2010
Summary
of Advances

in Autism Spectrum Disorder Research

IACC

INTERAGENCY AUTISM
COORDINATING COMMITTEE

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) was established by Congress under the Combating Autism Act of 2006 (CAA) to provide advice to the Secretary of Health and Human Services (HHS) and coordinate all efforts within HHS concerning autism spectrum disorders (ASD).

As mandated by law, the IACC has a membership composed of Federal officials from agencies involved in autism research and services and public members, including people with ASD, parents of children and adults with ASD, and members of the autism advocacy and research community. The diversity of the Committee ensures that a broad range of views and opinions is reflected and discussed in a public forum.

Under the CAA, the IACC is required to (1) develop and annually update a Strategic Plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor federal activities related to ASD.

In developing and updating the *IACC Strategic Plan for Autism Spectrum Disorder Research*, first released in 2009 and subsequently updated in 2010 and 2011, the IACC has laid out a framework for the pursuit of critical biomedical and services research. Through activities such as public meetings and workshops, publication of an annual *Summary of Advances in ASD Research*, dissemination of information regarding ASD research and IACC activities, gathering of public input and coordination of Federal activities related to autism, the IACC continues in its effort to provide guidance to the Department of Health and Human Services and to reach out to the broader autism community to find ways to work together to help people with autism and their families.

***

For more information about the IACC, see www.iacc.hhs.gov.

TABLE OF CONTENTS

THE 2010 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

INTRODUCTION

As part of the Combating Autism Act of 2006, the members of the Interagency Autism Coordinating Committee are required to develop an annual "Summary of Advances" to describe each year's top advances in autism spectrum disorder research. These advances represent significant progress in the early diagnosis of ASD, understanding the complex biology of the disorder, and identifying potential risk factors. They may also relate to work identifying effective treatments and services and studies of the national prevalence of ASD and necessary research infrastructure. The 2010 Summary of Advances provides short, plain language synopses of the top twenty research breakthroughs selected by the committee from a pool of 64 peer-reviewed articles nominated by the members. Articles are grouped according to the questions of the IACC Strategic Plan for ASD Research (available at www.iacc.hhs.gov). Citations for the articles selected for the Summary of Advances, as well as a complete listing of those nominated, are included at the end of the document.

ARTICLES SELECTED FOR THE 2010 SUMMARY OF ADVANCES

Question 1: Diagnosis - When should I be concerned?

Implementing developmental screening and referrals: lessons learned from a national project.

King TM, Tandon SD, Macias MM, Healy JA, Duncan PM, Swigonski NL, Skipper SM, Lipkin PH. Pediatrics. 2010 Feb;125(2):350-60.

In 2006, the American Academy of Pediatrics (AAP) issued guidelines on developmental surveillance and screening that included the recommendation that all children be screened for developmental delays at 9, 18, and 24 or 30 months of age. In addition, children who were identified as being at risk should be referred for a detailed evaluation by a specialist and enrolled in early intervention services. In an effort to improve the adoption of their guidelines, the AAP simultaneously launched a project to assess how well the guidelines were being implemented in 17 diverse clinical settings. The study found that while most pediatricians conducted the regular developmental screenings recommended by the AAP, there could be significant improvement in the issuing and tracking of referrals for children who fail screens. Based on patient records from the monitored sites, the practices were successful in screening over 85 percent of patients who returned for appointments at the recommended ages. In phone interviews, individuals working at the practices reported that the high rate of screening was accomplished by delegating responsibilities among staff and actively monitoring whether screens had taken place. However, several sites had difficulty consistently screening children during busy periods or after periods of staff turnover. Many practices also had difficulty issuing and tracking referrals for children who were deemed to be at risk for developmental delays – 39 percent of children who failed screens never received the recommended referrals to a specialist and an early intervention program. When tracking did take place, the

clinicians found that many parents had not followed through with the referrals. Based on the project, the authors conclude that more focus should be placed on the referral process and communicating with families about the reasons for the referrals.

Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies.

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Am J Hum Genet. 2010 May 14;86(5):749-64.

An international consortium of geneticists recommended that chromosomal microarray assessment (CMA) be used as the standard genetic test for diagnosing people with unexplained developmental or intellectual delay, autism spectrum disorders, or birth defects. Previously, a test developed in the 1970s called G-banded karyotyping was the standard assessment used, but a literature review conducted by the consortium showed that CMA has greater sensitivity, resulting in a greater likelihood of diagnosis (3% diagnosis rate using G-banded karyotyping compared to 15 – 20% using CMA). This is primarily because CMA has greater sensitivity for submicroscopic deletions and insertions of DNA known as copy number variations. Researchers were able to develop CMA after the Human Genome Project was completed in 2000, and it has become a commonly ordered test for patients with developmental concerns. However, formal best practice guidelines had yet to be issued recommending CMA as a first-tier diagnostic test. The consortium concluded that CMA should be used in place of G-banded karyotyping as the genetic test for patients with unexplained developmental or intellectual delay, autism spectrum disorder, or birth defects. G-banded karyotyping should only be used by those who have obvious chromosomal syndromes such as Down syndrome, a family history of chromosomal rearrangement, or a history of multiple miscarriages.

Automated vocal analysis of naturalistic recordings from children with autism, language delay, and typical development.

Oller DK, Niyogi P, Gray S, Richards JA, Gilkerson J, Xu D, Yapanel U, Warren SF. *Proc Natl Acad Sci U S A. 2010 Jul 27;107(30):13354-9.*

Researchers have developed technology assessing patterns of vocalization that can distinguish children with ASD from others with a relatively high degree of accuracy. Using a lightweight recording device clipped to clothing, researchers captured 1,486 day-long recordings from children diagnosed with ASD, language delay, and those who were developing typically. The children in the study ranged from 10 months to 4 years of age. Investigators created a program that analyzes patterns of speech (or the cooing and babbling that precedes speech) and is able to distinguish children with ASD from their typically developing peers with 86 percent accuracy. Of those with developmental disorders, children with ASD were reliably distinguished from children with language

delay with 70 percent accuracy. Vocalizations were assessed using 12 separate parameters but investigators found that the most important factor for identification was the child's ability to produce clear syllables through quick movements of the jaw and tongue. The authors discuss the potential for using automated analysis as a convenient and objective addition to diagnostic tests for ASD and language delay. Ultimately, vocal analysis could help to decrease the average age of diagnosis for children with ASD (reported to be about 4½ to 5½ years of age in the United States), allowing children to start interventions earlier. Future efforts will focus on fine-tuning the technology to better differentiate between different subgroups of language disorders.

A prospective study of the emergence of early behavioral signs of autism.

Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, Rogers SJ, Rozga A, Sangha S, Sigman M, Steinfeld MB, Young GS. J Am Acad Child Adolesc Psychiatry. 2010 Mar;49(3):256-66.e1-2.

The study found that children with ASD generally do not show signs of the disorder at six months of age but that a plateauing or loss of social skills is evident by the time they reach their first birthday. The finding suggests that behavioral symptoms of autism are not present at birth as hypothesized by the man who first identified ASD, Dr. Leo Kanner, but instead emerge after six months of age in most instances. The authors of the study note that there may be some cases where behavioral signs of ASD are present at six months of age or earlier but that this pattern of onset is probably less common than originally thought. The researchers reached these conclusions by comparing the social behavior of 25 infants who were ultimately diagnosed with ASD to that of 25 typically developing infants. Researchers observed the children at 6, 12, 18, 24, and 36 months of age and coded the frequency of specific types of social communication behavior (e.g., gazing at faces, social smiling, vocalizations directed at a listener, etc.). The children showed no difference in social behavior at 6 months of age but by 12 months, the majority of children with ASD had failed to gain new social skills or had lost previously acquired ones. Notably, the majority of children with ASD showed a gradual loss of specific social skills, particularly between 6 and 18 months of age. However, this subtle regression in development went unnoticed by most parents. This demonstrates a critical flaw in retrospective studies of onset using parent report. The authors note that the traditional models of autism (early onset of symptoms or dramatic regression after typical development) may not adequately portray how ASD emerges and suggest that additional models may need to be developed. Alternately, the onset of symptoms may be better represented by a continuum based on the amount and timing of regression.

Question 2: Biology - How can I understand what is happening?

Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report.

Buie T, Campbell DB, Fuchs, GJ 3rd, Furuta GT, Levy J, VandeWater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Pediatrics. 2010 Jan;125(Suppl 1):S1 -S18.

Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs.

Buie T, Fuchs GJ 3rd, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H. Pediatrics. 2010 Jan;125(Suppl 1):S19-29.

A panel of experts reviewed the medical literature on ASD and gastrointestinal (GI) disorders and developed a consensus report (Buie, Cambell, Fuchs *et al.*, 2010) and recommendations for evaluation, diagnosis, and treatment (Buie, Fuchs, Furuta *et al*., 2010). While GI issues are commonly reported among people with ASD, the actual rate of these co-occurring issues and the proper methods for diagnosis and treatment are not well understood. The panel reached a consensus that people with ASD who have GI symptoms should receive the same thorough evaluation as any other patient. In addition, the experts concluded that GI issues reported in people with ASD are also common to the general population and that there is not sufficient evidence of a GI disorder unique to people on the spectrum. Further, they stated that medical problems such as GI issues may manifest as behavioral problems in people with ASD and that the underlying cause may be difficult to diagnose, particularly if the person is non-verbal. It may be beneficial to coordinate behavioral and medical treatment simultaneously in these instances. The panel concluded that the bulk of the literature does not support the idea that diets restricting gluten and/or casein can lessen the symptoms of ASD. However, existing evidence has not ruled out the possibility that a particular subset may respond to a restricted diet. The panel advised those who choose to follow these diets to do so in consultation with a nutritionist. Currently, data do not support that intestinal inflammation, increased intestinal permeability (or "leaky gut"), food allergies, or immunological issues play a role in causing ASD. More research is needed to understand what, if any, part these issues play. Additionally, any future studies of ASD and GI should include genetic analysis to better define potential subgroups of individuals. Ultimately, researchers are working to gather enough information to develop evidence-based guidelines standardizing care for children with ASD who experience GI problems.

Describing the brain in autism in five dimensions – magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach.

Ecker C, Marquand A, Mourao-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC, Murphy DG. J Neurosci. 2010 Aug11;30(32):10612-23.

Using magnetic resonance imaging (MRI), researchers were able to identify people with ASD by measuring subtle differences in brain structure. The investigators used a complex mathematical process to predict whether or not the person had ASD based on five dimensions of the brain selected for study by the researchers. These dimensions included both size (volume) and shape of various brain regions. The researchers found that no one structural feature could definitively identify whether a person had ASD, but when all five dimensions were taken together, they could distinguish people with ASD from typically developing individuals with up to 90 percent accuracy. The technique showed a false-positive rate (misdiagnosing ASD in a typically developing person) of about 20 percent, and ASD identification was more accurate when measures were taken from the left hemisphere of the brain. The authors discuss the theory that brain structure changes are more prominent in the left hemispheres of people with ASD, resulting in enhanced asymmetry between and the left and right halves of the brain. The researchers also tested how accurately their technique could distinguish people with ADHD from those with ASD and found that the algorithm misdiagnosed ASD in someone with ADHD 21 percent of the time. Future research will be needed to refine the technique, but the study demonstrates its potential as a valuable tool for diagnosing and understanding the biological underpinnings of ASD.

Mitochondrial dysfunction in autism.

Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN. JAMA. 2010 Dec 1;304(21):2389-96.

A preliminary study found that children with classic autism were more likely to have impaired mitochondrial function and abnormalities in mitochondrial DNA when compared to their typically developing peers. Mitochondria supply energy to cells and have their own set of genetic instructions. Questions surrounding mitochondrial dysfunction and autism have long existed, and some have hypothesized that the inability to adequately fuel neurons could account for some of the cognitive issues associated with autism. Mitochondrial dysfunction has been linked to several other neurological disorders including Parkinson's disease, Alzheimer's disease, schizophrenia, and bipolar disorder. In the investigation, researchers randomly selected ten children with ASD participating in the Childhood Autism Risks from Genetics and Environment (CHARGE) study being conducted at the M.I.N.D. Institute in California and compared them with ten typically developing children also participating in the study. The investigators took blood samples from the children, who ranged from 2 to 5 years of age, and analyzed the mitochondria present in immune cells called lymphocytes. They found that the mitochondria in children with autism were consuming significantly less oxygen than controls, indicating lowered mitochondrial activity and decreased ability to supply energy to cells. Children with autism also had higher levels of pyruvate, the basic material mitochondria

transform into energy, suggesting that they were unable to process pyruvate quickly enough to meet energy demands. Hydrogen peroxide levels in the mitochondria were also elevated, which could indicate higher levels of oxidative stress – an imbalance that results in cellular damage. Oxidative stress can cause mitochondria to produce extra copies of DNA, which was seen in half of children with autism. In addition, two of the ten children showed deletions in their mitochondrial DNA. The study provides evidence that mitochondrial dysfunction may be more common in children with autism and warrants further research.

Neural signatures of autism.

Kaiser MD, Hudac CM, Shultz S, Lee SM, Cheung C, Berken AM, Deen B, Pitskel NB, Sugrue DR, Voos AC, Saulnier CA, Ventola P, Wolf JM, Klin A, Vander Wyk BC, Pelphrey KA. Proc Natl Acad Sci U S A. 2010 Dec 7;107(49):21223-8.

Researchers have identified patterns of brain activity that are unique to people with autism spectrum disorder. These distinct patterns, also called neural signatures, may be useful in diagnosis and identifying subgroups of people with ASD. Using functional magnetic resonance imaging (fMRI), investigators performed scans of 62 children, 4 to 17 years of age, while they watched animations of biological motion (movements such as walking or running simplified to dots representing the major joints). Children in the study were diagnosed with ASD, typically developing, or siblings of children with ASD who did not have the diagnosis themselves. The study found that children with ASD showed less activity in certain brain regions when viewing the biological motion than did typically developing children. Interestingly, their siblings showed similarly reduced brain activation patterns although they did not have ASD. These similar patterns of decreased activity shared by ASD children and their unaffected siblings are called "trait markers." The researchers also identified other distinct brain regions that showed decreased activity only in the children with ASD, which they termed "state markers." Because these state markers are unique to ASD children, they could potentially serve as biomarkers for the disorder. Finally, the scientists identified brain regions in unaffected siblings that showed heightened levels of activity that they termed "compensatory regions." The increased activity in these regions may provide clues about why – with similar genetic risk – only one of the siblings developed ASD. The study gives insight into the brain basis of ASD and may help to improve diagnosis based on the newly identified neural signatures.

A model for neural development and treatment for Rett syndrome using human induced pluripotent stem cells.

Marchetto MC, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. Cell. 2010 Nov 12;143(4):527-39.

Researchers were able to create a neuronal model of Rett syndrome, a disorder on the autism spectrum with a known genetic cause, using induced pluripotent stem cells (iPSCs) from people with the disorder. Studying neurons produced from human Rett syndrome patients may help scientists gain a better understanding of the biological basis of Rett syndrome and be useful in testing

potential drug interventions. This is the first time an iPSC model of ASD has been created. In the study, researchers collected skin cells from four female patients with Rett syndrome and five healthy controls. By introducing a retrovirus, the scientists were able to reprogram the cells to behave like embryonic stem cells – giving them the ability to become an assortment of different cell types. Using the iPSCs, the researchers created functional neurons that were identical in many ways to those found in mouse models of Rett syndrome and postmortem brain tissue from individuals with the disorder. The neurons created from the participants with Rett syndrome showed structural and functional defects when compared to the cells from healthy controls. They were found to have 50 percent fewer synapses, a reduced number of dendritic spines (which help to send cellular signals), and smaller cell bodies. The neurons also showed abnormalities in their signaling abilities. With additional tests, the researchers were able to show that the abnormalities seen in the neurons stemmed from the mutations in the gene MECP2 that causes Rett syndrome. With this knowledge, they were able to treat the neurons with several drugs, reversing the cell defects and restoring normal cell signaling. The effective drugs included insulin growth factor 1 (IGF-1), previously shown to restore function in mouse models of Rett, and the antibiotic gentamicin, which increased MeCP2 levels by suppressing a type of mutation that commonly causes Rett syndrome. The study suggests that drug therapies could be effective for children with Rett syndrome when used early in development, before symptoms arise at 6 to 18 months of age. The ability to create patient-specific cellular models of a neurodevelopmental disorder offers a powerful new tool for researchers studying potential drug treatments.

Longitudinal MRI study of cortical development through early childhood in autism.

Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E. J Neurosci. 2010 Mar 24;30(12):4419-27.

An imaging study conducted over several years confirmed what many researchers have long hypothesized – children with ASD experience a period of early brain overgrowth beginning at a very young age. While this hypothesis has been supported by studies of head circumference and cross-sectional magnetic resonance imaging (MRI) of the brain, it had not been confirmed through a longitudinal study of brain growth during the critical period when symptoms of ASD first arise. Using functional MRI, researchers collected brain scans from toddlers who were later diagnosed with ASD and their typically developing peers at several points between 1 ½ years and 5 years of age. The study included 193 scans from 44 typically developing children and 41 children who went on to be diagnosed with ASD at around 4 years of age. The scans showed that by 2½ years of age, the brain's two major components – white and gray matter – were significantly enlarged in toddlers with ASD when compared to their peers. The greatest amount of enlargement occurred in regions of the brain known as the frontal, temporal, and cingulate cortices. As the children with ASD aged, overgrowth was seen in almost all parts of the brain. There were significant differences between genders, with girls showing more dramatic overgrowth in more regions. This suggests that the abnormal brain development in males and females with ASD may be fundamentally different. Based on the results of this research, the authors recommend including younger children in future studies to determine

when brain overgrowth begins. They also suggest considering genetic information and other biomarkers to better understand the underlying biological processes that affect the brain and result in the symptoms of ASD. As a caveat, the authors note that autism is a very heterogeneous disorder and not all children with ASD show brain enlargement. Future studies may help to identify the different patterns of neurodevelopment of individual subgroups.

Question 3: Risk Factors - What caused this to happen and can it be prevented?

Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation.

Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D, Bonin M, Riess A, Engels H, Sprengel R, Scherer SW, Rappold GA. Nat Genet. 2010 Jun;42(6):489-91.

Researchers discovered that mutations to SHANK2, a gene believed to play a role in maintaining the inner structure of the synapse, were present in people with ASD, as well as those with intellectual impairment. Without proper structure at the postsynapse – the receiving end of cellular communication – neural impulses cannot be properly sent. A gene in the same family, SHANK3, has previously been linked with ASD. The researchers sequenced SHANK2 in 396 people with ASD, 184 people with mental retardation, and 659 typically developing individuals. They found instances of copy number variations (CNVs), submicroscopic deletions and insertions of DNA, in two people with ASD. The CNVs were *de novo*, meaning they had arisen spontaneously and were not inherited from a parent. Seven inherited changes in SHANK2 were also found in people with ASD or intellectual impairment – the fact that their parents were carriers of these variants but did not show signs of atypical development suggests that a certain threshold of mutation must be reached to result in a disorder. A single nonsense *de novo* mutation (a type of mutation that usually results in a nonfunctional protein product) was also found. Overall, the study is notable because it identified additional examples of overlapping genes associated with both ASD (with and without cognitive impairment) and intellectual disability.

Blood mercury concentrations in CHARGE Study children with and without autism.

Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Environ Health Perspect. 2010 Jan;118(1):161-6.

A study found that children with ASD have similar levels of mercury in their blood as typically developing children, after controlling for other factors that impact mercury levels. The greatest predictor of blood mercury levels was the amount of fish in the child's diet. Almost all fish contain a trace amount of mercury and some larger predatory fish like swordfish and tuna may contain high levels. (The study adjusted for the fact that children with ASD generally ate less fish than their peers.) Researchers measured mercury levels in three groups of children ranging from 2 to 5 years of age: those with ASD, those with another developmental disorder, and those developing typically. The children were all enrolled in a study investigating factors that may contribute to ASD called the

Childhood Autism Risk from Genetics and Environment (CHARGE) study. The children's mothers were interviewed to determine ways in which the child could have been exposed to mercury, including fish consumption, personal care products like nasal sprays that may contain mercury, and silver-colored mercury-based amalgam fillings. Vaccine information was collected from the children's medical records and was not found to have any association with blood mercury levels. Overall, children with ASD had similar blood mercury levels to that of the general population. Children with developmental disabilities other than ASD consistently showed lower levels than the other groups. Apart from fish consumption, tooth-grinding and gum-chewing with mercury-based amalgam fillings was also linked to higher mercury levels. The authors caution that the study did not investigate whether mercury exposure in either prenatal or early postnatal period plays a role in causing ASD because blood measures were taken from children who had already been diagnosed with the disorder.

Functional impact of global rare copy number variation in autism spectrum disorder.

Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bölte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BH, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, et al. Nature. 2010 Jul 15;466(7304):368-72.

Researchers studying the genetics of ASD have identified a set of rare genetic variations that may confer risk for the disorder. While ASD is known to have a strong genetic component, (studies of identical twins have shown a 90 percent likelihood that both siblings are affected, compared to a 10 percent rate for non-identical twins), the exact genetic causes of ASD are still under investigation. All known genetic causes of ASD account for only 5 to 15 percent of cases, leaving the majority unexplained. Previous studies have implicated mutations in several genes that relate to proper functioning at the synapse, the junction between neurons where cell signaling takes place, and other genes involved in neural development. In the study, researchers conducted in-depth genetic analyses to compare the genomes of 996 people with ASD to 1,287 typically developing individuals. They found that people with ASD had 19 percent more rare copy number variations (CNVs) – abnormalities in the number of copies of one or more sections of DNA. When taken individually, each CNV was found in less than 1 percent of people with ASD. These CNVs were most likely to occur in genes that had previously been linked to ASD and/or intellectual disability. By further investigating the genes where the majority of the CNVs occurred in people with ASD, the researchers identified four genes that had never before been associated with ASD. These genes, as well as others implicated in previous studies, seem to be involved in similar biochemical pathways in the brain – those involved in cognitive development or cell signaling and communication. The authors are hopeful that better understanding of pathways linked to ASD will eventually lead to targets for pharmaceutical treatments.

Altered functional connectivity in frontal lobe circuits is associated with variation in the autism risk gene CNTNAP2.

Scott-Van Zeeland AA, Abrahams BS, Alvarez-Retuerto AI, Sonnenblick LI, Rudie JD, Ghahremani D, Mumford JA, Poldrack RA, Dapretto M, Geschwind DH, Bookheimer SY. Sci Transl Med. 2010 Nov 3;2(56)56ra80.

Researchers have found that certain forms of the autism risk gene CNTNAP2 are linked to wiring issues in the brain that could explain problems with language acquisition and learning associated with the disorder. Using functional imaging scans to capture brain activity during a learning task, the researchers discovered that children with the risk gene had too many connections within the frontal lobe, the portion of the brain involved in learning and other higher-level mental functions, and too few connections between the frontal lobe and other parts of the brain. Long-range connections to the back of the brain were particularly weakened. Investigators looked at two variations of CNTNAP2 – one which conferred risk for ASD and another common variant of the gene which did not. In addition to connectivity issues between the front and the back of the brain, children with the risk gene also showed atypical connection patterns between the right and left hemispheres. Those without the risk gene generally had communication pathways in the frontal lobe that connected more strongly to the left side of the brain. Alternatively, children with the risk gene showed equal distribution between right and left hemispheres, suggesting that the variant rearranges the brain's circuitry and could interfere with language skills. Children with the risk gene showed these abnormal activation patterns regardless of whether they were diagnosed with ASD. The findings suggest that CNTNAP2 plays an important role in wiring neurons in the frontal lobe and that mutations to the gene could disturb this process. This theory builds on earlier findings showing that CNTNAP2 is most active during development of the frontal lobe. In the future, understanding how genes can affect brain function and behavior could improve ASD diagnosis and potentially lead to interventions that aim to strengthen necessary connections within the brain. The finding may also apply to other disorders associated with CNTNAP2 variants, including speech and language impairments, attention deficit hyperactivity disorder (ADHD), Tourette syndrome, and schizophrenia.

Question 4: Interventions - Which treatments and interventions will help?

Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model.

Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. Pediatrics. 2010 Jan;125(1):e17-23.

The Early Start Denver Model (ESDM) is the first comprehensive behavioral intervention for ASD shown to be effective for toddlers. This model uses a relationship-based approach that draws on elements of Applied Behavior Analysis (ABA) – a style of therapy that emphasizes breaking activities into small, measurable units that are then reinforced with reward. In this study, researchers performed a randomized, controlled trial of the intervention over two years and showed that it led to improvements in IQ, language abilities, and adaptive functioning (i.e., the skills necessary for everyday activities). It also reduced the overall severity of ASD, with a substantial proportion of the children changing from a diagnosis of autism to a milder classification of Pervasive Developmental Disability, Not Otherwise Specified (PDD-NOS). During the study, 48 toddlers diagnosed with ASD, 1½ to 2½ years of age, were randomly assigned to receive the Early Start Denver Model or an intervention commonly available in the community. Children in the Early Start Denver Model group received an average of 15 hours per week working one-on-one with a therapist trained in the technique. Parents were taught to continue the therapy at home for at least 5 hours a week. The other 24 toddlers worked with therapists in the area, receiving a range of conventional therapies, for an average of 9 hours a week and received an additional 9 hours of therapy in a specialized preschool or other group program. Overall, the average number of intervention hours was similar between the two groups. After two years, the children receiving the Early Start Denver Model intervention showed a 17.6 point increase in IQ compared to a 7 point increase in the comparison group working with community therapists. The children in the Early Start Denver Model group also showed continued growth in adaptive behaviors (e.g., brushing teeth, getting dressed, eating with utensils, etc.), while the other children fell further behind their typically developing peers. Notably, 7 of the 24 children in the Early Start Denver Model group had significant enough improvements to change from a diagnosis of ASD to PDD-NOS. Only one of the children in the comparison group had a change in diagnosis. This study is the first randomized, controlled trial of an intervention for toddlers with ASD and adds to the body of evidence supporting the importance of early diagnosis and treatment.

Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism.

Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. *J Autism Dev Disord*. 2010 Sep;40(9):1045-56.

A study found that a parent-led intervention for toddlers with autism improved the children's responsiveness to joint engagement and increased the variety of their play. Joint attention skills involve the ability to engage others using eye contact or gestures to communicate nonverbally (e.g., pointing to a toy, looking between an event and a parent to share interest). Research has shown

that children with better joint attention skills go on to have better language skills, suggesting that teaching joint engagement may be an important focus of early ASD interventions. During the study, parents were trained to lead 24 therapy sessions over 8 weeks. The interventions incorporated aspects of Applied Behavior Analysis (ABA) and focused on following the child's lead in activities and maintaining his interest. Parents were taught to engage his or her child by imitating his actions, talking about what the child was doing, repeating back and expanding on things the child said, and making eye contact throughout the session. Researchers assessed how strictly parents adhered to the treatment principles and how comfortably they led the session. After completing the parent-led intervention, the 19 toddlers showed that they had successfully moved from play that was primarily object-focused to play with increased levels of joint engagement. However, the intervention only improved the children's responsiveness to joint engagement initiated by the parent and did not improve the children's own ability to initiate joint engagement. While the study showed that most of the parents strictly adhered to the treatment protocol, the level of fidelity did not predict how well his or her child responded to the intervention. The quality of the parent's interaction during the session also did not affect outcome, nor did the type or amount of additional treatment the child was receiving. Notably, the study is one of the first to show that a parent-mediated intervention can improve joint attention skills and diversity of play. The authors note that it will be important to gauge how the effectiveness of parent-mediated interventions compares to those led by therapists.

Evaluation of comprehensive treatment models for individuals with autism spectrum disorders.

Odom SL, Boyd BA, Hall LJ, Hume K. J Autism Dev Disord. 2010 Apr;40(4):425-36.

A study evaluated 30 treatment models for ASD, assessing whether the procedures were well-documented, how many times the model had been replicated, and how much evidence existed to support the effectiveness of the model's interventions. Overall, the study found that the procedures for using the models, most of which were based on aspects of Applied Behavior Analysis, were well-documented in manuals or guides. However, few of the models had developed measures to assess whether the model was well-implemented. Most of the models had been replicated by others – almost half had been repeated two or more times at independent sites. The weakest aspect was proof of effectiveness – 16 of the 30 models had never published research on their effectiveness in a peer-reviewed journal. The authors evaluated the models using journal articles, book chapters, web pages, procedural manuals, and phone interviews with the models' developers. After assessing the evidence, the researchers found that five models scored highly on at least four of the six dimensions that were evaluated: the Denver Model, LEAP (Learning Experiences and Alternative Programs for Preschoolers and Their Parents), Lovaas Institute, May Institute, and PCDI (Princeton Child Development Institute). Models with low evaluation scores included the following: Hanen, Higashi, Eden, Summit, Lancaster, and Son Rise. These rankings can be used as a guide for researchers, service providers, and families faced with treatment decisions. In the future, model developers will need to create measures to verify that the model has been effectively implemented. Additional research will also be necessary to document that the interventions are effective.

Evidence-based practices in interventions for children and youth with autism spectrum disorders.

Odom S, Collet-Klingenberg L, Rogers SJ, Hatton DD. Preventing School Failure. 2010;54(4):275-82.

Investigators reviewed the research literature to identify educational techniques for students with ASD that have sufficient evidence to support their effectiveness. While education programs are expected to be built upon evidence-based practices, currently there are no guidelines to identify whether an intervention is adequately supported by research. After developing a set of criteria, the researchers identified 24 intervention practices that qualify as "evidence-based." The study evaluated individual instructional practices or strategies (e.g., social skills training groups, positive behavioral support strategies, etc.), rather than comprehensive treatment models like the Denver Model or Lovaas Model. For studies to be considered as evidence of the practice's effectiveness, they had to include children with ASD younger than 22 years of age, measure outcome, show that gains in a targeted area clearly followed the use of the practice, and have sufficient controls for comparison. The practice needed support from at least two experimental studies (subjects are randomly assigned to groups) or observational studies (subjects are not randomly assigned but researchers can draw inferences about the effect of the treatment from the data) carried out by independent researchers. Practices that could only be supported by single-subject design – where subjects function as their own control group – would be deemed evidence-based only if there were at least five studies from three independent research groups. (A combination of several single-subject design and experimental/observational studies was also allowed.) After identifying the list of evidence-based practices, the researchers developed a chart matching the practice with the improved skill areas (academic, behavior, communication, play, social, and transitions). Practitioners and families can use the chart to identify which evidence-based practice has been shown effective in the skill area related to the student's learning objectives. The team also constructed web-based modules that include implementation instructions and procedural guidelines for each of the practices. The authors note that the number of evidence-based practices is expected to grow as more literature on ASD interventions is published.

Question 5: Services - Where can I turn for services?

Can state early intervention programs meet the increased demand of children suspected of having autism spectrum disorders?

Wise MD, Little AA, Holliman JB, Wise PH, Wang CJ. J Dev Behav Pediatr. 2010 Jul-Aug;31(6):469-76.

Early Intervention programs may be strained by the increase in demand for ASD services and additional resources will likely be necessary, according to reports from state program coordinators. In 2007, the American Academy of Pediatrics recommended that all children be screened for ASD at 18 and 24 months of age. Since that time, most states have seen a greater demand for ASD evaluations and behavioral services. The Early Intervention program provides ASD services for many young children (less than 36 months of age) across the United States, including almost all lower-income children on the spectrum. While the program is funded through the Individuals with Disabilities Education Act (IDEA), each state is expected to coordinate its own program and as a result services vary across states. Widespread staff shortages have made meeting the additional demand for services difficult, with almost half of the Early Intervention coordinators reporting that children in their state or territory receive 5 hours or fewer of weekly services. Only four states reported that most children receive more than 20 hours a week, indicating that the majority of children in Early Intervention programs are not receiving the 25 hours of behavioral intervention recommended by the National Research Council. Reports of personnel shortages were common, with 89 percent of coordinators reporting a need for behavioral therapists, 82 percent reporting a need for speech-language pathologists, and 79 percent for occupational therapists. Staff shortages were more likely to occur in states with a greater percentage of African-American and Latino children. Almost half of states reported that these personnel shortages pose a challenge to creating Individualized Family Services Plans (IFSPs), which guide the early intervention process for children with disabilities and their families, within the required 45-day time limit. Notably, several of the coordinators commented that the intensity of the plans should be scrutinized as well – many programs will only include services in IFSPs that can realistically be provided in the state, rather than the optimal course of treatment (e.g., calling for 5 hours of behavioral therapy when 25 would be ideal). The authors conclude that more resources will be needed to meet the increased demand for services as a result of enhanced early screening. Dedication to strengthening local services will be particularly important during a time when budget pressure could result in deep cuts to available services.

Question 6: Lifespan - What does the future hold, particularly for adults?

While no articles directly related to Question 6: *What does the future hold, particularly for adult?* were selected by the committee for inclusion in the final *2010 IACC Summary of Advances in Autism Spectrum Disorder Research ,* three articles were nominated in this category and they are listed on page 24 of this document in the Full Listing of Nominated Articles.

Question 7: Infrastructure - What other infrastructure and surveillance needs must be met?

Changes in autism spectrum disorder prevalence in 4 areas of the United States.

Rice C, Nicholas J, Baio J, Pettygrove S, Lee LC, Van Naarden Braun K, Doernberg N, Cunniff C, Newschaffer C, Meaney FJ, Charles J, Washington A, King L, Kolotos M, Mancilla K, Ervis CA, Carpenter L, Yeargin-Allsopp M. Disability and Health Journal. July 2010;3(3):186-201.

Researchers analyzed changes in the rates of ASD in four states from 2000 to 2004 and found that the prevalence had increased by an average of 55 percent in the locations showing change. Using data collected by the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network, researchers found that prevalence rates had increased significantly in Georgia and Maryland (38 percent and 72 percent increases respectively). In Arizona, rates of ASD increased by 26 percent over the four years, but this figure did not rise to the level of statistical significance (meaning that the measured increase could have occurred by chance and may not represent the true prevalence change). In South Carolina, ASD rates dropped, but not by a statistically significant amount, effectively representing no change in prevalence. Investigators identified 8-year-olds who met the DSM-IV criteria for ASD by reviewing information about their development included in their available health and/or education records. The authors note that some of the increase in prevalence is due to heightened awareness, change in diagnostic criteria, earlier age of diagnosis, and the diagnosis of milder forms of ASD; however, taken together, these factors do not entirely explain the increase in prevalence and a true surge in the number of cases cannot be ruled out. Regardless of the cause, there is a dramatic change in the prevalence of ASD in some parts of the country, and more children are accessing services than ever before. In the face of such an urgent public health concern, the authors state that collaborative efforts to improve research and service systems for people with ASD will be essential, in addition to continued monitoring to better understand changes in prevalence.

ARTICLES SELECTED FOR THE 2010 SUMMARY OF ADVANCES

QUESTION 1: WHEN SHOULD I BE CONCERNED?

King TM, Tandon SD, Macias MM, Healy JA, Duncan PM, Swigonski NL, Skipper SM, Lipkin PH. Implementing developmental screening and referrals: lessons learned from a national project. *Pediatrics.* 2010 Feb;125(2):350-60.

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010 May 14;86(5):749-64.

Oller DK, Niyogi P, Gray S, Richards JA, Gilkerson J, Xu D, Yapanel U, Warren SF. Automated vocal analysis of naturalistic recordings from children with autism, language delay, and typical development. *Proc Natl Acad Sci U S A*. 2010 Jul 27;107(30):13354-9.

Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, Rogers SJ, Rozga A, Sangha S, Sigman M, Steinfeld MB, Young GS. A prospective study of the emergence of early behavioral signs of autism. *J Am Acad Child Adolesc Psychiatry.* 2010 Mar;49(3):256-66.e1-2.

QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Buie T, Campbell DB, Fuchs, III GJ, Furuta GT, Levy J, Van de Water J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics.* 2010 Jan; 125: S1 - S18.

Buie T, Fuchs GJ 3rd, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics*. 2010 Jan;125(Suppl 1):S19-29.

Ecker C, Marquand A, Mourao-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC, Murphy DG. Describing the brain in autism in five dimensions—magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *J Neurosci.* 2010 Aug11;30(32):10612-23.

Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN. Mitochondrial dysfunction in autism. *JAMA*. 2010 Dec 1;304(21):2389-96.

Kaiser MD, Hudac CM, Shultz S, Lee SM, Cheung C, Berken AM, Deen B, Pitskel NB, Sugrue DR, Voos AC, Saulnier CA, Ventola P, Wolf JM, Klin A, Vander Wyk BC, Pelphrey KA. Neural signatures of autism. *Proc Natl Acad Sci USA*. 2010 Dec 7;107(49):21223-8.

Marchetto MC, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell.* 2010 Nov 12;143(4):527-39.

Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci.* 2010 Mar 24;30(12):4419-27.

QUESTION 3: WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D, Bonin M, Riess A, Engels H, Sprengel R, Scherer SW, Rappold GA. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. *Nat Genet.* 2010 Jun;42(6):489-91.

Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Blood mercury concentrations in CHARGE Study children with and without autism. *Environ Health Perspect.* 2010 Jan;118(1):161-6.

Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bölte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BH, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, et al. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature.* 2010 Jul 15;466(7304):368-72.

Scott-van Zeeland AA, Abrahams BS, Alvarez-Retuerto AI, Sonnenblick LI, Rudie JD, Ghahremani D, Mumford JA, Poldrack RA, Dapretto M, Geschwind DH, Bookheimer SY. Altered functional connectivity in frontal lobe circuits is associated with variation in the autism risk gene CNTNAP2. *Sci Transl Med*. 2010 Nov 3;2(56)56ra80.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. *Pediatrics.* 2010 Jan;125(1):e17-23.

Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *J Autism Dev Disord*. 2010 Sep;40(9):1045-56.

Odom S, Collet-Klingenberg L, Rogers SJ, Hatton DD. Evidence-based practices in interventions for children and youth with autism spectrum disorders. *Preventing School Failure.* 2010 May;54(4):275-82.

Odom SL, Boyd BA, Hall LJ, Hume K. Evaluation of comprehensive treatment models for individuals with autism spectrum disorders. *J Autism Dev Disord.* 2010 Apr;40(4):425-36.

QUESTION 5: WHERE CAN I TURN FOR SERVICES?

Wise MD, Little AA, Holliman JB, Wise PH, Wang CJ. Can state early intervention programs meet the increased demand of children suspected of having autism spectrum disorders? *J Dev Behav Pediatr.* 2010 Jul Aug;31(6):469-76.

QUESTION 6: WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

No articles were selected from Question 6. For a list of articles that were nominated in this category, see the Full Listing of Nominated Articles, page 24.

QUESTION 7: WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Rice C, Nicholas J, Baio J, Pettygrove S, Lee LC, Van Naarden Braun K, Doernberg N, Cunniff C, Newschaffer C, Meaney FJ, Charles J, Washington A, King L, Kolotos M, Mancilla K, Ervis CA, Carpenter L, Yeargin-Allsopp M. Changes in autism spectrum disorder prevalence in 4 areas of the United States. *Disab Health J.* 2010 Jul;3(3):186-201.

FULL LISTING OF NOMINATED ARTICLES (SELECTED ARTICLES APPEAR IN BLUE)

QUESTION 1: WHEN SHOULD I BE CONCERNED?

Chowdhury M, Aman MG, Scahill L, Swiezy N, Arnold LE, Lecavalier L, Johnson C, Handen B, Stigler K, Bearss K, Sukhodolsky D, McDougle CJ. The Home Situations Questionnaire-PDD version: factor structure and psychometric properties. *J Intellect Disabil Res.* 2010 Mar;54(3):281-91.

King TM, Tandon SD, Macias MM, Healy JA, Duncan PM, Swigonski NL, Skipper SM, Lipkin PH. Implementing developmental screening and referrals: lessons learned from a national project. *Pediatrics.* 2010 Feb;125(2):350-60.

Mandell DS, Morales KH, Xie M, Lawer LJ, Stahmer AC, Marcus SC. Age of diagnosis among Medicaid-enrolled children with autism, 2001-2004. *Psychiatr Serv.* 2010 Aug;61(8):822-9.

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010 May 14;86(5):749-64.

Norris M, Lecavalier L. Screening accuracy of Level 2 autism spectrum disorder rating scales: A review of selected instruments. *Autism. 2010 Jul;14(4):263-84.*

Oller DK, Niyogi P, Gray S, Richards JA, Gilkerson J, Xu D, Yapanel U, Warren SF. Automated vocal analysis of naturalistic recordings from children with autism, language delay, and typical development. *Proc Natl Acad Sci U S A*. 2010 Jul 27;107(30):13354-9.

Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, Rogers SJ, Rozga A, Sangha S, Sigman M, Steinfeld MB, Young GS. A prospective study of the emergence of early behavioral signs of autism. *J Am Acad Child Adolesc Psychiatry.* 2010 Mar;49(3):256-66.e1-2.

QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Buie T, Campbell DB, Fuchs, III GJ, Furuta GT, Levy J, Van de Water J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics.* 2010 Jan; 125: S1 - S18.

Buie T, Fuchs GJ 3rd, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics*. 2010 Jan;125(Suppl 1):S19-29.

Chamberlain SJ, Chen PF, Ng KY, Bourgois-Rocha F, Lemtiri-Chlieh F, Levine ES, Lalande M. Induced pluripotent stem cell models of the genomic imprinting disorders Angelman and Prader-Willi syndromes. *Proc Natl Acad Sci USA*. 2010 Oct 12;107(41):17668-73.

Chao HR, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, Neul JL, Gong S, Lu HC, Heintz N, Ekker M, Rubenstein JL, Noebels JL, Rosenmund C, Zoghbi HY. Dysfunction in GABA signaling mediates autism-like stereotypies and rett syndrome phenotypes. *Nature*. 2010 Nov 11;468(7321):263-9.

Ecker C, Marquand A, Mourao-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC, Murphy DG. Describing the brain in autism in five dimensions—magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *J Neurosci.* 2010 Aug11;30(32):10612-23.

Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN. Mitochondrial dysfunction in autism. *JAMA*. 2010 Dec 1;304(21):2389-96.

Kaiser MD, Hudac CM, Shultz S, Lee SM, Cheung C, Berken AM, Deen B, Pitskel NB, Sugrue DR, Voos AC, Saulnier CA, Ventola P, Wolf JM, Klin A, Vander Wyk BC, Pelphrey KA. Neural signatures of autism. *Proc Natl Acad Sci USA*. 2010 Dec 7;107(49):21223-8.

Marchetto MC, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell.* 2010 Nov 12;143(4):527-39.

Mostafa GA, El-Hadidi ES, Hewedi DH, Abdou MM. Oxidative stress in Egyptian children with autism: relation to autoimmunity. *J Neuroimmun.* 2010 Feb 26;219(1-2):114-8.

Palmieri L, Papaleo V, Porcelli V, Scarcia P, Gaita L, Sacco R, Hager J, Rousseau F, Curatolo P, Manzi B, Militerni R, Bravaccio C, Trillo S, Schneider C, Melmed R, Elia M, Lenti C, Saccani M, Pascucci T, Puglisi-Allegra S, Reichelt KL, Persico AM. Altered calcium homeostasis in autism-spectrum disorders: evidence from biochemical and genetic studies of the mitochondrial aspartate/glutamate carrier AGC1. *Mol Psychiatry.* 2010 Jan;15(1):38-52.

Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: Cause or effect? *Biochim Biophys Acta.* 2010 June - July;1797(6-7):1130-1137.

Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci.* 2010 Mar 24;30(12):4419-27.

Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. *J Neurosci.* 2010 Nov 3;30(44):14595-609.

QUESTION 3: WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D, Bonin M, Riess A, Engels H, Sprengel R, Scherer SW, Rappold GA. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. *Nat Genet.* 2010 Jun;42(6):489-91.

Campbell DB, Warren D, Sutcliffe JS, Lee EB, Levitt P. Association of MET with social and communication phenotypes in individuals with autism spectrum disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2010 Mar 5;153B(2):438-46.

Curtis JT, Hood AN, Chen Y, Cobb GP, Wallace DR. Chronic metals ingestion by prairie voles produces sex-specific deficits in social behavior: an animal model of autism. *Behav Brain Res.* 2010 Nov 12;213(1):42-9.

Gallagher CM, Goodman MS. Hepatitis B vaccination of male neonates and autism diagnosis, NHIS 1997-2002. *J Toxicol Environ Health A.* 2010;73(24):1665-77.

Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC, Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gécz J, DeLisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nat Genet.* 2010 Mar;42(3):203-9.

Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Blood mercury concentrations in CHARGE Study children with and without autism. *Environ Health Perspect.* 2010 Jan;118(1):161-6.

Hunter JW, Mullen GP, McManus JR, Heatherly JM, Duke A, Rand JB. Neuroligin-deficient mutants of C. elegans have sensory processing deficits and are hypersensitive to oxidative stress and mercury toxicity. *Dis Model Mech.* 2010 May-Jun;3(5-6):366-76.

Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *J Pediatr.* 2010 Apr;156(4):525-31.e2.

Keil A, Daniels JL, Forssen U, Hultman C, Cnattingius S, Söderberg KC, Feychting M, Sparen P. Parental autoimmune diseases associated with autism spectrum disorders in offspring. *Epidemiology.* 2010 Nov;21(6):805-8.

Kern JK, Geier DA, Adams JB, Geier MR. A biomarker of mercury body-burden correlated with diagnostic domain specific clinical symptoms of autism spectrum disorder. *Biometals*. 2010 Dec;23(6):1043-1051.

Lancet. Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet.* 2010 Feb 6;375(9713):445.

Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry.* 2010 Nov;167(11):1357-63.

Lintas C, Altieri L, Lombardi F, Sacco R, Persico AM. Association of autism with polyomavirus infection in postmortem brains. *J Neurovirol.* 2010 Apr;16(2):141-9.

Olczak M, Duszczyk M, Mierzejewski P, Wierzba-Bobrowicz T, Majewska MD. Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal. *Folia Neuropathol.* 2010;48(4):258-69.

Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bölte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BH, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, et al. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature.* 2010 Jul 15;466(7304):368-72.

Price CS, Thompson WW, Goodson B, Weintraub ES, Croen LA, Hinrichsen VL, Marcy M, Robertson A, Eriksen E, Lewis E, Bernal P, Shay D, Davis RL, DeStefano F. Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics.* 2010 Oct;126(4):656-64.

Schieve LA, Baio J, Rice CE, Durkin M, Kirby RS, Drews-Botsch C, Miller LA, Nicholas JS, Cunniff CM. Risk for cognitive deficit in a population-based sample of U.S. children with autism spectrum disorders: Variation by perinatal health factors. *Disability and Health Journal.* July 2010; 3(3) 202-212.

Scott-van Zeeland AA, Abrahams BS, Alvarez-Retuerto AI, Sonnenblick LI, Rudie JD, Ghahremani D, Mumford JA, Poldrack RA, Dapretto M, Geschwind DH, Bookheimer SY. Altered functional connectivity in frontal lobe circuits is associated with variation in the autism risk gene CNTNAP2. *Sci Transl Med*. 2010 Nov 3;2(56)56ra80.

Shelton JF, Tancredit DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Res. 2010 Feb;3(1):30-9.*

Shoffner J, Hyams L, Langley GN, Cossette S, Mylacraine L, Dale J, Ollis L, Kuoch S, Bennett K, Aliberti A, Hyland K. Fever plus mitochondrial disease could be risk factors for autistic regression. *J Child Neurol.* 2010 Apr;25(4):429-34.

Smith MJ, Woods CR. On-time vaccine receipt in the first year does not adversely affect neuropsychological outcomes. *Pediatrics.* 2010 Jun;125(6):1134-41.

Yap IK, Angley M, Veselkov KA, Holmes E, Lindon JC, Nicholson JK. Urinary metabolic phenotyping differentiates children with autism from their unaffected siblings and age-matched controls. *J Proteome Res.* 2010 Jun 4;9(6):2996-3004.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Arnold LE, Farmer C, Kraemer HC, Davies M, Witwer A, Chuang S, DiSilvestro R, McDougle CJ, McCracken J, Vitiello B, Aman MG, Scahill L, Posey DJ, Swiezy NB. Moderators, mediators, and other predictors of risperidone response in children with autistic disorder and irritability. *J Child Adolesc Psychopharmacol.* 2010 Apr;20(2):83-93.

Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. *Pediatrics.* 2010 Jan;125(1):e17-23.

Frankel F, Myatt R, Sugar C, Whitham C, Gorospe CM, Laugeson E. A randomized controlled study of parent-assisted Children's Friendship Training with children having autism spectrum disorders. *J Autism Dev Disord.* 2010 Jul;40(7):827-42.

Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *J Autism Dev Disord*. 2010 Sep;40(9):1045-56.

McCracken JT, Aman MG, McDougle CJ, Tierney E, Shiraga S, Whelan F, Arnold LE, Posey D, Ritz L, Vitiello B, Scahill L. Possible influence of variant of the P-glycoprotein gene (MDR1/ABCB1) on clinical response to guanfacine in children with pervasive developmental disorders and hyperactivity. *J Child Adolesc Psychopharmacol.* 2010 Feb;20(1):1-5.

Odom S, Collet-Klingenberg L, Rogers SJ, Hatton DD. Evidence-based practices in interventions for children and youth with autism spectrum disorders. *Preventing School Failure.* 2010 May;54(4):275-82.

Odom SL, Boyd BA, Hall LJ, Hume K. Evaluation of comprehensive treatment models for individuals with autism spectrum disorders. *J Autism Dev Disord.* 2010 Apr;40(4):425-36.

QUESTION 5: WHERE CAN I TURN FOR SERVICES?

Brookman-Frazee L, Taylor, R, Garland, A. Characterizing Community-Based Mental Health Services for Children with Autism Spectrum Disorders and Disruptive Behavior Problems. *J Autism Dev Disord.* 2010 Oct;40(10): 1188-1201.

Wehmeyer, MI, Shogren KA, Smith TEC, Zager D, Simpton R. Research-Based Principles and Practices for Educating Students with Autism: Self-Determination and Social Interactions. *Education and Training in Autism and Developmental Disabilities.* 2010 45(4): 475-86.

Young J, Corea C, Kimani J, Mandell D. Autism Spectrum Disorders (ASDs) Services: Final Report on Environmental Scan. *Prepared for the Centers for Medicare & Medicaid Services.* 2010 Mar 9.

Wise MD, Little AA, Holliman JB, Wise PH, Wang CJ. Can state early intervention programs meet the increased demand of children suspected of having autism spectrum disorders? *J Dev Behav Pediatr.* 2010 Jul Aug;31(6):469-76.

QUESTION 6: WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

Chowdhury M, Benson BA, Hillier A. Changes in Restricted Repetitive Behaviors with age: A study of high-functioning adults with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders.* 2010 April-June;4(2):210-216.

LeBel J, Huckshorn KA, Caldwell, B. Restraint use in residential programs: why are best practices ignored? *Child Welfare.*2010;89(2):169-87.

McDonough JT, Revell G. Accessing employment supports in the adult system for transitioning youth with autism spectrum disorders. *Journal of Vocational Rehabilitation.* 2010;32(2):89-100.

QUESTION 7: WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Durkin MS, Maenner MJ, Meaney FJ, Levy SE, DiGuiseppi C, Nicholas JS, Kirby RS, Pinto-Martin JA, Schieve LA. Socioeconomic inequality in the prevalence of autism spectrum disorder: evidence from a U.S. cross-sectional study. *PLoS One.* 2010 Jul 12;5(7):e11551.

Gilberg C, Billstedt E, Sundh V, Gilbert IC. Mortality in autism: a prospective longitudinal community-based study. *J Autism Dev Disord.* 2010 Mar;40 (3): 352-57.

Liu KY, King M, Bearman PS. Social influence and the autism epidemic. *AJS.* 2010 Mar;115(5):1387-434.

Mazumdar S, King M, Liu KY, Zerubavel N, Bearman P. The spatial structure of autism in California, 1993-2001. *Health Place.* 2010 May;16(3):539-46.

McDonald ME, Paul JF. Timing of increased autistic disorder cumulative incidence. *Environ Sci Technol.* 2010 Mar 15;44(6):2112-8.

Rice C, Nicholas J, Baio J, Pettygrove S, Lee LC, Van Naarden Braun K, Doernberg N, Cunniff C, Newschaffer C, Meaney FJ, Charles J, Washington A, King L, Kolotos M, Mancilla K, Ervis CA, Carpenter L, Yeargin-Allsopp M. Changes in autism spectrum disorder prevalence in 4 areas of the United States. *Disabil Health J.* July 2010;3(3):186-201.

Saemundsen E, Juliusson H, Hjaltested S, Gunnarsdottir T, Halldorsdottir T, Hreidarsson S, Magnusson P. Prevalence of autism in an urban population of adults with severe intellectual disabilities - a preliminary study. *J Intellect Disabil Res.* 2010 Aug;54(8):727-35.

van Meter KC, Christiansen LE, Delwiche LD, Azari R, Carpenter TE, Hertz-Picciotto I. Geographic distribution of autism in California: a retrospective birth cohort analysis. *Autism Res.* 2010 Feb;3(1):19-29.

INTERAGENCY AUTISM COORDINATING COMMITTEE MEMBER ROSTER

For member bios and more information about the Committee, visit
http://iacc.hhs.gov/about/member-roster.shtml

CHAIR

Thomas R. Insel, M.D.
Director
National Institute of Mental Health
National Institutes of Health
Bethesda, MD

FEDERAL MEMBERS

James F. Battey, M.D., Ph.D.
Director
National Institute on Deafness and
   Other Communication Disorders
National Institutes of Health
Bethesda, MD

Linda Birnbaum, Ph.D.
Director
National Institute of Environmental
   Health Sciences
National Institutes of Health
Research Triangle Park, NC

Ellen W. Blackwell, M.S.W.
Division of Community and Institutional
   Services
Disabled and Elderly Health Programs
   Group
Center for Medicaid and State
   Operations
Centers for Medicare & Medicaid
   Services
Baltimore, MD

Coleen Boyle, Ph.D.
Acting Director
National Center on Birth Defects and
   Developmental Disabilities
Centers for Disease Control and
   Prevention
Atlanta, GA

Henry Claypool
Director
Office on Disability
U.S. Department of Health and Human
   Services
Washington, DC

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health
Bethesda, MD

Alan E. Guttmacher, M.D.
Acting Director
Eunice Kennedy Shriver National
    Institute of Child Health and Human
    Development
National Institutes of Health
Bethesda, MD

Gail R. Houle, Ph.D.
Associate Division Director
Research-to-Practice Division
Early Childhood Programs
Office of Special Education Programs
U.S. Department of Education
Washington, DC

Larke N. Huang, Ph.D.
Senior Advisor on Children
Office of the Administrator
Substance Abuse and Mental Health
    Services Administration
Rockville, MD

Walter J. Koroshetz, M.D.
Deputy Director
National Institute of Neurological
    Disorder and Stroke
National Institutes of Health
Bethesda, MD

Sharon Lewis
Commissioner
Administration on Developmental
    Disabilities
Administration for Children and Families
Washington, DC

Peter van Dyck, M.D., M.P.H.
Associate Administrator
Maternal and Child Health
Health Resources and Services
    Administration
Rockville, MD

PUBLIC MEMBERS

Geraldine Dawson, Ph.D.
Chief Science Officer
Autism Speaks
New York, NY

Gerald D. Fischbach, M.D.
Scientific Director
Simons Foundation Autism Research
    Initiative
New York, NY

Lee Grossman
President and CEO
Autism Society
Bethesda, MD

Yvette M. Janvier, M.D.
Medical Director
Children's Specialized Hospital
Toms River, NJ

Christine M. McKee, J.D.
Rockville, MD

Ari Ne'eman
Founding President
Autistic Self-Advocacy Network
Washington, DC

Lyn Redwood, R.N., M.S.N.
Co-Founder and Executive Director
Coalition for Safe Minds
Tyrone, GA

Denise D. Resnik
Board Member and Co-Founder
Southwest Autism Research and
   Resource Center
Phoenix, AZ

Stephen M. Shore, Ed.D.
Executive Director
Autism Spectrum Consulting and
Assistant Professor of Special Education
Adelphi University
Newton, MA

Alison Tepper Singer, M.B.A.
President
Autism Science Foundation
New York, NY

Marjorie Solomon, Ph.D., M.B.A.
Assistant Clinical Professor
University of California, Davis
   School of Medicine and
    M.I.N.D. Institute
Sacramento, CA

NIH/NIMH Office of Autism Research Coordination Staff

6001 Executive Boulevard, Room 8185, Bethesda, MD 20892
Email: IACCPublicInquiries@mail.nih.gov

Susan A. Daniels, Ph.D.
Acting Director

Elizabeth M. Baden, Ph.D.
Policy Analyst

Erin H. Bryant, M.J.
Science Writer/Editor

Sara E. Dodson, Ph.D.
AAAS Science & Technology
Policy Fellow/Health Scientist

Nicole Jones
Web Developer

Miguelina Perez
Management Analyst