional data if that would be helpful to people, but really what we're

looking at is then how are people in the community subtyping. And this can go into a big discussion in terms of the accuracy of subtyping in general. We've sort of just taken a stand in saying well, the literature is telling us that there are some challenges with subtyping by PDD and OSS, Asperger's and autism, although we recognize for an individual that could be very helpful for clinical planning. But we're really looking at the large population picture here. So you can again, as I mentioned, 41 percent of children were identified with autism so we could go back and say okay, of our prevalence estimates of 9 per 1,000 you estimate 40 percent having autism. You can get a general idea from there.

Dr. Insel: But it sounds like you've just begun to demark an objective for the Strategic Plan going forward. If you think about this as a resource, that's just the kind of thing that one could begin to ask.

Dr. Rice: Definitely.

Dr. Insel: In the future.

Dr. Rice: And on the side, a challenge we have is as the DSM-V comes up, you know, how we're going to handle that and how that affects prevalence. We'll continue to use the same method, but we'll have to overlap with the new criteria as well.

Dr. Insel: Absolutely. Last question. Lyn.

Ms. Redwood: Cathy, I had two sort of just questions and then an overall general comment. One, you mentioned that the educational records were very important to have and they were - had a lot of rich information. I'm wondering if there's a way to make it mandatory that we obtain the educational records from those sites and provide additional funding. From what I've heard funding is partially the issue for not being able to get the medical records. And also, it's concerning that the sites are changing, like the sites were not the same for the previous study in 1994 and I know

you have to put those sites back out again for grants. But is it possible to keep the sites consistent over time? And then my third comment comes from the autism community and there was a lot of frustration voiced on the list that this data that had been available for some time was released on the Friday afternoon before Christmas and it was somewhat buried in the media. And when you have a disease that's affecting 1 in every 70 boys, to me that's an urgent public health crisis. And I know that CDC has the resources available to really be able to respond to such public health crises. We witnessed that with, you know, H1N1 and E. coli epidemics so I'm just wanting to know if you could address why it was released at that particular time and what - the community feels as though there's just not that sense of urgency over this issue. So I'm wanting to know what CDC plans to do next.

Dr. Rice: Okay. So back to your first question. So in terms of the education

records, although each of the sites participating are public health authorities and are able to access information for public health purposes in, say, medical and clinical settings, there's not the same kind of rules and regulations for education data, and education records have their own set of laws that are there to protect individuals and protect family's privacy. And so that's a much larger issue that CDC doesn't have the authority to change that law, rule and regulation that's there to protect the education domain. This comes up for a variety of issues and it's a very challenging - and I don't mean to speak for the Department of Education - but a very challenging issue in terms of, again, protecting the privacy versus serving public health. It comes up for issues of asthma and autism. And so that's something over the years we've worked very carefully. Department of Health and Human Services has worked with Education to try to find a solution to this and they've been working

together right now with no clear solution other than to let states determine on an individual basis how they want to handle this issue.

Ms. Redwood: Do you select states though where you're able to get educational records and make that one of the entrance criteria - part of the system?

Dr. Rice: One of the challenges, again, because there's not a law giving authorization to make that happen that's difficult for us to require, but we've definitely weighed it very heavily in terms of the review criteria. We currently have the next request for proposals out right now that's due next month for the next iteration of the ADDM network and that's a criteria that's had a lot of emphasis placed on it, accessing education data.

And then also, to speak to your second question, in terms of the consistency of the sites we have to balance in terms of - although we have these sites that competed and

were part of the network initially we get requests every day from other states that want to determine who has autism as well and it's a resource issue. So we're trying to balance, maintain the consistency with being open for new sites to be able to determine the prevalence of autism. Again, in the current FOA we've placed a very high emphasis in the criteria for having an existing surveillance system, being able to have comparable data to speak to trends and being able to look further into trends. So we've tried in this iteration to go forward and not just say it's not just about establishing initial prevalence, it's about going further and comparing back in time. So that's how we've tried to address that within the mandate we have as a federal agency to be open and allow free competition.

Dr. Insel: What about the timing of release?

Dr. Rice: So in terms of the timeliness, so as I mentioned a little bit about

what goes into a surveillance year for the 2006 data those data were finalized in the summer of last year and in the publication process - and then the data had to be analyzed and go through the publication process. We worked extremely hard to get those data out as quickly as possible with all efforts to have them come out within 2009, to have them come out as early as possible. Now, when it came in terms of when all the edits were done, when the publication schedule could fit us in, when all of the various other issues in terms of CDC communications were put in the balance, in terms of being a study author we didn't have a great deal of choice there so that we're just - you're next on the docket. In some ways we could have at that point pleaded to delay it for later in time, but then that would have been another delay and we didn't want any more delays. So we did our best to get the data ready in a quality way as quickly as we possibly could. Certainly I think there was quite a bit of media

attention. All the major news networks covered it, we had stories in pretty much every newspaper and I think given the timing I was very pleased with the interest in the media and their genuine concern for the findings and trying to get that information out.

Dr. Insel: Okay. I really want to move on because we're so far over, and we're going to circle back to some of these issues because we'll be talking about surveillance when we get to the Strategic Plan later. I'm sorry we're this late, but I want to make sure we hear from Dr. Linda Birnbaum who's the Director of the National Institute of Environmental Health Sciences. And Linda, I don't know how long your remarks are, but we should probably try to wrap everything up by 12:30 so there still will be a lunch break.

Dr. Birnbaum: Okay, sorry guys. I'll go as quickly as I can. Having grown up in New Jersey I'm used to talking fast. So I want to briefly talk about some of the - one of the

points that Andy Feinberg made when he was speaking which first of all, we've got to get beyond this idea that conditions or diseases have a - are caused by genes or are caused by environment. In fact, both things are involved and we have to understand the interplay between genes and the environment as a priority. So we know that autism research is an integral part of our larger program supporting children's environmental health research. There are a mix of research approaches which are needed from population-based studies to laboratory investigations of relevant mechanisms, and again we heard about that a little today. In order to prove or support some of the epidemiology findings we're going to need to have some of the cell and rodent work to support it. We're partnering extensively with other federal agencies and public stakeholders in order to ensure discovery and rapid translation to public health, and we have fundamental investments in exposure science and toxicology which we believe

will benefit research.

So I just briefly wanted to mention our children's environmental health and prevent centers. These are NIEHS and EPA partnerships that were started in 2001. These are co-funded centers. We've got 11 of them. They've recently been re-competed, or a group of them have, and will be announced in a month or two about continuations in new ones. But this again was a program which was created to enhance the communication, innovation and research in children's environmental health. And the focus of this, these are multidisciplinary programs that span all the way from molecular biology to epidemiology to translation in all involved the community partnerships. We don't believe that we can do environmental health without having the community group involved in the design of research as well as the interpretation and the implications of the work.

Now, one of our first centers that was established in 2003 is the University of

California at Davis Children's Center, and this center has focused on autism etiology and supports a variety of research projects and services and facility cores, and this morning you've already heard about a number of the publications that have come out of this group. But there are - at the moment there's the epidemiology of autism risk which is one product, the clinical and cellular immunology and mouse models are the three major projects with the cores and again, outreach and translation.

So the large study that has gone on here is the CHARGE epidemiology project which is the Childhood Autism Risk from Genetics and the Environment. And this is a case-controlled study with three different groups of children. Children with autism spectrum disorders are compared to children with developmental delays and children who are developing typically, and the children are ages 2 to 5 years when they are recruited into the study. And the goal of the

study is to identify causes and contributing risk and protective factors for childhood autism and understand the heterogeneity of what may be involved. And the population is we're recruiting - so far we've recruited 1,300 families. We'll have about 2,000 children involved in this study. And we're making sure that the diagnoses are clinically confirmed, and we're taking extensive information on environmental, medical, lifestyle, socio- and demographic information and phenotypic information, and we're trying to link this to state of the art labs through the center cores.

Now, as I said before results are coming out from this study. You know, any time you start a large epidemiology program there's always a couple of years of setup before you begin to see the results. Well, we're starting to get them now and I think one of the most important was the study that just came out a few months ago demonstrating that when corrected for

fish consumption, blood mercury concentrations are similar for children with ASD versus normally developing children. We're currently following up on that and looking at hair levels as well to confirm that we also see it there. There are gene expression differences that have been reported in autism spectrum children versus normal children, particularly in NK cells. These are a kind of immune cells that are present in circulation. So again, again going back to a little of what Andy Feinberg said that you know in fact we're finding that immune cells can serve as markers of what may be going on in other parts of the body.

Again, talking about the MECP2 promoter and we're clearly finding differences here in the methylation of this promoter in ASD children versus normally developing children. And I think some of the most important stuff that we're reporting and I think that this may be something we want to discuss more about more emphasis on this is in fact that we are seeing

that there are numerous immune markers which are distinguishing children with ASD from children who are normally developing. So we're finding that there's an increase in maternal auto-antibodies which are able to reach the fetal brain, and we're finding that there are differences in total IgG levels which IgG is the major immunoglobulin circulating in the blood and those total levels are reduced, but specific IgGs and in this class the subtype IgG4 levels are increased. We're also finding that there are decreases in the level of TGF-beta and TGF-beta is a very important signaling factor which is involved in a number of different developmental and immune properties as well.

We found in this population very high levels of regression and this is as high as 44 percent which is higher than we heard before which I think the high was about 30 percent that was just reported. And this was when both language and social skills were taken into account. We've also found that there appears to

be differences in sleep patterns in normally developing children versus children with ASD. And we're finding that there's some changes in lipid subclasses in children, and that this - the docosahexaenoic acid (DHA) is a major lipid which is present in membranes that are in the brain, and if you alter membrane proteins within the brain you can alter nervous transmission within the brain.

So the other study I wanted to talk about is the EARLI study which is the Early Autism Risk Longitudinal Investigation which we are co-funding with NIMH and NICHD and NINDS. And this is one of the projects that also came out of the ACE network R01. And again, Dr. Feinberg is - he is involved in one of the centers that is participating in this as well as four other sites, and in this case the unique nature of this study is that we are focusing on enrolling women who already have one autistic child but are planning or hoping to have - to become pregnant or at a very early stage of a

second pregnancy. The idea being is that this cohort will have an increased risk of having another child with autism spectrum disorders and therefore we may have a greater ability to detect what factors are playing into this risk, looking at the interactions between genes and the environment. Another important part of this study is again it's a prospective study. So we're going to be following the children for up to 10 years. We're looking or following the women and their children for up to 10 years. We're taking real-time data collection during early periods of development. Again, there was a question earlier about are we taking prenatal measurements and the answer here is yes, as well as a series of other measurements. So we're avoiding some of the disadvantages of trying to look back in time. Now, enrollment just started just less than a year ago and we're targeting to have 1,200 mothers in this study.

So again, there's a wide array of data and biological specimens that are being

collected starting hopefully before pregnancy, throughout pregnancy and up until at least age 3. And for the mother we're taking blood, hair, urine, saliva, placenta, cord blood and breast milk, a wealth of information. We're also taking paternal samples because we really don't know, you know, what may be the role of is there a genetic component or again, I keep saying "genetic" but I will come back and say "epigenetic" role that the father or the mother may be playing here. We're also - from the baby we're taking meconium which is the first stool, we're taking urine, hair and blood, and we're looking at the older sibs in this study and so that we'll take blood from these older children so that we can compare what we see as potential biomarkers in the blood of the older children who have autism and then potentially in the blood of the younger children who may or may not develop the condition.

So some of the hypotheses that we're looking at is, as I said, it's a 10-year study.

We're not waiting 10 years to report out the results. We have some exemplary aims that we're trying to get going right away so that we're hopeful that within five years we will have some results that can be accomplished with a smaller sample size than the 1,200 mothers. Some of these are going to demonstrate the feasibility of the studies, and here we're really focusing on the relationship between the risk of autism and autoimmune biomarkers in the mothers, environmental exposures to the mothers, epigenetic vulnerability, and gene-environment interactions. And the infrastructure here and the data collection is under the auspices of the ACE R01 projects and should provide lots of opportunities for other studies and pursuit of additional hypotheses. And so we are collaborating here with the Infant Brain Imaging Study with Autism Speaks and we're also involved here with the Environment, Perinatal Epigenome and Risks for Autism and Related Disorders which is part of the NIEHS and NIH Epigenetics Roadmap

program.

Now, I just wanted to briefly mention some of what has been done that we've been involved in under the stimulus program. And we provided funding for four new NIEHS projects solicited through the Heterogeneity of Autism Initiatives. And these examine a range of exposures being investigated for association with autism risk, trying to leverage resources that were already being supported through other organizations. So for example, Dani Fallin who we heard mentioned earlier at Johns Hopkins is looking at the Genome-wide Environment Interactions Study for Autism. We're working in California looking at the issues, for example, of the environmental chemicals that are of great concern to many people right now which are the PFCs, things like PFOA and PFOS and seeing if there's any - if we see any relationship there in the Early Markers of Autism Study. We're looking at the role of air pollution and Rob McConnell is chairing this effort to look at the

interaction between certain genes that have been associated with autism or suggested to be involved and also just looking at what's happening in air pollution. And then looking - we're working actually on the international scene in a Finnish national birth cohort funding studies that Alan Brown at Columbia is looking at at some of the prenatal factors and autism risk.

We also provided supplements to existing grants, and this did one of the main things that the ARRA program was aimed at which was increase jobs. So we hired additional outreach coordinators for the EARLI study and that means we're moving faster in enrolling people. We hired new personnel to increase the analysis and disseminations of finding from our UC-Davis CHARGE study. We support home visits for dust collection also under this CHARGE study so we can get better environmental measures.

Now, we have as I said a major focus on involving the community in our activities.

So we have recently established an umbrella - a program called the Partnerships in Environmental Public Health. And so under this program we did provide additional funding to the UC-Davis center to increase the interaction with diverse communities. And so all of the information that's being generated there is being translated into Spanish as well as English so that we can better communicate with the large Hispanic population in that area. In addition, we supported for an Autism Risk Communication conference that was held just a couple of months ago where we were including parents, educators, community clinicians and so on were all concerned, and this was focusing on some of the ethical issues about how do you actually communicate issues of autism risk to not only - to parents, but to educators in the community.

Now, we've heard a lot about epigenetics and epigenomics so I'm going to be able to sail through some of this. And again, this program is examining the impact of gene-

environment interactions and diseases by looking at alterations in gene expression. And again, just to - again that we are looking at the relationship between changes in this key DNA methylation pathway, the MECP2 enzymatic activity and organic pollutants in neurodevelopment, again at the UC-Davis. Davis has a long history in looking at different persistent organic pollutants and their role in neurodevelopment, but the epigenetic component is kind of new. And then we co-lead with other parts of NIH the cross-NIH Roadmap efforts in epigenomics trying to understand the importance of epigenetic marks. And you heard a lot from Andy Feinberg this morning about the possibilities in the environment and perinatal epigenetic and risk for autism. We also are co-leads at NIH for the Genes, Environment and Health Initiatives, and we're hopeful that this is going to provide new tools for autism researchers to measure our exposures and identify interactions of exposures with genetic

variation. So NIEHS leads the Exposure Biology Program which is really kind of a technology development program where we're developing some rapid sensitive sensors that can be used on an individual basis to really measure exposure, and the Genetics Program which is led by NHGRI to identify genetic variants.

Now I just wanted to briefly mention what's going on in some of our intramural program here because we have actually a large intramural research effort in neurobiology, not specifically autism at this point although we are looking to increase our investment in that area. But the Laboratory of Neurobiology looks at the cellular and molecular processing in both the developing and the aging nervous system that changes its vulnerability to environmental exposures. And the Synaptic and Developmental Plasticity Group is looking at the regulation of synaptic effectiveness and there has been a suggestion that changes in synapse development may play a role in autism spectrum disorders.

So some of the major areas that we're investigating here are we're looking at transcripts from regulation by neuronal activity, synapse elimination during brain development and critical periods of plasticity during development.

Our epidemiology group which is one of our largest programs studies a wide range of health effects linked to environmental exposures and our pediatric epidemiology group has been looking - for many years looking at the effects of environmental chemicals on childhood growth and development. We also have a biomarker-based epi group which is focusing on the health effects of early exposure to background levels of environmental contaminants and under this effort we are collaborating with a collection of additional biological specimens from pregnant women in the Norwegian Mother & Child study which was mentioned this morning. And this is a long-term prospective cohort of 100,000 pregnant women and their babies, so it has the

opportunities to provide a great deal of information. And these samples are going to be used for some investigation of autism gene-environment interplay in the autism birth cohort study which is within MoBa.

I just briefly wanted to mention the National Toxicology Program which I also chair or direct I should say, and the NTP is a cross-agency effort involving CDC and FDA as well as NIH. And its function is to coordinate toxicity testing across the federal government as well as to actually develop and conduct toxicity testing. And in the past much toxicity testing has focused on cancer as an endpoint. Well, there's increased interest right now and we're working - beginning to develop our evaluation and methods to look at neurodevelopmental outcomes. Again, these are all in rodent - largely in rodent models I should say. So we're currently exploring the development of an integrated testing protocol where we're looking at the effects of developmental exposure not

only on the reproductive and the immune systems which we've done for quite a long time, but focusing on the nervous system as well. And we're going to expand to look at both sensory, motor and cognitive endpoints in these testing programs.

So in sum - and I really tried to go fast, Tom - our funding has grown considerably over the past 10 years but I do have to say I don't think it's where it needs to be. Our investment last year was about $9.3 million. We are not one of the bigger institutes but I think that we need to be looking at increasing our investment in this area. Our supported studies range from human epidemiology to mechanistic laboratory investigations. The infrastructure for the very large-scale epi studies is in place. We're already beginning to see results from the CHARGE study and we are anticipating within a couple of years to begin to see results from EARLI which we are optimistic will shed some light on the interactions between

environmental factors and genetic factors. We're beginning to look at or we're beginning to identify certain biological markers for actual subtypes of autism related to specific immune alterations and we're beginning to increase our support for basic research in neurotoxicology and exposure science which is essential for understanding and informing the human studies. Now, as we go forward in autism research we will focus on opportunities that are identified in the Strategic Plan and coordinate with other federal agencies as well, obviously, as the communities involved. So I just wanted to make sure to thank the different NIEHS staff who are key to the effort here. Cindy Lawler who you all know who has represented our institute when I can't come on the IACC and does a great job as well as some of our other intramural studies and our extramural investigators who are leading the extramural effort. So thank you.

(Applause)

Dr. Insel: That was a whirlwind tour

of NIEHS. Thank you, Linda. We can take one minute for questions or do people want to break for lunch? I think we're breaking for lunch. Thank you very much. Let's plan to return I'm going to say at - it's 12:30. At 1:40 - 1:20 so we can pick up a little bit of lost time. See everybody here at 1:20.

(Whereupon, the foregoing matter went off the record at 12:33 p.m. and resumed at 1:21 p.m.)

Dr. Insel: We're going to move on with the agenda which you see on the screen in front of you. The afternoon is really committed to doing committee business and much of this has to do with trying to get the Strategic Plan for ASD Research ready to submit. So I'm going to ask Della to help us through much of the afternoon business session so we can make sure we get everything done that we need to in the timeframe that we've got. So let's wait just a moment as others come back into the room. Okay.

So first order of business is to -

we're going to go back to the Strategic Plan for Research. You will have received the edits electronically last week. The main business part of this that's changed is the question about budget recommendations. Remember, the law requires not only an annual update, but that all objectives have budget recommendations that go along with them. So we weren't able to do that. We wanted to get input from program and they have provided recommendations for every one of the new objectives that you inserted. In addition, the other thing that we decided at our meeting in December was that we wanted to make sure the plan was more readable and so we asked two members of the committee, Lyn Redwood and Alison Singer, to sit with this and to try to harmonize the language so that the plan would fit together in a more coherent way. So there were some changes made on that basis and then there's been some language added in based on the conversations that we had in December. So you'll see there's a section on surveillance, a

section on epigenetics, there are a number of things that the committee had talked about but you'll be seeing them for the first time. And those are usually shown as highlights in the documents that you received last week.

So let me open this up. The issue for us is that this is effectively due by the end of this month because it's an annual update and we submitted our first version of the plan just in time for a new Secretary right after the last inauguration January 20, 2009. So we're right on target if we can get this done today to be able to submit a final update. And then the other thing we need to do is, and we'll do this after we finish our work here, is to decide what to do about the process for updating for the 2011 version. Okay. Comments or issues with what you've got in front of you? We now have seven questions instead of six and there have been changes made to each one of them, especially with the budget.

Dr. Hann: So also I just wanted to

point out one additional document that you have. It's a document that's in blue and white and grey. This is the listing of all of the changes that have been made with regard to the budget estimates. The budget items which are objectives that are listed in white are the new ones. So those have been - we worked with the program from not only NIH but also HRSA and CDC in some cases to obtain the estimates. So we pulled those out for your. As we did last year we voted on content essentially and then you all separately voted on the amounts.

Dr. Insel: What's your pleasure? Are we ready to move this forward? Are there pieces of this that we need to talk about? Ellen?

Ms. Blackwell: I hope I can get it organized enough to make sense here. I noticed when I read the revised version that there were a couple of differences between the version that we reviewed in November and the version that was sent to us on Thursday evening. And be patient

with me please just for a moment because this is a lot of paper as everyone can see. On Page 7 of the current version before us in Chapter 5 there's a transposition under the objective that says, "Test four methods to improve dissemination, implementation and sustainability," we had had that as a long-term objective at five years and this just says three, so if we could replace the years back to five that would be great.

Also, on Page 4 of Chapter 6 we had moved an objective regarding medication use in challenging behaviors for people with autism to Chapter 4 so I would suggest that we also move the research opportunity to Chapter 4. That seems appropriate. Also, in our previous discussion in November we have - in fact CMS has engaged in activity, the state of the state review of policy services and supports for people with autism and their families. We have this as a research opportunity in Chapter 6 and my understanding was that it would be included

in the new Chapter 7. However, it is not included in Chapter 7 so I would propose that we restore it to Chapter 7 as both a research opportunity and a short-term objective which is how it existed in the previous plan and in the preceding drafts.

Dr. Hann: Just one point. Based on the December 11 discussion with the committee the - in Chapter 7 those items previously that were listed as opportunities became resources, to provide listings of available resources. And so the state of state is listed as one of the available resources, research resources, but there is no longer a section called opportunities in Chapter 7, research opportunities.

Ms. Blackwell: Well I understand that, but it is also a short-term objective. So okay. And then -

Dr. Insel: You lost me on that.

Ms. Blackwell: Sorry.

Dr. Insel: So state of the state -

Ms. Blackwell: State of the state somehow -

Dr. Insel: Where is it in this plan?

Ms. Blackwell: It's just listed as a resource, not as a recurring objective.

Dr. Insel: So that's Page 8, the CMS state of the state review?

Ms. Blackwell: Yes, but I would propose that we -

Dr. Insel: Oh, so just point of clarification. I think what was supposed to go into research resources were existing resources that all could use. Does this exist currently?

Ms. Blackwell: No. So I would actually take it out of the research resources section and put it back into the short-term objectives section.

Dr. Insel: I guess some of this thought this was already completed, but it's not done.

Ms. Blackwell: Years.

Dr. Insel: Two years? So when is it

supposed - so is it 2011 or 2010?

Ms. Blackwell: Well, we just began operation so we'll be working with OMB to get the clearance package started in the next month or two and convening a technical advisory panel next month, so two years. Or maybe 18 months, we'll see.

Dr. Insel: Do you recall what the budget was for this in its earlier -

Ms. Blackwell: Yes, we had actually had it in here. In the November meeting we had as a short-term objective, "Conduct an annual state of the states assessment of existing state programs and supports for people and families living with ASD, $300,000 per year." And I believe that number is probably about appropriate.

Dr. Insel: So this may just have been a misunderstanding. I think some of us thought this was already funded and was going to be ready for primetime. So is there a problem if we move it back to where it was? Does anyone

see a concern about that? So this would be - we don't have a short-term objectives section, do we? In this? So we can just put it under both short- and long-term objectives with that date and that budget. So we'll just restore it.

Ms. Blackwell: That would be great.

Dr. Insel: The other issue on the investigation of the use of medications for challenging behaviors, I was pretty certain that we all decided that that was going to move to Chapter 4 just as you said, so I suspect this is just an oversight.

Ms. Blackwell: Just an error.

Dr. Insel: Okay.

Ms. Blackwell: And then I had one more question. Christine and I were wondering, we recall - we could be wrong, but we had - under our short-term objectives we had the promising practices papers that describe innovative and successful services - being implemented in communities that benefit the full spectrum of people with ASD that can be

replicated in other communities. This was a project that our group was really interested in and again, I seem to recall that this was going to translate over to Chapter 7, infrastructure, but somehow it got dropped off as well.

Dr. Insel: Anybody have a memory of how that was handled? I don't remember discussing it.

Ms. Blackwell: I think you were gone at that part of the meeting so it isn't your faulty memory.

Dr. Insel: Okay.

Dr. Hann: Ellen, is that Chapter 5?

Ms. Blackwell: It is Chapter 5, correct, Page 6 of the November version.

Dr. Hann: Okay. I have my notes here as they are from our discussions in November and yes, support promising practice papers was to be moved to Chapter 7.

Ms. Blackwell: Okay, thanks.

Dr. Hann: Is it an objective? It's not really a research objective, is it?

Ms. Blackwell: We had it in here as a short-term objective. I think it goes to sort of a larger issue that we might want to talk about if we talk about Chapter 7 which is the community infrastructure piece which seems to be maybe a little bit weak or missing. I mean, we've got the state of the states back in there now, we've got these promising practices papers, but overall I know Lee had some comments about Chapter 7. It seemed like it may just be missing a couple of paragraphs about community infrastructure and states. So that would certainly go along with the promising practices papers and also the state of the states. And it may be that Chapter 7 is our Version 1.0 of Chapter 7. That's how I started thinking about it when I first saw it, but to at least get these objectives restored might handle the problem.

Dr. Insel: I see heads nodding so I think everybody is in agreement with you on that. Is that something that we can do quickly,

Della and Susan, so that this won't hold up the report?

Dr. Hann: I think what I would argue is for the record is to read through all the changes that Ellen has just requested and then we have to take a vote to make certain that people are on board.

Dr. Insel: Okay, well this - so we'll do that. Let's just see if there are any other issues or comments. There's one very minor thing in Chapter 6 that I noticed. There's an objective listed as short-term on Page 5 which looks it's to be completed by 2018 so it looks like that perhaps - it's the comparative effectiveness research objective. It at least looks like that might have been more of a long-term objective rather than a short-term.

Dr. Hann: So what happened was when we went back with wording changes to some of the objectives and this was one of them that had a wording change. We went back to program. They

then modified the dates. For those that had wording changes it also meant a significant change in the way the science was to be conducted. So that had originally been a short-term one because I believe it focused primarily just on clinical trials, and then the wording was changed to focus more on comparative effectiveness research and so therefore the date was modified.

Dr. Insel: So I would recommend that that be shifted to being a long-term objective rather than a short-term just from the timeframe. Are there other modifications or any concerns as you look at this document? We are now very close to making it a wrap. What we want to do today is get your final suggestions, making sure you've looked at the budget recommendations and then vote on this as a final document that we can send forward. Ms. Blackwell: On Page 4 of the introduction there's an error in the name of Chapter 6.

Dr. Insel: So that's the - what

other infrastructure and surveillance needs must be met. What is the final title for that? Because I have the - I think it's meant for Chapter 7. Ellen?

Ms. Blackwell: Chapter 6 is now - I think it refers particularly to adults. And that's missing from that introductory section.

Dr. Insel: What is the particularly for adults?

Ms. Blackwell: What does the future hold particularly for adults.

Dr. Insel: Okay. So that can be added.

Ms. Blackwell: Yes. Thank you.

Dr. Insel: Lyn?

Ms. Redwood: Tom, I have a question about some of the dates. You know, as part of our core values we have a sense of urgency and it's just with some of the new dates that have been added here I'm wondering if there's any way to speed the science up. A lot of these dates are 2015. One is, "Launch two studies that

focus on perspective characterization of children with reported regression to investigate potential risk factors." I would think we could do that in under five years and I'm just wondering whether or not we can - or how staff came up with some of the dates.

Dr. Hann: Could I ask sort of a point of procedure, please? I'm finding it very difficult to follow you all in terms of the changes that are being requested. So if we could start chronologically and move through the document from the beginning, from the introduction and move forward that would be incredibly helpful. Because we want to make sure we capture what it is you'd like to have changed.

Dr. Insel: So is there - we haven't heard anything from the introduction. Right now we're just sort of fishing to see whether there's anything else.

Dr. Hann: Ellen had a correction.

Dr. Insel: So other than that one

title change is there anything from the introduction? What about the first chapter? Second chapter? We're on a roll. Okay. First chapter. Comments here? Anything?

Dr. Hann: Date issues either for any of the objectives?

Dr. Insel: Well, so I guess I go back to Lyn's comment. Just as an example the very last objective, "Identify and develop measures to assess at least three continuous dimensions" was listed as an $18 million recommended budget. So that just carried over. Okay, all right. Anything else from Chapter 1? Chapter 2? So here we had a number of new objectives and this may go to Lyn's question about the timeframe of 2015. Actually, almost all of them it looks like, all the short-term ones are 2015. So what's the sense of the committee about that particular issue in terms of timeline?

Ms. Redwood: Are they doable in two years? I guess I think of short-term as being

shorter than five years.

Dr. Insel: I wonder if part of what was driving the dates which came in many cases from Program was they were thinking if this is something we want to do we would put out an RFA. If we put out an RFA today in 2010 it would be for research that would be funded at the earliest in late 2011, potentially 2012, and if it was a 2-year project you'd be into 2014 or close to that. That is the reality of the solicitation review structure.

Dr. Koroshetz: Tom, a question. The wording - and this was launch studies. So is the date the time of the launch?

Dr. Hann: Yes. In the past it has been sort of the launching and conducting, but did not necessarily imply that it had to be finalized.

Dr. Insel: So Lyn's question would be why would it take five years to launch the two studies, not even to complete them but just to get them started. Jim?

Dr. Battey: Well, just to reiterate the typical NIH process for solicited research which is what this would be. Let's say for example an RFA went out tomorrow. You'd want to allow four to six months for individuals to get in an application, then you have to arrange for a review, and then you have the review, and then it has to go to the next advisory council, and then it has to be - the branch management has to work it over and actually make the award. It just, you know, you burn through well over a year before you actually get started doing the research.

Dr. Insel: But even if it were a full year, even if it were a full two years, if the objective is just to get started on these projects it doesn't sound like that would take five years to get started.

Dr. Battey: No, it wouldn't take five years to get started. It would probably take five years to complete them though.

Dr. Insel: Right. And we knew from

the Recovery Act that if there's really an urgency we can do this in three months instead of 15 months if we have to.

Dr. Battey: You can do expedited council review by email. I mean, there's a lot of things you can do to shorten up the timeframe, but that's - that has only been done under extraordinary circumstances at NIH.

Ms. Redwood: See, I guess I think that autism is an extraordinary circumstance and I would really like to see - I think something like that would reflect a sense of urgency versus just sort of the status quo. That's my own personal opinion as a parent.

Dr. Insel: Say it again?

Dr. Briggs: Sounds feasible to launch by 2012, to implement by 2015.

Dr. Insel: Does Program want to speak to this, or there's issues that we're not thinking about that we should be thinking about? Anne? Thanks.

Dr. Wagner: I think -

Dr. Insel: It's on. Yes, you're fine.

Dr. Wagner: I think launching - I mean, I think that we were thinking of completing by 2015, so I think if the launch were - if you wanted to move up the launch, the date up, one could do that.

Dr. Insel: Okay. That explains the discrepancy. So I think then you're talking, as Josie says, 2012 would be short-term to get started, right? So that's a change that we would make to all of those that say launch, and then for anything that's completed we'd move to - looks like none of these are completed. These are all just getting started. So for short-term we'd dial it back from 2015 to 2012. Does that sound reasonable?

Dr. Battey: I think that's reasonable.

Dr. Insel: Okay. Thanks, Lyn.

Dr. Hann: Just for point of clarification, will that also apply to the very

last objective, long-term objective, which wouldn't be long-term any longer?

Dr. Insel: So I would assume if we put that as a long-term objective that would have been a later launch date. But Cathy?

Dr. Rice: Well it seems that one's dependent on some of the short-term objectives so it makes sense that it launches after the short-term.

Dr. Insel: So does the group want to leave that as it is and we'll change the short-terms to 2012. We ready to move to Chapter 3? There's a lot of language, a lot of text that's been added to this chapter around the topic of epigenetics. I'm assuming you're okay with that? In a way it actually sounds a lot like what we heard this morning. Ms. Blackwell: Actually I noticed that and I applauded. I thought it was very, very well and clearly written. I would point out that in the first line 4 there needs to be a question mark added to be consistent with the rest of the

questions.

Dr. Insel: Looks like that might have been a formatting injury. So have we got that? Do you see that, Della? Okay. Any other comments before we get to the objectives which are beginning on Page 9. Issues, comments? Lyn, do we have the same concern about dates here or does this look better? Now we're in the dark. Okay, now we're back in the light. Any changes, any concerns about dates or budgets? Chapter 4. Cathy?

Dr. Rice: I did have one comment just about the - on Number F or Letter F, Line 12.

Dr. Insel: Which chapter are you on?

Dr. Rice: Oh, the last one. Chapter 3. That it was changed to at least one, and I know we've wanted to have at least, but just at least one seemed like a low threshold, that I would say at least two maybe.

Dr. Insel: What did we - I don't, again, remember where we ended up on the

discussion in December on this.

Dr. Hann: So actually it was from the November discussion and it was left at "studies." So we needed to provide some sort of grounding as to numbers of studies in order to do the budget recommendation so we elected the "at least one" so that way we have the $4 million and that way if that's modified we can use the $4 million and multiple it by the number of studies.

Dr. Insel: So this isn't a ceiling, it's a floor?

Dr. Rice: Yes, I was just thinking since it was changed from studies that we should do a minimum of at least two since it was studies as in the intent was for it to be plural even though this is a floor. But just to push it a little bit further.

Dr. Insel: So if we think back to the discussion, what was the sense of the group at that time? What do you want to do now? If you want to open this back up we can figure out

how you want to handle this.

Ms. Redwood: I agree with Cathy.

Dr. Insel: There must have been some confusion about it before if it said "studies." I assume that the intent was it for to be more than one. Walter, is that? So Cathy, your recommendation is that we say at least two and that we double the recommended budget accordingly, or scale it?

Dr. Rice: Yes.

Dr. Insel: Well, unless I get real heartburn on this we're going to keep going forward. Okay. We're moving on to Chapter 4. Questions or issues here? And here the objectives begin on the bottom of Page 7 and so 7, 8 and 9.

Ms. Blackwell: I think this was the chapter where we talked about adding the research objective for the pharmacy and also the short-term objective, correct? I just want to keep the "illustrate" in there.

Dr. Hann: So the objective "For the

effectiveness of medication commonly used to treat comorbid conditions" is the last objective on Page 9 of this chapter. What didn't make it though, Ellen, was the opportunity.

Ms. Blackwell: Right, thank you.

Dr. Hann: So we need to add the opportunity which reads, "Investigation of the use of medications to control challenging behaviors in people with ASD, particularly adults."

Dr. Insel: Right, so I don't think we want to change the wording, but we want to put it in the right place. Okay, so that's moved to this chapter as an opportunity and it matches with the objective. And then what has changed from the last meeting - this is actually a chapter that didn't have a lot added or modified, but we did break up the trials, the RCTs, randomized controlled trials to include the different age segments, and that does change the budget a bit and they've been staged a little bit as well. Walter?

Dr. Koroshetz: So on Number 8, the three randomized controlled trials, adjusting and co-occurring and conditions by 2010. So if they're not already underway it's not possible to get it done in 2010.

Dr. Insel: Yes, but I don't - I don't think we want to start shifting if we failed to do something that was in the plan from last year. We may want to revisit it next year, but if we haven't done this by 2010 I think we have to ask ourselves why not and so I don't want to lower the bar at this point. If others feel differently I'm happy to discuss, but I just think that would be a bad precedent to set, if we kept shifting the goal post as we go along.

Dr. Janvier: I just wanted to go back to that issue about challenging behaviors. On Page 9(c) sounds better to me because comorbid conditions and specific behavioral issues are not always challenging behaviors. So I'm not sure that they really match. To me

you're talking about, for example, treating attention and concentration which is not necessarily a challenging behavior.

Ms. Blackwell: I think our group was in fact mostly concerned with medications being used perhaps inappropriately for adults with challenging behaviors, but I believe it was Ed who pointed out last time that we might want to also look at this issue in the child population as well. So you're absolutely right, but I'm not sure that that expresses what the intent was.

Dr. Insel: Yvette, are you making - what would you recommend changing? Is the word "challenging" the problem, or is the objective not matched with the research opportunity?

Dr. Janvier: The latter, and I think what Paula said earlier kind of was ringing in my ears as I was reading this. I agree with what's written in (c) but again, dealing day to day with the childhood population we use medications for all kinds of treatment reasons

that are not necessarily challenging behaviors. It's kind of limiting and I don't think it covers the spectrum of medication used.

Dr. Insel: So I just want to make sure we understand what you're saying. Is (c) the way it's worded now appropriate? Is that what you -

Dr. Janvier: Yes, that's -

Dr. Insel: So that's not a problem.

Dr. Janvier: So the other component that was moved from somewhere else that includes challenging behavior needs to be adapted to match what's here in (c).

Dr. Insel: Although a lot of times the research opportunities don't quite match the objectives. I wouldn't worry so much if there's not a 1:1 correspondence. I think the idea we wanted to convey with the opportunities was what's out there that we know about that can be done and the objectives sometimes strayed from that a little bit. Hopefully not too much. Alison, you had a question.

Ms. Singer: On short-term Objective F we're talking about convening a workshop and it's by 2012. I would like - I mean, I think we could convene a workshop this year. And I'm not sure why it's then budgeted for - it's actually budgeted for two workshops over two years rather than one workshop for this year. I think because it had a 2-year horizon there was $25,000 a year for two years. I would like to see us change that to 2010 and there we really just need the money for a single workshop.

Dr. Insel: What's the sense of the group?

Ms. Redwood: I agree, Alison, totally. I'm just wondering though how many people. You can easily go through $25,000 in a workshop in a day.

Ms. Singer: Yes, we should put the whole $50,000 in one workshop.

Ms. Redwood: In one workshop, okay great. I was thinking you were splitting it in half.

Dr. Insel: What year are you proposing we do this?

Ms. Singer: This fall.

Dr. Insel: So 2010.

Dr. Briggs: So I wonder if there was some program input as to what the right timeline is to plan this. It might end up if it's fall, that's Fiscal Year 2011.

Dr. Wagner: I can tell you what our thinking was. We were thinking about doing this as the R13 which is the way we usually solicit applications for workshops and we were thinking of $50,000 for the one year, not for two years. So we were letting time to come in for people to propose an R13 which is the mechanism that we usually do for - we often use for workshops. So one can move it up, but we weren't thinking $25,000 a year, we were thinking $50,000 for one workshop.

Dr. Insel: We're just trying to figure out whether this is something the IACC could do. Usually the way we do workshops or

meetings is through a competitive process which goes through peer review if it's done at the institute level. But if this is something the IACC would really feel strongly about we could try to bankroll it in another way. Jim?

Dr. Battey: I think you'll get a better workshop if you use the R13 mechanism. Allow people to compete.

Dr. Insel: Is there any reason we couldn't do this by - let's say it were going to be done in November it would still be 2011; that's the next fiscal year. So if we change the date from 2012 to 2011 and if it gets done earlier so be it, if not. I mean, if there were IACC money that would be another option, but we can figure out later whether the committee wants to push this forward themselves.

Dr. Battey: I think 2011 is reasonable.

Dr. Insel: Alison, that doable? Lee?

Mr. Grossman: Yes, we were one of

the principal funders of the GI Consensus Study and that $50,000 is considerably low if you're going to do something on the scale that we did. It probably turned out to be closer to $200,000 with the writing and getting the supplements and convening everybody. I mean, you could actually do the conference for about $75,000 to $80,000 but all the other supplemental work you have to include in that as well.

Dr. Insel: At NIH usually a $50,000 workshop is what we - that's actually the max that we will spend in a year, but it may be because we're just, as you saw with our cafeteria, we go - we don't do Cadillac version on anything. This is not - at least in terms of a quality of the meeting it's not going to be a Lexus.

Ms. Redwood: Tom, I'm wondering, because I think Lee has a good point about having something that's of publishable quality whether or not there would be opportunities for collaboration with other organizations on this

the same way ASA collaborated with organizations to do the GI workshop. So that might be something that would be a nice public-private partnership.

Dr. Insel: That's a great idea, and Lee if you wanted to spend that much money on such a workshop we would be happy to work with you and provide some piece of it.

Mr. Grossman: Actually we were going to come to you for the funding this time, for the follow-up.

(Laughter)

Dr. Insel: In any case, it sounds like this will be either a fall or winter, so 2011 is probably where we're going to end up. Anything else from this chapter? Moving on to - yes.

Dr. Hann: If I could just go back. So are we - I just want to make sure I'm understanding this, that we're comfortable then with the long-term Objective C in terms of its wording. We are also comfortable with adding

under Opportunities the investigation of the use of medications to control challenging behaviors in people with ASD, particularly adults. Okay, just wanted to make sure. Thank you.

Dr. Insel: And we'll be changing the timeframe on F from 2012 to 2011, but not changing the budget. Chapter 5.

Ms. Blackwell: I think we previously spoke about the year error, it's just a mistake, on Page 7. It should save five years under B instead of three years. You got that, right Della?

Dr. Hann: Yes.

Ms. Blackwell: She got that.

Dr. Insel: Any other corrections, deletions, comments? Chapter 6.

Ms. Blackwell: On Page 4 of Chapter 6 this was the one where we had just talked about moving the research opportunity to Chapter 4, but I also wanted to bring it up on Line 11, this was something that Christine and I talked about this earlier today. Our group had a lot

of discussion about housing challenges and how they might be different for people with autism and I'm not quite sure that that ever - I mean, my memory is failing me because we looked at this so many times, but I think at one point we may have actually had an objective for this, but I would propose that we move this research opportunity to Chapter 7 because I think it is more of an infrastructure issue.

Dr. Hann: But then it becomes an objective.

Ms. Blackwell: I'm sorry?

Dr. Hann: To move it to Chapter 7 to become an objective, because there are no research opportunities -

Ms. Blackwell: Oh, there are no research opportunities in Chapter 7.

Dr. Hann: At this time, that's correct.

Dr. Insel: And I thought this was actually relevant to the whole concern about the transition to adulthood.

Ms. Blackwell: Yes, it's fine to leave it here. And then my other thought about it was if you want to leave it here that's fine and then I think next year when we start our discussions again we might want to talk more about what it would look like as an objective. If that's okay with folks. Because it was important to our work group and they brought it up over and over that housing is in fact a huge challenge for people with disabilities and did it look different for adults with autism than it does for other groups. Okay.

Dr. Insel: You bring up a more general issue, Ellen, which is we eventually need to go back and see how - what kind of an alignment we have between these opportunities and the objectives because there are some opportunities that we don't seem to be exploiting and that'll be something to think about next time around. The other place, I think we pointed this out before is on Page 5 that Program had shifted the dates on B and so

it sounds like that was long-term. You got that? Anything else from Chapter 6?

Chapter 7? This may be left over from the earlier version, but on the first page on Line 16 I'm not sure it's fair to say that NIMH launched NDAR. I can ask our NDAR people. It was really an NIH - from the beginning it was multiple institutes. Dan, Mike, is that fair to say? So it should say NIH not NIMH. Other comments?

Mr. Grossman: This is Lee and this may have been covered in the last meeting that I missed, but when I was looking at the infrastructure needs it occurred to me that - and I'm trying - I'm pressed to find out in what other part of the plan this is covered, but it was evident in the conference that we did when we brought everybody together that there was a dearth of applied research either being applied for or being conducted in this field, and I thought maybe in the infrastructure area that that would be something that we could focus on.

Applied research, educational research, community-based outcomes, what type of infrastructure is needed that we can build off those models.

Dr. Insel: Is that something for 2011? I mean, for our next version? Because I don't think we're going to be able to do that before today. It's - unless there's someplace in here you think we can tweak a bit, but it sounds like that's another section of plan that needs to be developed.

Mr. Grossman: I'll leave it up to the discretion of the committee.

Ms. Blackwell: I have a question about the -

Dr. Insel: I'm sorry, before we go on, I mean we have to make a decision about this because as I said this is something we want to be able to submit probably this week and so it's a question of to what extent do we want to add new features here.

Dr. Battey: I think if you want the

new feature to really reflect full input and be developed well I would wait till 2011. There just isn't time to do it in a half an hour today.

Dr. Briggs: It almost sounds like it is heading for a set of specific research objectives rather than in itself a research objective.

Mr. Grossman: Yes. So I guess what I would ask is just for the committee's consideration that this becomes a high priority the next time, which will probably start when, next month? Looking at the next revisions? So that it does become a high priority going forward.

Dr. Insel: Thank you. Okay. There was another hand that I saw up.

Ms. Blackwell: I had a question about this new section on research workforce development because we had a number of discussions about workforce development overall, and when I read this, particularly the section

on Page 5 and then the objective on Page 8 I definitely got that this was to expand the scientific workforce, but I wasn't sure if in terms of infrastructure even though we talked a little bit about how to help the services workforce in Chapter 5 if - is this exactly what we talked about in our previous discussions? I mean, it's not that it's a bad thing, but did we talk - I mean, I guess I thought that it would be a little bit broader.

Dr. Insel: My sense was that was - this actually goes back to the very beginning of when we talked about what would be in the plan and when we sort of said we want to cut this at that particular joint between research and services, particularly in the realm of workforce we're talking about discovery and what's the workforce we need to be able to solve those questions, cause, treatments, those kinds of issues. So I don't think the services workforce, as important as it would be, that really would end up in a research strategic

plan. But again, I'll leave that open if others disagree.

I had a comment about the surveillance section which again doesn't involve much in the way of objectives, but just the text. I just thought this was one of the best 1-page descriptions of what we know and what we need that I've seen, so this in some ways builds on Cathy Rice's presentation from a couple of hours ago, but it just is a very concise look at where the field is and recognizing where the gaps are in our knowledge with some, I thought, great ideas about how to take it forward. So I think this is - I don't remember how this came up in the last few meetings, but this I think is a really excellent addition to the Strategic Plan. Makes it much stronger than the 2009 version.

So this ended up with - we ended up with this kind of epilogue of the research resources on Pages 8, 9 and 10 and even into 11. Many of them are very heavily focused on NIAID

projects and I don't remember that we've talked about this list or whether this is actually the list that we want to include, but I wondered how relevant some of these resources are for the ASD research community.

Ms. Blackwell: Tom, what specific area are you referring to?

Dr. Insel: Well, there's a whole series from - on Page 9. Clinical Proteomic Centers for Infectious Disease and Biodefense, NIAID Proteomics Research Centers, Structural Genomics Centers for Infectious Diseases, Systems Biology for Infectious Disease Research. Maybe those are research resources that will be helpful, but I'm just not sure how they would be used or what the - how they ended up here, whereas there are many, many other things going on at NIH that are not here.

Ms. Blackwell: I don't know how this got in there either. Does anybody else know?

Dr. Daniels: I can speak to that. The NIH ACC was asked to provide this

information and NIAID is an ex officio member of that group, and so they provided those and so we inserted them. But that was just what they offered.

Dr. Koroshetz: Yes, they kind of looked a little odd to me. I noticed the same thing yesterday. I'd vote to take them out.

Ms. Blackwell: I agree.

Dr. Insel: Should we take out the NIAID - at least the biodefense and many of these others that - clinical proteomics, as wonderful as that is, is probably not something that will be a useful resource in this sense for this community because most of that's around pathogen biology. It's not going to be related. The same with the PFGRC, the Pathogen Functional Genomics Resource Center, a terrific opportunity if you're interested in malaria; probably not so useful if you're interested in autism.

Dr. Hann: So removal of the NIAID resources. Okay.

Dr. Insel: Okay? All right. So we are - anything else from Chapter 7? We are now through the whole text. Della, I'll turn this over to you so we can get a vote on whether we're ready to finalize this update.

Dr. Hann: Walter, did you have a comment?

Dr. Koroshetz: Minor wording thing on Page 5 in the workforce. It may just be English in the sense that - I was a little confused by the number of trainees. My understanding is that there's trainees on the training grounds, so I thought maybe there should be a new sentence. These are in addition to trainees supporting more than 300 NIH grants focused on autism. That number we don't know, is that right?

Dr. Hann: Correct.

Dr. Koroshetz: So it's just -

Dr. Hann: Okay.

Ms. Blackwell: And also Della, you made a note that you would take out the state of

the states that doesn't exist yet.

Dr. Hann: That we would insert it.

Dr. Insel: It's going to be shifted over so it gets done.

Ms. Blackwell: Oh, okay, but it will come out of the research resource section.

Dr. Insel: So it'll get inserted with its original budget and original timeline.

Dr. Hann: Yes.

Dr. Insel: Okay.

Ms. Singer: I have a question on two of the resources listed under non-government resources. I'm not familiar with Project RedCap or Project RexDB.

Ms. Redwood: I was going to ask that same question too.

Ms. Singer: As non-government resources. I've never heard of those. Have other people heard of those?

Dr. Insel: Can anybody help us on this? ACC? Anne, do you know anything about this? I think we just lost two additional lines

here. Okay. If we don't know about them I'm assuming if they turn out to be extremely important we can put them into a later version like next year.

Ms. Redwood: The other thing, Tom, with these private resources I'm just wondering -

Mr. Lacy: RedCap is a clinical management system funded by NCRR that could be used by researchers to capture clinical data in their own system. So it's a free set of software that anybody can use if you belong to the consortium. RexDB is a commercial software application by Prometheus Research that many autism sites are using for the very same function.

Ms. Redwood: I wonder if we should really be promoting things that are commercial in nature in our plan? I would like to see it restricted to those things that are free to researchers, otherwise you know, I think we could get into some trouble with that.

Dr. Insel: I completely agree with that. I think we want to get away from proprietary software. But Dan, if the RedCap is - that's freely available as an NCRR product then that's not an issue here.

Dr. Battey: I think if you go with anything that's commercially available and proprietary you look like you're advertising for them and that's not, I think, an image that we want to portray with the Strategic Plan.

Ms. Redwood: Does anybody know what ISAAC? Oh, so that's -

Dr. Insel: Yes. Any other comments? All right. Della?

Dr. Hann: Well, I have a question though. We are inserting as now a research objective into Chapter 7, "Supporting promising practice papers that describe innovation and successful services and supports being implemented in communities that benefit the full spectrum of people with ASD that can be replicated in other communities." So we are

going to need financial - I mean, a budget figure for that and a year. We can follow up with you separately to do that, but we will need to have that information if it sits as an objective.

Ms. Blackwell: Tomorrow.

Dr. Hann: Okay.

Dr. Insel: So with that as the outlier, if that's the one thing that will need follow-up, could we go ahead and vote on all of these other recommendations and put this document to bed?

Dr. Battey: I'll make a motion then to, with the amendments suggested at this meeting and the inclusion of the budget figure by tomorrow that we accept the Strategic Plan and go forward.

Dr. Insel: Second?

Dr. Hann: Wait, there's one other budget one that's missing. So just so you know that. It's also in Chapter 7. I believe it's K. This was one that we thought we had a lead

on in terms of budget and then -

Dr. Insel: It's "I" I think.

Dr. Hann: No, it is K. In Chapter 7, Page 8 beginning Line 4, "To develop a web-based toolbox to assist researchers." Our program, the NIH program people really thought after they took a look at it that this was something that might be better answered by the experts at HRSA. And "I" also. You're right Tom, "I" also is missing. But it doesn't really -

Dr. Insel: Doesn't look like there's a budget that would go with "I."

Dr. Hann: Doesn't need a budget.

Dr. Insel: It doesn't require money.

Dr. Hann: Yes. But K does.

Dr. Insel: So those two will be added in by tomorrow? Yes?

Dr. Hann: I don't know. HRSA?

Dr. Insel: Peter? We can get the toolbox, we can get some insight from you?

Dr. Hann: Yes, it's on Chapter 7,

Page 8, Line 4. Yes, K.

Dr. Insel: We have a nomination - or we have a proposal for voting on this. Is there a second?

Dr. Briggs: Second.

Dr. Insel: All in favor of accepting these updates with the two remaining budgets to be added? Can I see a show of hands?

(Show of hands)

Dr. Insel: Anyone opposed?

(Show of hands)

Dr. Insel: The document carries. Thank you. We got it done in time. And you will get a final version of this once we have these last two budgets added in. This leads to I think a reasonable question which is how do you want to do this next time and is this process the best process, or is there a better way for us to do our annual updates of the Strategic Plan? And I know a couple of you are relatively new to the committee, but when I said at the outset today that we met 17 times this

past year many of those meetings were about the Strategic Plan, most of them, and not the plan itself but the update of the plan. So the question for the committee is, as Lee said, we're going to start working on the next update now. How do you want to do it? And we could take a moment just to tell you what we currently do. We have a subcommittee of I believe six or eight members, is that right? Who are responsible for pulling much of this together, but a lot of the heavy lifting comes to the full IACC which is responsible for voting on every change that we make in the plan. So maybe we could start this by just sharing your experience of doing it this past year, what worked, what didn't work and what you would like to see us change for the next time around. Cathy?

Dr. Rice: Two things that were - or one thing that was extremely helpful was starting with the summary of advances so we started out knowing what has occurred newly and what would inform the research plan. So I

definitely think that that's helpful to take that as our first step is to see what's come out. Second thing in terms of I can't remember now if they're called workshops or work groups that we assembled for each question. I found it would have been much more helpful to have them understand that the goal was to rewrite objective and maybe have them not just suggest a lot of things, but to go right into rewriting objectives. It felt like there was some variability in how some of the work groups were handled in doing that and it'd be nice to have a clear definition that the goal was to actually rewrite the objective.

Dr. Insel: Lyn?

Ms. Redwood: Tom, one of the things that we talked about doing that we didn't get to do this year was actually to take the money that we spent this past year and to apply it to the plan to identify gaps. So we have that information now so I think our first step is to do that. I also think the subcommittee could

probably look over the plan and at least outline the things that we know right now, like Lee's concerns that need to be added back in. There were several other things that came up during the last meeting that we said would roll over to Version 3 and get those on the table. And then one of the things that I think didn't work and I thought it was a wonderful idea that just went astray was selecting the people who would be at the workshops, and that it became more of a popularity contest in a way versus actually identifying the expertise that we needed. And we've been saying over and over again that we've lacked people with a toxicology background and it's been two years now, so I think we need to really look at the areas that we think we need experts and then identify those best experts in the field for the areas that we think are gaps or underfunded or under-represented in the plan.

Dr. Insel: Let me underline your first comment. We probably really need to take some time to figure out where those gaps are. I

was just looking at the NIH 2009 budget numbers and it looks like there's about $196 million that have been invested which is up from $123 last year, 2008, so this is a really opportune time. That's combining our base budget with the Recovery Act money, but we really ought to take a look at how many of these 60 or so objectives have money behind them at this point and where the gaps are before we start looking at a whole new set of objectives that we want to develop. And how many of them can we take off the list? Because by 2011, 2012 some of these ought to be completed.

Other thoughts about this? Yvette?

Dr. Janvier: I just thought there was a tremendous amount of time and effort both from the workshops and the phone calls, and I'm not sure it really translated directly into a benefit. I mean, we're talking about a conference and I'd much rather see a major conference where the public is going to benefit than, you know, hours of these meetings that

just, again, just to me didn't translate, at least maybe the section I was in, into a significant change or benefit to the committee or the plan.

Dr. Insel: Is that because, as Lyn is saying, the right people weren't at the table, or because there wasn't the right focus, or there wasn't the organization around getting to something that was new and different? What's your sense of the problem?

Dr. Janvier: Yes. No, some of the right people were definitely at the table, but there were other people that maybe weren't the right people. And I think that the direction was not, okay, rewrite this. I'm not even sure that people - that I kept reiterating since I had been involved with the plan, this is what the concept was and then we went off in a different direction, and then the IACC wanted us to come back to the original direction. It's a tremendous amount of, I mean, hours and hours in meetings on the phone over this. Just didn't

seem to have a positive effect.

Dr. Insel: Ellen?

Ms. Blackwell: Well, I think it might have been different for our group, Yvette, because - I mean, maybe Chapters 5 and 6 were always the weakest chapters. We had a great group of people and I think we did make significant progress. My other recommendation is, and you guys all heard me make this before, that we please treat the chapters separately in the future and not lump together chapters because that was quite difficult for our group. So I certainly propose that we treat each chapter separately and not bundle them.

Dr. Koroshetz: I guess just going back to something I said before and that is organizations, when you have a Strategic Plan you put your investment in and usually the follow-up is okay, this was the plan, what happened, you know, what didn't happen that we wanted to happen, and then there is certainly the ability to say that certain things have been

finished and completed or are now relevant, or that other things have become more important. But it seems to me that I would propose that the next version instead of being a rewrite would be, you know, we had the plan, this is what happened, this is what didn't happen, and then there were certain additions that need to go to the plan. So as opposed to a rewrite it's more of an amendment to the previous plan. I don't know if that's within the purview of what you guys do, but if you do guidelines for instance for a disease you don't rewrite the guidelines every couple of years, you do updates to the guidelines. So the statement is the guidelines remained as they were with these exceptions, and then you go through the critical exceptions. I think it gives you the ability to focus on what's really new and what needs to be done next as opposed to going back and getting entangled in words and meanings and nuances. That's my take on the process. I don't know if that fits with what you want to do.

Ms. Redwood: Walter, I think that's a wonderful idea. One of the things I was thinking when I looked back over the actual language from the Combating Autism Act, it says to develop an annually updated summary of advances in autism spectrum disorder research which is on the agenda next. And I'm wondering whether or not when we go through this plan and analyze it which I think is the first thing the strategic planning subcommittee needs to do when we meet is if we could use that information with what we've funded, what we've learned as our summary of advances and submit that to Congress and then that also will help us provide some framework for the areas in the plan that we need to work on and supplement that have not been accomplished yet. And I think that might be more helpful to us as a tool or a process to go through when we update the plan and it would also fulfill the requirement of an update to Congress as well.

Dr. Insel: So that was always my

understanding of the intent was that the updates were based on the summary of advances. That is, that we would - we'd find something entirely novel and then you would modify that part of the plan accordingly. I didn't think that it was the intent of the language and the law that we would rewrite this every year because then it's not a Strategic Plan, it's just a - it's basically a moving Rorschach test depending on who's at the table, and you don't want - that's not any way to spur progress or to focus a field. I had one of the chapters. I did - Stephen and I, Stephen I think is still with us, did Chapter 4 and I think we didn't feel that there was - that the differential between time commitment and output was that great. We actually, it was very efficient. We had a few meetings but they went very quickly. I sense, and I guess this is really seconding what Linda's already said, that it would have been better to have people at the table who weren't sort of the usual suspects, and maybe even

people who are not involved in autism research in some cases, but people who could help us realize what was having the greatest impact in diabetes or heart disease or cancer or some other area so that we could bring that in to this field. Because often the breakthroughs are not happening in this field that are happening elsewhere, and so that's a way of kind of refocusing the field. And we didn't do that, so I guess in going forward I would think about, and maybe this would be easier to do in a meeting format rather than an updating the plan format, but can we begin to hear from other than the usual suspects and from people who have not been so involved in autism research so far, particularly in the realm of interventions and in some of the issues around Chapter 3 as well. Lee and then Alan.

Mr. Grossman: Yes, I think what you just said was perfect and feeds into what I was going to say. When I look at this plan there's a lot in there, so as we move forward I think

that it's extremely important that we focus to make sure that what's in the plan is working and working well. I think what I saw in the process from the first year to this iteration was a lot of tweaking, probably much more than what needed to be done in that we were going about changing what we had originally done in many areas. So if we focus on what we already have in there and try and make sure that that's done well, then I think that that will free us up to what I feel is the most important aspect than what we're missing in the plan and that really is addressing the sense of urgency. I don't believe that the plan still does that. I don't think that it deals with the people that are living with autism today. I don't think it addresses the needs of the families today and I think that that can and should be part of our plan and should be an important aspect. What we're looking at, intervention services, treatments, anything that can help people in the relatively near future that will make a

difference in their lives.

Dr. Guttmacher: I think - I have several comments. I'm more concerned that if we continue to re-perfect the plan that we become endlessly enmeshed with the plan. While we want the plan to be good, at the end of the day we're not trying to craft the perfect plan, we're trying to move the field ahead. And I worry if we spend the efforts of the incredible people around this table just on the plan that we'll lose sight in some ways of what we're really trying to accomplish and that is to maybe take some aspects of the plan and see how we're really doing here. Is that something we should maybe have some working groups or meetings or whatever about this year, et cetera, et cetera. So I think the plan is really pretty darn good. Could it be better if we continue to sort of climb through it, absolutely, but I'm worried that that wouldn't be the best use of our time.

Dr. Insel: Henry?

Mr. Claypool: I would agree

generally with the comments about the use of time and coming in towards the tail end I really did notice how intensive this process was to work this through. One thing we might consider as a process should the membership of the committee change to allow incoming members to take some ownership of the Strategic Plan. So I'm not suggesting that you open back the Strategic Plan up and have a lengthy annual process again to develop it, but strike a balance in terms of finding a way to have that should there be new members appointed an opportunity for them to identify some with what's included in here, and then quickly move to I think the recommendations that other committee members are making.

Dr. Insel: Yvette?

Dr. Janvier: Speaking to what Lee mentioned, for me the two days of the scientific workshops - I know there were three and I can only remember two autism researcher's comments, Catherine Lord and Rebecca Landa, and they - of

the two days their comments stood out to me that we sit and we write goals and make a plan, but we make comments on how difficult it is to actually implement and complete many of the types of studies that we're looking for. And they made these comments out of frustration. I think Deborah Fein may have been another person. That maybe we really need to address and I'd rather see us spend the time to fly these people in and address the barriers for implementation of many of these well-conceptualized studies that we're recommending.

Dr. Insel: Gail?

Dr. Houle: One of the things that comes to mind is that the time next year might be spent in looking at the outcomes of the plan rather than focusing so much on what the plan itself says. I think that that would provide more information. You've already got the plan and the update and the outcomes. When I look at the projects that are being funded in public and private, and can you take - can anyone take a

group of those projects and kind of topically look at the outcomes of the work that's being funded?

Dr. Insel: That certainly seems to be one of the themes is that it's time to step back and take a look at what's coming out of this, not just add more items to the list.

Ms. Redwood: The other thing we talked about early on was what type of metrics we would use to evaluate success of the plan and I think that's something we need to spend some time on too. Was it a published study? Was it something that moved the science forward? So how do we know when we've accomplished some of these things our level of success.

Dr. Insel: Other comments or questions? How well do you think this plan defines priorities for the field? It's one of the things you want from a Strategic Plan, right, is to communicate to the field if you can only do one thing this is what we'd like to see you do. Have we done that? The flip side, I

guess that question that often comes up with Strategic Plans is that you use them to tell people what not to do. So you also use it to focus both in a positive and in a negative way. Has this plan now gotten so inclusive and so comprehensive that it allows everybody to do anything that they want rather than focusing the field on things that we really need?

Dr. Koroshetz: I think it's got a lot of things in it so yes, you can't say here's the one thing they said you should do because there's so many different things. But I think, you know, it covers many different bases so I think people come to autism research from many different areas and for each area there's priorities. But I don't get the sense that - I mean, we like cures. Those are good. But I still think - I mean, I actually feel that it looks like a really good plan to me. I think to my mind it does convey this urgency that we need to do something. I wouldn't sell it short on that end. I think the call to action is in the

plan. It hits a lot of different bases in terms of services, basic research, all the different problems, different throughout the age spectrum. I think it's trying to be all-inclusive so I think it doesn't tell you one thing, but I think it's a pretty good plan. I think it's very comprehensive.

Ms. Redwood: I would hope the research community would think everything in there was a priority.

Dr. Insel: But the reality is that given the capacity which we mentioned in Chapter 7 people are going to have to select and the question is whether we've communicated clearly enough about what needs to be done. I guess my sense is there may be two impediments to that. One is I'm not sure we would agree on priorities, but the second is the one that you brought up before, Lyn, that I don't think we know enough about where the gaps are and that's something we can do in this next few months is to take a look at this and map it against what's

currently funded. We've done that already in one iteration, but it wouldn't hurt to go a little deeper into that and actually have a conversation with the committee to actually put it out there so you can see of the seven chapters where is the funding going, what are the things that are likely to get completed, what are the things that really are going to need more of a push. Yvette?

Dr. Janvier: I guess I was just thinking, you know again, thinking about the sense of urgency that - and being on the outside of government that I think more entrepreneurial models like the way the Simons Foundation goes after researchers and then cultivates them to work on projects. And even possibly Autism Speaks with smaller amounts of money targeted could be more effective in actually accomplishing some of these goals. I mean, I think this cumbersome, it takes X amount of months to do this process and R this and R that, different formulas. I think it's very

challenging to move things along quickly with the current government process and I think in the private sector, whether it's a private foundation, small or large, we should maybe think about - look at those models for more effective results let's say.

Dr. Battey: The issue though is this is public money and so we have to have a fair and open competition for the scientists who will get the money to do the research. So we can't operate the same way organizations in the private sector can where they can just go out and find somebody and write them a check. The difference is it's public money and it has to be stewarded in a way that's fair and equitable.

Dr. Insel: But actually, the plan never says who's going to do the work, all it does is it lays out objectives and raises questions and the IACC doesn't have any money so we don't - we're not funding anything here. So if it turns out that more of the work is getting done privately than by CDC or NIH I think that

would be a really important observation and something we should track. I think it was Lyn who brought up earlier that as we look at the major signs of progress when we do these annual updates on progress in the field we should also look at how they were supported to determine how many of them came from public, private or how many of them were done in Singapore or Germany. Alan?

Dr. Guttmacher: Yes, that's a very good. I think if the plan is effective it's the kind of document that all kinds of groups will use to think about, gee, how should they be spending their funds, their efforts, et cetera, including if we do do the assessment, really look at what are the unmet needs at this point. That would particularly I think help guide maybe some more entrepreneurial, faster moving, et cetera, et cetera. There's nothing that could be better than for us to be quote unquote "scooped" in terms of getting some of this done so I think that's what we should be doing is you

know highlighting some areas where maybe there hasn't been enough attention paid, et cetera, et cetera, to encourage whoever to fill those voids.

Dr. Insel: Jim?

Dr. Battey: In fact, if you look at dollars spent per year on biomedical research in the United States there's far more dollars being spent in the private sector than there is coming from NIH. And in particular in the area of clinical research and clinical trials, far, far more private money is out there than there is public money. So I would guess that in this area it will be true that at least half, maybe more than half of the dollars invested in the issues raised by the Strategic Plan will come from organizations other than the federal government.

Dr. Insel: Cathy?

Dr. Rice: And I think that in the last process having the budget breakdown by the public and private was very helpful and you know

very informative to see it was almost 35 percent even at that time was by private organizations. So I think we need to consider that when we're evaluating the plan that we figure out how to include those funders and make sure that they are at the table in terms of the objectives that they've met as well.

Dr. Insel: So it seems to me the next step is for us to charge this - we have the subcommittee that's responsible for doing the annual update. As Henry suggested, it may be time for us to think about whether new - there's new members who could be added to that subcommittee so that we can make sure that we're rotating IACC members through this. But would you be comfortable with the idea of charging them with coming up with a better process, or maybe a different process for this next tweak? Is that what we can call it, Walter, is the next - because we do not want another rewrite of - we don't want to have to go through a full, you know, another complete reformatting of this

thing. But - use your mic.

Dr. Koroshetz: Well, an update of the plan as opposed to a tweak or a rewrite.

Dr. Insel: Well, we called it an update this year so that wasn't - that by itself didn't -

Dr. Koroshetz: We can make it an update.

Dr. Insel: We could really make it an update rather than a rewrite. But we - I'm just trying to fish here for what you want to do for the next step and I think there are a lot of ideas, and I'm hearing a range of concerns. I didn't hear anybody say that we had the perfect process this past year.

Dr. Battey: I think the next step is to evaluate the progress that's been made in the gap areas and the plan that - as it exists today.

Dr. Insel: Would you like this committee, the subcommittee that worked on the update to do that?

Dr. Battey: Absolutely.

Dr. Guttmacher: It seems to me the focus really is not on the plan so much as how is the plan being implemented.

Dr. Janvier: And I think the researchers involved in successful projects, they need to be surveyed or brought together in some format to look at the barriers and maybe then working together with some of the autism advocacy groups we could try to address some of the barriers to completing and implementing the research projects.

Dr. Insel: It's a good point I think that we should be thinking about this broadly. There are two major funders out there besides the federal government. And as you can see from the information that we handed out in the fall they represent about a third in this case of all funding. So we should be making sure that they're part of the conversation about what we're going to do next, and also identifying where the gaps are. Maybe it's a gap for us and

not for them. And that would be good to know. Okay. So if I'm - Lyn.

Ms. Redwood: Tom, just one final comment. It's been frustrating each year that we get to the end and there's always things we want to do and we don't have enough time. It's always rushed. So I'm wondering whether or not at this meeting we could go ahead and ask staff if they could start with some of the process. Last time I think it took awhile for us. We had our first meeting and then we started collecting data, and if we could start that process now which would put us a little bit ahead in the schedule of doing these updates. So if staff could go ahead and send out the same request that we did last year to the private funders to find out what they funded this year. And if we could go ahead and start that assessment of applying those dollars that NIH spent, the different agencies around the table, DoD, to what we have now in our objectives I think we'll be ahead of the game. So can we go ahead and

make that decision today?

Dr. Insel: What is the schedule for getting that information that we got last year? That's an annual process, right?

Dr. Hann: Well, it's becoming an annual process. What's important for NIH, but I think the timing actually will be fine for this year is that the NIH budget figures for 2009 are public. They are not public at this moment in time. They will become public when the President gives his State of the Union address, so that's when the information for 2009 becomes public and that needs to happen in order for NIH to be able to publicly display. It doesn't mean the analysis can't start. That's why I'm saying we can start the analysis pieces of it, but it can't become public until that period of time. I can't speak for the private funders. I don't know what kind of timeline they do there or for other federal agencies like CDC and DoD who cooperated last year as well. So.

Dr. Insel: And State of the Union is

next Wednesday, Tuesday? So it's just next week. So that wouldn't be an impediment. So maybe we could decide to try to get this before there is a subcommittee meeting so that would be something for the subcommittee to chew on. We already have a lot of this from what we've done previously. We actually looked at this map of how the ARRA funding, Recovery Act funding, mapped onto the Strategic Plan. So this would now be enlarging it to get the base grant funding from NIH.

Dr. Hann: So I think - Susan and I were just conversing about this. So it is a tedious process, it takes awhile, it takes awhile for the funders themselves to first of all pull together the information to send it to us, and then it takes us a little while to be able to compile it all and to produce some sort of reasonable, interpretable set of documents that goes along with it. The other thing was we weren't sure if you wanted to augment the request. In the past we've just said the list

of grants and the dollars to go with the grants on a yearly basis. That's all we've ever asked for. If you also then want to have folks indicate prominent publications that have resulted from that work so that they can provide that information to us. Again, it's not so much of an issue for the NIH system because we are able to do that now for our public access policy and so forth, but we can't reach into the private to be able to do that and to know what sources and what documents are emanating from those areas.

Dr. Insel: Alison?

Ms. Singer: Last year we also had the private foundation data sorted according to the objectives in the Strategic Plan. Was that done by OARC or is that done by the - because that was very useful in terms of identifying gaps.

Dr. Hann: We asked them to do that because we did not want to take the prerogative of placing their grants in various places. So

we did ask that of the funders and that therefore this also adds to the time in terms of being able to do that task.

Ms. Singer: So that speaks to getting started sooner rather than later.

Dr. Insel: Right.

Dr. Janvier: And I would say too for the summary of advances that we could start on that early also, since -

Dr. Insel: We're going to talk about that right after we take a break. That's our next topic. Okay. So I think we're getting a pretty good sense of - well, there's really - is there a vote that we need to do here, or is this really just - what's the vote, Della?

Dr. Hann: So the motion - what I'm hearing is that you're requesting for the OARC staff to initiate the portfolio analysis by sending the request to all funders for the work that they supported in 2009 that's relevant to the plan and that they would organize their responses back to us according to the new plan.

Not the old one, but the new plan, and then we can begin that analysis. But what I don't know is if you want us to add the publications.

Ms. Redwood: I wouldn't think they would have publications if it's something they've just funded this year unless it was a really fast -

Dr. Insel: I think we're looking for money and for commitments. So if we do need to vote on that I thought that was a pretty good consensus. Is there anybody opposed to that idea? I think you have a charge. And then once we have that together we can get the Strategic Plan update work group together, subcommittee together, to start to chew over this and to look for gaps. Let's take a 5-minute break and come back and we'll then begin to talk about the summary of research advances and how we want to go forward with that.

(Whereupon, the foregoing matter went off the record at 2:51 p.m. and resumed at 2:57 p.m.)

Dr. Insel: There are really two procedural issues we want your input about. The first is the 2010 Summary of Research Advances. We want to go back to thinking about the best way to do this and we need some input from the committee on that. And then following that there's been some conversation over the last couple of meetings about how we address public comments and we'd like to get your input about the best way to do that as well. So I'm going to ask Della Hann to take us through the issues around the Summary of Research Advances. And after that very quick presentation I think you'll be able to see what the major issues are.

Dr. Hann: Okay. Hopefully this will not - some of this actually is just a review to make sure we're all on the same page. So as we've talked about already today Summary of Advances is required by the Combating Autism Act. And the last - this committee has produced two versions, two editions I should say of the Summary of Advances and last year it was a

process that was fairly intensive, but based on discussions of the committee did not make a result that everybody was happy with and so we'd like to remedy that. One can be intensive, but you would like the product therefore to be something of value. So we've identified several options for you to consider and to think about, and these ideas germinated actually through discussion of the committee during the process last year. So one way to go about doing the Summary of Advances would be for each member of the committee essentially to do self-nominations of research papers that they consider to be of value and want to see become part of the Summary of Advances. That would be then - through the self-nomination process each of you would nominate, say, up to three of those and then the committee could work as a whole in terms of winnowing that down into a number of publications that you wish to have in the summary. Alternatively we could use a process that we sort of started last year where OARC

generated a list of publications based off of NIH grants as well as news publications in terms of what hit the news, I should say - they're still research papers, but it's what became newsworthy - and categorize them according to the strategic chapters of the plan. We've already done an initial sort of overview of that and we're talking about roughly three hundred publications that would be pulled up through such a search process. Last year we had done something similar to that and it was a rather daunting task to look at all of those publications, and so one way that that could be augmented this year would be for members to self-select in terms of areas of the Strategic Plan they wanted to concentrate on. Therefore, they would just look at that listing. So that could be like 60 to 70 papers.

The other thing that you all discussed last year too was to think about the number of final publications to be included in the list. There was some discussion as to

whether the Summary of Advances really needed to be something similar to a top 10 or top 20 that may or may not be evenly distributed across the chapters of the plan. Alternatively, one could be more democratic essentially and have three to four, say, for each chapter which would be 18 to 24 publications in total.

The other part of this that folks discussed last year was the final product. In both the 2009 and 2008 versions we - OARC worked to take the listing of publications and integrate them into a narrative that roughly followed the themes, the six themes of the original plan. That was sometimes a difficult task that - it wasn't so difficult to say which theme the paper went to, but in terms of then the multiple papers didn't necessarily flow in a coherent manner. Another way to do this is to do just a collection of independent short summaries and say this is the collection that the committee considers to be part of the Summary of Advances. Again, much more like what

other organizations do when they do a top 10 or top 20 type of listing.

So today what ideally I think as we stated in the last conversation, it's important to begin to really formulate a plan here at this meeting today so that it can be initiated. That way we can be working with the committee potentially by email and that by the time of the April meeting which is April 30 that there is a final listing of publications that you all get to see and vote on and say yes, this is the list, however big or long you wish it to be, to be included as well as the format and then we can take that listing and prepare it according to the format that the committee wants to have and have therefore the final draft available in July, at the July meeting. And I believe that's it.

Ms. Redwood: Della, I have a question and I tried to get to this a minute ago. Does a Summary of Advances have to be only published research? Because I'm reading this in

the law completely different, that the Summary of Advances and the things they're specifically saying we need to address are things such as - related to cost, prevention, treatment, early screening, diagnosis and I'm wondering by just selecting 20 or 30 articles and writing about each one that doesn't really feed into the development of our Strategic Plan the way it would if we were looking at these and making it more broad than just research. Like, one of the things we've found Cathy pointed out is that the age of diagnosis really isn't getting younger. We're not making progress there and I think we need to acknowledge that and say, you know, this study came out and we found this and really critique everything that's happened the entire year and not just limit it to publications in a way. I don't know that I'm saying that very clear. Where it would be more helpful to us than doing the plan because otherwise we just have a list of articles and we write a little bit about it, we turn it in and I just don't

know that it really is that beneficial to us as a committee, to the public, or to our planning process. I'm just throwing that out there.

Dr. Insel: I'm not sure I follow you. So what would be research advances that wouldn't be published? What were you thinking?

Dr. Koroshetz: I'll give an example. So the issue came up of educational resources being available - educational records being available to do surveillance and that you can almost - if there was a program, of course government people can't do this, to make that more widely available throughout the country. That could potentially be an advance if it was pushed and it was working that had nothing to do with publications. It would be a resource that then becomes available for autism research that's not in a publication.

Dr. Insel: Or a repository I suppose. You know, if you established a repository is that kind of the - a research advance of sort. But I thought that, again, the

gist of this would be to get a sense of how we were delivering on the plan. How is it being implemented and what's coming out of it. But that may be -

Dr. Koroshetz: - have to do with what the stumbling blocks are to getting the plan implemented and some of those you may see in the paper, but probably - the paper is actually predisposing you to see the things that work and not where you're stumbling blocks are. I guess the question I think that you're getting at is how well do you want - Summary of Advances and progress on the plan, how well do you want to - is that really one effort or not. It almost sounded like maybe there's two components, which is fine too where you have a draft of, you know, scientific advances that you can put forth and those are probably mostly publications, but the real work is how - what stood in the way of the implementation of the plan. That may or may not be available in published literature. Does that make sense to

you, Lyn? Ms. Redwood: Yes.

Dr. Koroshetz: Maybe there's two things going on here as opposed to one?

Ms. Redwood: I'm just trying to think of a way that we can evaluate the plan and at the same time have that serve as our Summary of Advances, and then we've identified gaps and then it helps us to do our update. I'm just trying to figure out a way we can do that where these two processes can be blended together.

Dr. Insel: Exactly. That makes a lot of sense.

Dr. Houle: I think that there is benefit in identifying gaps, but we also need to look at who or what is able to intervene to address those gaps or barriers. For example, the one that's given about the education, there's FERPA, Federal Education Records Privacy Act, which is a congressional act and so Department attorneys have been working with the Administration on that for a long time to interpret that. It's good to identify it. I'm

not sure what - well certainly government representatives could not do anything in terms of advocating to Congress. You look totally confused, Lyn.

Ms. Redwood: Yes, I'm just trying to think of a way we can do this process, meet the requirements of the law and use it to do our update to the plan at the same time.

Dr. Houle: Right and I think gaps and barriers, but to go a step beyond and look deeper as to what would it take to address those barriers is something worthwhile instead of just listing these are barriers and not digging beyond the surface as to how would we go about addressing that. Because I mean this identification has been discussed a few times today, but not really looking deeper at the reason for this barrier.

Dr. Insel: But is that really what is - it's up here on the screen. Is that what the law is asking for? It's not really looking at a list of impediments or barriers. They're

asking for an update of Summary of Advances in research, right? Peter, you had a comment.

Dr. van Dyck: Well, to me it kind of makes a difference what's primary. If we're evaluating or updating the plan then research articles are chosen related to the objectives or the - what you said you were going to do in the plan rather than a list of just what might be the best research, articles in general selected at random separate from the plan. Most of those may end up there, but they may not all and rather than doing the list of research articles and then making them fit the plan it seems to me if you start with the plan, update the plan then it falls into place a little better.

Dr. Insel: Alison?

Ms. Singer: I think though that there's also some value in just choosing the best published research without looking at the chapters of the plan, because that itself would provide information on where there are gaps with regard to implementation of the plan. So I

think if we discover that there is no - there were no major advances in Section 6 then that really speaks to our need to focus in on ensuring that more funding is going to the objectives in Section 6.

The other point that I wanted to raise is I felt this last year and I feel it again. Putting out a Summary of Advances for 2009 beyond the - in the second half of 2010 to me does not really speak to the sense of urgency. So I think if we went with the summary version rather than the narrative version it eliminates this whole need for the step of preparing the final document and we would be able to get the document out in April rather than in August. I think by August we're thinking about 2011.

Dr. Insel: I think you lost us. Can you go forward a couple of slides? So when you say the summary versus the narrative, which one is that?

Ms. Singer: These were the two

options. One was the narrative and one was to do the short summaries. The summaries I think we would be able to review, narrow down and vote on them at the April meeting. It wouldn't require the additional step of drafting a narrative and coming up with a way to tell the story of all of the research that was selected. So it would reduce the amount of time it would take to complete the project by two and a half months. We'd be able to get it out in the beginning of May rather than in August. Am I - you're shaking your head.

Dr. Hann: Obtaining the list from the committee of what it is that you all want to have summarized will take time, and I don't think that'll happen today at this meeting. So I think that will take at least a month to acquire that. So that moves us towards the end of February, the beginning of March. I don't know if we can actually have then a document drafted and prepared based off of, depending on however many we do, by the end of April.

Dr. Insel: Let me ask you as a committee, how helpful were the Summary of Advances that we did last year? How did you use that? Did anybody find that useful, useless? Was it - does anybody know about it?

Dr. Janvier: I actually used it.

Dr. Insel: Yvette?

Dr. Janvier: When I did presentations to my clinical staff, I actually went through many of the - read, you know, many of the summaries that were relevant to the clinical work that we do so I found it very helpful. But you know what I was going to say is I think just what we started out with this morning as an example, that I think we have a good idea of the top 10 or the top 20 articles over the past year. They've already been in the news. This is not going to be a shock to most people and each of these articles has an abstract so to translate that into more readable narrative wouldn't be that challenging. I'd rather go for a focused approach, things that

have significance, but I think Dr. Insel you've been bringing those up at almost every meeting so we have a good place to start. And if somebody - people have articles that they find important they should be able to get that to you very soon and I agree, we should get this out quickly.

Dr. Insel: Chris?

Ms. McKee: I use the Summary of Advances too and I - not everything that I really, really liked made it into the summary and - but we passed them out to parents in the community and we were able to advocate for some changes in programming for our children. So I kind of like the idea of having a broader list rather than everybody coming up with three. Well, let's really look at what's out there and then disseminate as widely as we can to help the community.

Dr. Insel: Cathy?

Dr. Rice: But I do like tying them to the Strategic Plan chapters. You know,

sometimes that is tricky because they overlap, but at least coming to agreement of having several per chapter. But there may be some that - something Alison said reminded me of this - that might not fit in one of the chapters and that's what - this is an important finding that we didn't really account for. And so in some way that could help us identify a gap. So maybe having an "other" box for other key findings. And then something we were talking about before, it sounded like that Walter, your example maybe goes more in the infrastructure chapter, that there may be some components of infrastructure that really aren't published studies. That's where we're looking for what kind of advances have helped push forward the research. Are there more traineeships, are there more things that could be an advance but not necessarily published. So that would be the place I think we'd put those unaccounted for things.

Dr. Insel: So if I'm hearing this right it sounds like the gist of the discussion

is to go with these focused short summaries, not with this integrated narrative of 20 pages or whatever. Is that what most people feel would be most useful? And then - everybody's head is shaking, or going up and down, not shaking side to side, so that's a good thing. And then the question would be - if we go back one slide, Della - how much - I'm hearing a couple of things. You want to have it somehow tied to the Strategic Plan but you don't want to have it dictated by the chapters of the Strategic Plan, is that correct? You don't want us to say there has to be three to four per chapter, but let's look at the best stuff out there and then we can link it to the plan and then be able to show where the gaps are if something - if there's a chapter that never has an advance. Am I hearing that correctly? Yes. Lyn?

Ms. Redwood: I think it's important to identify the research even though it might not have been the best thing out there or made the top 10 list, but it was something on either

services that would fit into our plan. We need to make sure we know that too, so even if it wasn't the top 10 but it meets an objective I think we should acknowledge it and use that for informing our plan as we move forward with our next update.

Dr. Insel: So yes, I think I'm stuck on the same issue that you keep coming back to, that we want this to somehow be useful for the update, right? And so I'm not clear on how you separate that out. I agree, you know, you want to know if there's something that really does allow you to now take something off the list of what's in the plan, you want to know that before you do the update, and I don't know whether the first bullet will do that, but maybe it would, or maybe it could.

How will we get to the top 10 or 20 publications? How do you want to get those? Do you want to generate them, do you want OARC to generate them, do you want - is there an approach that - what we did last time was

painful, yes, was a huge amount of labor for everybody. Remember we sent out those long lists and then we had a difficult conversation because not everybody actually went through the lists and not everybody read all the abstracts, so there was a lot of - but it was a considerable burden for everybody to go through this. We could do that again. We could change that. How do you want to go forward with that? Lee?

Mr. Grossman: I have a point of clarification here, because we were discussing that at this end. Sorry. If you go back to the summary a couple of slides back where it talks about what's required by the Combating Autism Act. We were somewhat confused because at the first part it talks about research and then there's this "and" part, "and access to services and supports." So that we understand, are we still looking at research under access to services and supports, or is the "and" a standalone where some of the summaries can be

strictly on access to services and supports?

Dr. Insel: What you see there is what we've got to work with.

Mr. Grossman: Well, so what I will assume is that it's a standalone, that part of the Summary of Advances is access to services.

Dr. Insel: That would be a very different kind of process because it wouldn't be restricted to *Nature*, *Science* and *Cell*. I mean, we'd be looking at a different sort of input.

Ms. Blackwell: It's always difficult to try to determine exactly what the Congress means when it writes language. I mean, I think we might have - I mean, obviously we interpreted "previously" to mean we could take it chapter by chapter. I mean, "access" is a completely, as you pointed out, different exercise and access looks like the state of the states, you know, what is access to services? That's a whole different activity.

Dr. Insel: So as Lyn was just asking, is this something that the services

subcommittee would take on and provide let's say three or four bullets that would be relevant to access or supports? If you felt that there - maybe there aren't significant advances that you would cite, but if there were some. Frankly, I don't know how to get them from the research literature because they're not going to be there. So what would be the best way to identify the breakthroughs in access or supports? Or maybe there's nothing that comes to mind.

Mr. Grossman: Bad time for Henry to be out of the room. Well, again, if it's related to research then that's something that we'll have to dig deeper. There's certainly plentiful documentation about access to services that are out there.

Dr. Insel: And I might add that probably one of the top 20 from this past year is the Mandell paper which goes through the health disparities issues that came out in November or October. So that's likely to be on

the list anyway. So I still need some help from the committee about how you want to do this. I think we made a little bit of progress. It sounds like you don't want the narrative, you want to have the 10 or maybe 20 items that will be in lay language and explain clearly. You want to have this more rapid turnaround so it doesn't happen at the end of 2010 when it's for 2009. How do you want to come up with that list of most exciting breakthroughs for 2009? Alison?

Ms. Singer: I would say that based on the experience of last year where I think there were maybe only four or five of us who went through the whole long list of 300 papers that had been published and it almost really turned into Summary of Advances by four people on the committee, that it might be a broader representation and more people might have input if we went with the other suggestion of having each person suggest three or four and then narrow it down from there. I think if we all

suggest three or four it's likely there would be a lot of duplication anyway, although three or four may be small. I mean, considering that there's going to be duplication we might want to say each person can recommend five to ten and then see where we go from there. I don't think that's going to result in a list of 300 because I think a lot of people are going to overlap like Mandell.

Dr. Insel: That's a proposal. Okay.

Ms. Redwood: But does that get us to using that information to update the plan. If there were 300 articles out there published I'm wondering if we shouldn't still look at all of those, and I think what we did last year was we put all of them on the website or something but then we had certain ones that we highlighted as being in the top. And I know since we did this last year I created a folder where every new research article that I thought was good I drug over and put in that folder so I could just dump that when this issue came up this year. I don't

know.

Dr. Insel: Chris?

Ms. McKee: Was the large list ever made available to the public? So it became something that parents could then go to and read and utilize, parents, people in the community. Rather than self-selection, I would really opt to make that very broad because each one of us brings to the table a unique expertise, whereas if you pull - have OARC do it from the general publications you get a much broader range of publications that people can use. I think it's also beneficial, I liked it, the fact that we were able to then suggest additions to the list. It was painful to read all of that, but you do it because you're sitting on this committee and so I liked the process and I think that we need to provide the community with as much information as we can to help parents out there.

Dr. Hann: Let me propose a hybrid, listening to various opinions here today - you don't have to accept it - that we could do the

300-some odd listing but it would simply be a listing. There would not be any summaries from that, and then you all would self-select either from that list or from whatever list that you find is valuable to you and those would become summarized, but that the full listing would become available as a resource. So that sounds like it meets your needs.

Dr. Insel: Where does the 300 come from? Where does that list come from?

Dr. Hann: So because of the tools now that NIH has we can, for all of the grants that NIH lists as autism-related grants we can do a search on what those grants produced in 2009. So that's a huge part of that 300, in addition to which, because of the other services that we do within the NIH we have a clip service for all of science, it's not just unique to autism, but we have a clip service on a daily basis of what's in the news, what are the topics, so that we can go into and go through that listing too for things that weren't done by

NIH. We're not the only ones in town that do things. So for example, the recent CDC and HRSA things earlier in the year and so forth, they were in the news. And so we would be gathering that type of information, or if there was an important other kind of breakthrough that came through but wasn't affiliated with an NIH grant we would be pulling it from the news service essentially. So that's where that list of over 300 would be coming from.

Ms. Redwood: Would it be too labor-intensive to take that 300 and just identify which question of the plan, like this one is two, this is four. Not detailed down to which objective, but just which question?

Dr. Hann: Yes, that's what we did last year. So the list that's currently on the web of the full however many it was, I'll say 200 right now, is broken down by the various areas of the plan.

Dr. Insel: So let me see if I understand the proposal. So OARC would get the

broad list of publications that seem most relevant, organize them by the seven chapters of the plan, the group would have access to all of those, and then each of us would send forward our next favorite, whether it's three, five, ten. Is that the proposal? And then there would be a final list which would be a set of 10 to 20 brief summaries that would go forward as the Summary of Advances.

Dr. Hann: So, speaking to the self-nomination process now, I think if we had - if we allowed up to 10 papers per person that you're going to be generating a list of potentially 180 papers that would then - the committee is going to need to vote on to determine which of those are going to make it to the top 20. So I think - because now we have a 2-step process. We have a process where we go through and we churn up everything essentially that just becomes a listing of available literature, but that doesn't supplant or replace this committee selecting the top ones somehow

through a self-nomination process of those that they wish to have summaries written for.

Dr. Insel: So Della, I want to make sure I understand what you're suggesting. So let's say we each send our five favorite papers together. I would assume that there's going to be enough overlap in there that you're not going to end up with 90 papers. It's going to be something probably on the order of 30 to 40. Is that fair?

Dr. Hann: Is that the size of the summary then, that you want each of these 30 to 40 to be written up? I guess I'm trying to understand the magnitude and the scope of the summary piece. I get it in terms of the lit review, I understand that part of it, but I'm lost now in terms of how many you want summaries for and the process by which you wish to identify those that there are summaries written for.

Dr. Insel: Well, I thought what we did last year, because we had this same

conversation a year ago, right? And remember we were trying to decide whether it was 220 or 20 and I think we ended up with 34. Susan, what was the final number? Thirty-seven, which might have been too many. I mean, if the committee - and it may be to say that we're going to identify the top 10 as too few because that was such a broad plan and such a broad scope. Ten is not going to be covering all the bases. If we were to decide on something like 20 advances, would that be in the comfort zone for the committee? What I'm trying to get to here is a consistent approach to this so that we don't have this conversation a year from now about how we want to do this again. I think we felt last year didn't really work and everybody agreed that we needed to do something that was a little more efficient, but I mean presumably we could all send in our favorite, our top five, and then you would write advances - or write summaries of the 20 that got the most support, that had the most votes. Cathy?

Dr. Rice: I'm just concerned that we make it tied to the Strategic Plan and so I guess I worry that if we each send in five in no category that we'll end up with lots of repetition and none in a particular question. And so what if each member of the committee submitted two to four for each question? So that's more of a burden on the committee members so people might not like that suggestion, but making sure that we target across each one and then also have a placeholder for advances that are not accounted for in one of those questions as well.

Dr. Insel: The issue with that is that there are some areas that are not really moving that much, and so one could argue that to have two or three for Chapter 2 or Chapter 3 and then to have two or three for Chapter 6 or 7 is not really parity, that you may want to really, in line with the law, lay out those places where you've got - you can point to the most significant discoveries in the previous year. I

don't think it does spread across the plan which is a problem, but that's the reality.

Dr. Rice: Yes, I meant in terms of the initial nomination and putting papers forth, but in the end - so if we're each putting forth, so it may be more likely some questions everyone is submitting four and there's not as much overlap. And so you end up with more papers in certain topics, but at least there's an effort for each person to think through the different questions and say, well, let me go out and search and see if there's anything in this topic. Again, it's another cumbersome way of looking at it, but it's another option.

Dr. Insel: So I guess my sense is that you know part of being on this committee is that you do know what's happening because people are looking to us as the leaders and experts in this field and if we don't know what's significant from 2009 we've got a real problem. It shouldn't be that difficult for us to decide where the real advances are, especially if we're

supposed to be responsible for directing the field towards where they need to be going. One would expect that each of us follows this literature and knows enough to be able to identify where the opportunities are and where the advances have been. I guess I don't see the problem with our being able to each come up with five - maybe that's not the right number - but some small number that we would put forward and you would - OARC would look at that list from 18 people and from that cull down to something like 20 important discoveries, or 20 really significant findings that could be easily summarized. Walter?

Dr. Koroshetz: If you want to do it actually quickly, and you may not want to do it this fast, you basically could have people submit their top X but actually give a number. You know, this is my number 1, 2, 3, 4, 5 so then each article is actually going to get a score and you'll have an objective measure at the end whereby the top ones will rise to the

top. So it's that kind of a voting process.

Dr. Insel: And that would be based on the 200 or so that would be -

Dr. Koroshetz: I don't think I have any problem with somebody generating something that's not on Della's initial list and adding that in.

Dr. Hann: I was seeing them as two separate processes, to be honest with you.

Dr. Koroshetz: So you merge what people want, what Della comes up with, merge that into one big list, send it out, people have to pick their top 10 and give a number. Dr. Hann: Or - I guess I was thinking a little bit differently. I was thinking that we would generate the list of 300 let's just say for purposes of argument, and that would just be the literature review. It's just the review of the literature. So it would be a citation index. And then you all independently would identify papers that you thought were relevant and that you wanted summaries for. Some of them may be

on that list, some of them may not because you may be tapping into sources that we didn't reach in our methods. There doesn't need to be - it doesn't need to happen at the same time. They can be two separate activities.

Ms. Blackwell: I was kind of liking Tom's suggestion that we go with our top five and then as far as letting them fall into the chapters let the chips fall where they may, you know, instead of as you said assigning them to chapters. I mean, if there's nothing in a chapter there's nothing in a chapter, but 10 is going to generate a lot to sort through and may even cause some confusion. I think 18 people, our top five each, that should take us where we need to go.

Dr. Insel: Any further thoughts about this?

Dr. Hann: So what I hear - so if we could just sort of bifurcate this a bit just so we're absolutely 100 percent clear. So first of all, if we could take a vote on the idea of

simply doing a citation listing of articles that were produced in 2009 that are relevant to the Strategic Plan and autism. Right, and OARC will divide it up and that'll just be a listing. All right good. Sounds like everybody is on board with that. Now, for those that will have a prepared summary for the articles, what I heard was that each member wishes to nominate up to five. You don't have to. If there's only one or two, there's only one or two that you think are relevant, that you will then do that self-nomination process, send that to OARC, we will compile that listing. That could be up to 40-some odd articles assuming everybody's was distinct and different, or it could be very short. Do you all want to see that compiled listing and particularly if it's very long? Winnow it back to like 20?

Ms. Singer: But I think at that point we're only looking at the list, not the summaries. I don't think you do the summaries until we vote and decide on around 20.

Dr. Hann: That's what I was asking about, about doing the decision for the 20.

Ms. Singer: Okay, but I would also like there to be an option of more than five if we're going to put a vote, because I think five is, I mean, given how long the plan is and how many objectives there are in the plan and how much happened this year I think five is too few. I also think that there's going to be a lot of overlap. I mean, I think we could probably as a group agree on five right now and then work on the next five. So I mean, there are five in here that you presented and I think at each meeting we've talked about a few, so to say five I don't think is going to get the diversity and the breadth that we want.

Dr. Insel: I think we're hearing that already, Della, that there's going to be enough overlap that even if you did 10 per person I don't think you're going to end up with 90. I think you're going to end up with about 60 and we can then winnow that down to a smaller

list. In terms of what the final list looks like last year we ended up with 37, whatever that was, and some people felt that was still too long, that probably again, if you want really to provide real rigor here you want to be talking about the top 20 or something like that. Is 20 a number that, given - plus or minus 5 depending on what comes in. Does that sound reasonable to the committee? Okay. So Della, let's just put this together as a proposal and see where we're at.

Dr. Hann: Okay. I'm not going to do the big lit review because I think we have concurrence on that. So the process then for nomination, that each member will nominate up to 10 articles and send that listing to OARC. We will then compile that list and send it back to you to do electronic voting of those that you consider to be the top 20. We will compile the vote and bring that, the results essentially of that vote, to you - well no, that doesn't meet your timing issue. We'll bring the results of

the vote to you in April. We won't have the summaries then in April. That's assuming that you all agree and it's clear what the top 20 are. That's the risk that we take.

Ms. Singer: But we'll agree on some and for the ones on which we agree we can get started on the summaries. I mean, I don't think we have to wait. I think we should look for opportunities to speed the process, not -

Dr. Hann: I'm fine with that, but I'm just saying that that - I think given in the past when we've done electronic voting things have not always been very clear. So you're right, there will be a pool that is, and then there's going to be a pool that will probably be more nebulous.

Ms. Redwood: In terms of speeding it up, would it be possible for the committee members when they submit an article of their top five or ten to put a little summary and then we've got the summary there already?

Dr. Insel: I think OARC really likes

that idea.

(Laughter)

Ms. Redwood: That might cut down the number of articles that we submit too.

Dr. Insel: That's a great idea. Okay. Have we got a plan? I think we're ready to move on. Della, are you comfortable with this?

Dr. Hann: Okay. So what I hear then is that I will send out a memo probably in the next day or two asking you to send in your top up to 10 research articles that you feel were noteworthy in 2009. We will compile that list, send it back with instructions for voting on your top 20. We will then take that and if you have a summary that you'd like to offer that would be lovely of those. And we will use your votes to determine what the top 20 are for the preparation of the summaries.

Dr. Insel: And just to clarify because this came up last year, what 2009 means is that the publication date, not the - this

includes e-pub, is that right?

Dr. Hann: There was confusion - in the last two years there have been confusion with e-pubs because usually e-pubs come out prior to the actual, quote, "publication date." It's you all's decision. Last year we decided it had to be the actual publication date, not an e-pub.

Dr. Insel: Right. So that means there were some papers that came out in January of 2009 that we didn't use, even though we all knew about them. So it will be actual publication, paper publication, from January 1, 2009, to December 31.

Okay. We have one last item here that we want to talk about with you which is a little bit about where we started today and that has to do with procedures for addressing public comments to the IACC. And I believe that Susan and Della have prepared some slides for this as well.

Dr. Hann: At the very end of the

December meeting there was discussion - that was what I remember most clearly - I think there were other times that the committee has talked about this as well - in terms of the committee's response to public comment, be they either public comment that is done orally to the committee or provided in writing. So we thought it would be useful first of all to describe what we currently do and then for you all to determine if there's any changes that you would like to that process. So just as background, we received about 132 written comments in 2009. That's separate from the RFIs and the town halls, so this is just over the transom, people writing in or in response to the Federal Register notice when we announce meetings. So it's about an average of 11 per month, or 18 for each of the IACC full meetings. We also receive a great number of requests for materials and factual information such as transcripts and things such as that. So the numbers that we gave you, the 132, does not include those kinds

of requests. Currently, we do send a response to requests for materials and factual information and then we'll provide them the factual information if we have it available. We also send thank-you notes in response and indicate that their comments will be forwarded to the full committee which we do do. We also then provide you the written comments to each of the - for each of the meetings. So essentially what it is that we are not doing, just to make it clear, while we do respond and say thank you and that your comments will be forwarded, we do not prepare responses on substantive issues. They are writing to this committee so therefore we have not provided any kind of response in terms of that. They come to you for you to consider in your deliberations and your conversations.

So we can continue the process that we have started. We can also continue the process that we have started and also potentially do an augmentation to provide time

at each full committee meeting for you all to discuss any of the comments that you have received and to have a way of acknowledging those comments. That's basically all I have.

Dr. Insel: So as a way to introduce this even further, if you - in your package there are written comments that are really very extensive, including one person who sent a full book for this particular meeting. And what Della is saying is that up until this point - because we haven't discussed these openly at this meeting we haven't responded, other than to say that your comments are appreciated and will be distributed. But often the comments have very specific questions built into them, or specific concerns about the IACC which we do not or have not responded to. So the question for you is how you would like to handle this going forward.

Mr. Grossman: I'm just curious to find out how do other FACA committees handle this? Is there any policies?

Dr. Hann: No.

Mr. Grossman: That makes it harder.

Dr. Hann: No, the important part for FACA which I believe we are doing is that the information is provided to the committee members, and it is.

Dr. Insel: Well, and I would add that because it's a FACA committee it's not like I can write a response back on behalf of the committee without having some discussion here. Everything has to be transparent. So that's another reason for our not responding previously because we haven't discussed most of these things. Alan?

Dr. Guttmacher: There is no official you must do this, you're a FACA committee. My experience on other FACA committees has been that they're handled the same way they have been thus far at this committee. That is, they're received, looked at by the members and then you know, brought in to the deliberations as the members see fit or do not see fit.

Dr. Insel: The same could be said for the oral comments that are made at the meetings. We have generally listened politely but not responded even when there are questions asked or suggestions made. I mean, today was a very good example. We had two people who brought very specific requests to us about changes to the Strategic Plan but we this afternoon did not return to those requests and discuss them. So there is no policy other than everything happens in the open and everything's transparent, but there's no requirement for a response. It's really up to the committee how you want to handle this.

Ms. Redwood: You know Tom, personally it just seems like we're not being responsive when somebody gets up and asks a direct question or makes a suggestion and I think we all sort of have opinions or could respond to it. And I think in some way we should try to, even if it's just some acknowledgment after they present or after they

send something. It just doesn't seem like we're being very responsive when we don't say anything back and just say thank you and next speaker. I don't know how the other committee members feel about it, but I'm always finding myself wanting to somehow comment or respond.

Dr. Insel: That's where B comes from up here.

Ms. Blackwell: Maybe a way to approach this is, I know we've talked before about having a town hall meeting which is a different - a different activity, but we did have a town hall meeting last June and we did respond. So maybe the public comments is a different procedure from having a town hall meeting. I don't know. But we have talked about having an IACC town hall meeting, it just hasn't gone anywhere.

Dr. Insel: So that could be in addition to, but we still would be left with the question of what to do at this meeting when people make public comments either in writing or

with oral comments and how we handle those. Yvette?

Dr. Janvier: I just felt today that with the comments which were going to be affecting what we did today, I mean, I did hear and listen and it affected my thought process in how I personally was approaching some of the issues. So I felt that was better than tagged on at the end of the day. The comments at least today were very relevant to the issues we were working on and I did hear those myself.

Dr. Insel: Would it make sense to do what we did today which is to open the meeting with public comment, or maybe after the minutes or sometime early in the meeting and then to save time at the end of the day. So rather than getting into an immediate response, save time at the end of the day like we're doing now to have some discussion of the public comments and to be able to weigh in on some of the things that we've heard, and then decide on what kind of a response might be most appropriate. Would that

be helpful? Would that feel more responsive? I don't think you're the only one who feels that this is - the committee has been non-responsive. I think there's a sense around the table that people are uncomfortable with the way this is handled now which is to politely nod and then go on to the next speaker.

Dr. van Dyck: Another way to handle it might be to have the discussion as you suggest at the end of the day, but related to the next meeting's agenda to decide if any issues heard in public context rise to the level of informing the agenda in a more detailed way.

Dr. Insel: Great idea, yes.

Dr. van Dyck: So that would be responding, but not responding to every individual comment.

Dr. Insel: Okay. Other thoughts about this.

Ms. Redwood: Tom, there's also problems I think with - I've heard from the community with the public comment having to sign

up in advance, and sometimes I think actually for this meeting the agenda wasn't posted yet, but the deadline had already passed for submitting your public comments. If you didn't know what was going to be discussed, you're at a loss for knowing what type of comments you would want to make during the meeting, so maybe if there was more consistency with that and then having an opportunity like Paula suggested today to actually comment at the end of the day on things that were discussed during the meeting. Because when you do it in the morning then you've lost that opportunity.

Dr. Insel: That's complicated though because I'm not sure how to do both. Because if you want to make sure that there's time in the beginning of the day to hear what people bring to the meeting. And then if we decided to have another public comment period at the end of the day in response to what people have heard, and then we're going to have a discussion around those public comments it pretty soon becomes all

public comment. And you can tell today it's taking - we're not particularly quick at getting through some of the business issues and policy issues that we have to do. And I feel strongly that we need to use a good chunk of the meetings for educating both ourselves and the public about what's hot in science so that people are up to speed on that.

Ms. Redwood: Could we also develop maybe a 1-page narrative of the IACC and what we're working on so when people do submit comments versus just a thank you. I know my mother recently wrote a letter to the President about something and she got this form letter back and it explained, you know, what they were doing and what they were working on and so I'm thinking maybe we could even come up with something like that that would be more responsive.

Dr. Insel: Cathy?

Dr. Rice: Just to follow up. I definitely like having the comments in the

morning because as Yvette said it informs my thinking and ideas on what we discuss for the day, but also having the written comments earlier, ahead of time so I have more time to process if that's ever possible is very helpful, and that hopefully every committee member is reading those and taking that, you know, into account. But I also like Peter's idea of being very focused of what has come up that can inform our next agenda because I do worry that if we open it up for a long period of response to every single comment, then people are going to feel like well, they didn't get to my comment, they did get to my comment, and that if we have a very focused objective of how we're talking about them and we all make the commitment to read and process and incorporate the comments that we hear and get ahead of time and incorporate that into a response to people, all of those things may address the issues a little bit more.

Dr. Insel: A point of information.

This 7-day advance notice, is that a FACA requirement? Where does the seven days come from?

Dr. Hann: We have an obligation to find ways to be able to manage the meeting, and so we - and particularly now and hearing too that the committee wants to receive the comments as early as possible so they can take it into consideration, that was why that was placed there, in order to have time to be able to get the comments, to make the copies, get them out to you all, have them in the books, et cetera.

Dr. Insel: Other thoughts about this? So what I'm hearing you say is that you want to have the written comments well ahead of time so that they can inform what we talk about, the public comments can be done at the early part of the meeting, and then we circle back at the end of the day, reflect on what it is we've heard and use that either as the basis for the next agenda or at the very least as the basis for a response, both for the oral comments as

well as the written comments that we would have received. And I would assume that this would be at least a 30-minute conversation that the committee could have. Does that sound like the way forward and a way to be more responsive? It's not ideal, but within the constraints of the time we have. Della, is this something that you want votes on? Okay. So that's a proposal. In favor?

(Show of hands)

Dr. Insel: Opposed?

(Show of hands)

Dr. Insel: I think the motion passes. So we have a process that will change a little bit how we set up the next meeting. Okay. Other issues or items for your colleagues? Anything that you want to make sure we all know about, upcoming meetings, new things that are important or items related to the IACC? Ellen?

Ms. Blackwell: I think Henry should talk a little bit about the community living

initiative.

Mr. Claypool: Sure. I can provide a little bit of information about - where to begin. The President on the anniversary of the Olmstead decision which some of you may be familiar with the Medicaid program and issues of institutionalization versus serving individuals in the community. The Supreme Court had a landmark decision in 1999 about the rights of individuals with disabilities to live in the most integrated setting appropriate to their need. So the tenth anniversary the President announced the Year of Community Living. Secretary Sebelius then formed a coordinating council within HHS that consists of agencies that - CMS, AOA, SAMHSA, HRSA, ACF, the Office on Disability is kind of the lead coordinator of this effort and we also have the research shop, ASPE, at the present. And we've formed five working groups, one on services, another on housing, another on workforce. We have a data and quality group and we also have a kind of a

communications group to help us inform stakeholders of our progress and facilitate our communication within the working groups and within the Department. So we are really beginning our heavy work in earnest in this new year since we now have a full complement of political appointees to fill out the Secretary's coordinating council. Our most recent and final appointment was Pam Hyde who is now the SAMHSA administrator. So our work goes forward now.

We are having a town hall meeting in San Diego later in February and there will be a more formal public announcement later this week of that, what we're calling a stakeholder dialogue coupled with a listening session. And again, we're interested in learning more about how we can advance the issues around community living for people with disabilities and seniors. We're not limiting them to the issues associated with just those folks that would be, say, at risk of institutionalization or that might have significant disabilities or

functional impairments that require, again, a significant amount of support. We're looking for opportunities to attach issues that are disability- and aging-related that do have a strong connection to community living, but again they don't have to rise to this level of unjustified institutionalization which was what the Court found. So this work, I think you'll find it has some real connection to autism. I think the challenge will be looking at the Strategic Plan and trying to find those areas where we can advance the work of the committee through the unique opportunity we have at the coordinating council which is really to try and bring greater alignment to the programs that are offered at CMS, AOA, SAMHSA and HRSA around these community living efforts. So that might be a little bit of information and at the next meeting I guess we'll have more information about people that would like to provide some input into how this coordinating council and the working groups go about carrying out their

charge that the Secretary has given us.

Dr. Insel: Great, thanks for that update. Anything else that we should hear about? I should let you know that the Office of the Secretary is interested in expanding the IACC so I think perhaps by our next meeting we may have some additional colleagues around the table. We'll need a slightly larger table in that case. But I know that that process is underway and it's just a question of jumping through all of the various hurdles that come with joining a FACA committee. So we'll let you know more as that evolves. Okay. If there's no other business I want to thank all of you for your engagement here and we got a lot done today with the update of the plan and some new processes for strategic advances and for public comment, and we'll look forward to seeing you at the next meeting which is in April. April 30, probably in the same place. Thanks everybody.

(The meeting adjourned at 4:00 p.m.)