

The Interagency Autism Coordinating Committee

2011 Summary of Advances

in Autism Spectrum Disorder Research



OFFICE OF
AUTISM RESEARCH
COORDINATION
NATIONAL INSTITUTES OF HEALTH

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is charged with providing advice to the Secretary of Health and Human Services (HHS) and with coordinating all efforts within HHS concerning autism spectrum disorder (ASD). It was established by Congress under the Combating Autism Act of 2006 and renewed under the Combating Autism Reauthorization Act of 2011.

Membership of the committee includes a wide array of Federal agencies involved in ASD research and services, as well as public stakeholders who represent a variety of perspectives from within the autism community. This makeup of the IACC membership is designed to ensure that the committee is equipped to address the wide range of issues and challenges faced by families and individuals affected by autism.

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 completing these tasks, the members of the committee have worked collaboratively to advance biomedical research and coordinate services that will make an impact for people with ASD and their families.

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

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THE 2011 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

INTRODUCTION

Each year the IACC releases its annual list of scientific advances that represent significant progress in the field. The twenty studies selected have given new insight into the complex causes of autism and potential risk factors, studied clues that could lead to earlier diagnosis, and evaluated promising early intervention strategies. The advances also address the prevalence of ASD both in the U.S. and internationally, as well as the service needs of people with ASD across the lifespan. The 2011 Summary of Advances provides short, plain language synopses of the top research breakthroughs selected by the committee from a pool of 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 2011 SUMMARY OF ADVANCES

QUESTION 1: WHEN SHOULD I BE CONCERNED?

Disrupted neural synchronization in toddlers with autism – Dinstein I, Pierce K, Eyer L, Solso S, Malach R, Behrmann M, Courchesne E. *Neuron*. 2011 Jun 23;70(6):1218-25.

A study of sleeping toddlers identified patterns of abnormal neural activity that could aid in the early diagnosis of autism and help to understand underlying causes. Using functional magnetic resonance imaging (fMRI), researchers found that 72 percent of children with ASD showed decreased synchronization across brain hemispheres in areas commonly associated with language and communication. This decreased synchronization was rarely seen in typically developing children, or those with delayed language development who did not have autism. Strong synchronization between the right and left hemisphere of the brain is critical for proper functioning, and there is evidence of disrupted synchronization in neurological disorders such as schizophrenia and Alzheimer's disease. While disrupted synchronization has been documented in adults with autism, researchers had been unable to study the phenomenon in early childhood because toddlers cannot remain still long enough to undergo a brain scan when awake. Researchers were able to overcome this challenge by performing scans on sleeping children; neurons remain synchronized between regions of the brain with similar function even while resting. The brain scans revealed that weak neural synchronicity is evident in the early stages of autism and that the strength of synchronization is linked to the degree of the child's symptoms — children with the weakest neural synchronization exhibit the most severe impairments. The researchers note that measures of neural synchronization could one day play a role in early autism diagnosis, particularly because the measure can be taken while the child sleeps.

Detecting, Studying, and Treating Autism Early: The One-Year Well-Baby Check-Up Approach – Pierce K, Carter C, Weinfeld M, Desmond J, Hazin R, Bjork R, Gallagher N. *J Pediatr.* 2011 Sep;159(3):458-465.e1-6.

A five-minute checklist filled out by parents at the one-year, well-baby check-up has been shown to predict autism or other developmental delays in about 75 percent of cases. This easily implemented tool is the first validated autism screen for infants and could help pediatricians identify autism even earlier than the evaluations at 18 and 24 months of age recommended by the American Academy of Pediatrics. The screening tool, called the *Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist*, developed by Dr. Amy Wetherby and colleagues, was filled out by parents in the waiting room and took pediatricians only two minutes to review, providing a quick way to identify young children at risk for ASD. The study followed 137 pediatricians in San Diego County who used the tool to screen almost 10,500 infants. About 12 percent of infants screened were flagged by the questionnaire as at-risk for ASD and referred for further evaluation at a clinic. The study followed 184 infants who failed the screen until three years of age and found that 17 percent (32 children) ultimately received an autism diagnosis. Of the remaining children, 30 percent were identified as having a learning disability, 5 percent with a developmental disability, and 20 percent as another type of disability. Overall, the screen yielded about a 30 percent false-positive rate, meaning that 1 out of 3 infants flagged as at-risk during the initial screen did not subsequently receive a developmental disorder diagnosis. The findings demonstrate that the checklist is a convenient and effective screen for autism and other disabilities at the one-year, well-baby check-up – improving the chances of early detection and increasing the opportunity for early intervention. Notably, all 137 pediatricians who participated in the study were still using the checklist when the article was published – a significant improvement from the only 22 percent who were screening at one-year check-ups prior to the study.

QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Mutations causing syndromic autism define an axis of synaptic pathophysiology – Auerbach BD, Osterweil EK, Bear MF. *Nature.* 2011 Nov 23;480(7375):63-8.

New research reveals that two genetic forms of autism, fragile X syndrome and tuberous sclerosis, are actually caused by opposite malfunctions – while fragile X is caused by overproduction of proteins at the synapse, tuberous sclerosis is caused by underproduction. Interestingly, while the causes of fragile X and tuberous sclerosis are distinctly different, both disorders often result in intellectual disability and autism spectrum disorder. Researchers made the discovery while studying mGluR5 (Metabotropic glutamate receptor 5), a receptor on the surface of neurons that is key in aiding communication at the synapse – the junction between neurons. During normal signaling, the mGluR5 receptor binds to the neurotransmitter glutamate after it is released across the synapse, resulting in the production of new synaptic proteins. Fragile X protein (FMRP) halts protein synthesis to ensure that the appropriate amount is produced – in fragile X syndrome, changes to the gene that controls FMRP allow synaptic

proteins to continue production unchecked, resulting in too much protein. Researchers have previously shown that introducing a substance to block mGluR5 reverses some of the symptoms of fragile X, and human drug trials are currently underway. Armed with an understanding of the underlying causes of fragile X, researchers in this study examined mice with tuberous sclerosis mutations and discovered something surprising. In this case, the disorder was caused by the opposite malfunction – too little protein synthesis at the synapse, which could be treated with a drug stimulating mGluR5. Further, when the researchers bred the two mice together, many of their autistic features went away. The findings of the study indicate that proper brain function can only occur within a narrow range of mGluR5 protein synthesis – changes in either direction lead to syndromes with similar behavioral symptoms. This also suggests that drug treatments for autism spectrum disorder will need to be individually tailored, as conditions that appear similar may have quite different underlying causes.

Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits – Peñagarikano O, Abrahams BS, Herman EI, Winden KD, Gdalyahu A, Dong H, Sonnenblick LI, Gruver R, Almajano J, Bragin A, Golshani P, Trachtenberg JT, Peles E, Geschwind DH. *Cell*. 2011 Sep 30;147(1):235-46.

A new mouse model of autism, created by eliminating a gene strongly associated with the disorder in humans, shows promise for understanding the biology that underlies ASD and testing new treatments. By eliminating the CNTNAP2 gene (contactin associated protein-like 2), researchers were able to create mice with behaviors that closely mimicked those of its human counterparts – the mice exhibited repetitive behaviors, abnormal social interactions, and irregular vocalizations, in addition to experiencing seizures and hyperactivity. CNTNAP2 is thought to play an important role in the development of language, and variants of the gene have been linked to an increased risk of autism and epilepsy. Prior to experiencing seizures, the mice showed signs of abnormal brain circuit development – researchers observed irregularities in communication between neurons and their migration within the brain. These observations complement earlier studies suggesting that children with autism carrying a CNTNAP2 variant have a “disjointed brain.” The frontal lobe is poorly connected with the rest of the brain but shows an overconnection with itself, resulting in poor communication with other brain regions. Notably, the mice in the study responded positively to risperidone, an antipsychotic medication approved by the FDA to treat symptoms of irritability and aggression associated with ASD. While their social interactions did not improve – risperidone has not been shown to improve social function in humans – there was a marked improvement in repetitive grooming and a decrease in hyperactivity. Creating an animal model of autism that closely resembles the symptoms and behaviors in humans may be an important tool in understanding neural development in autism and developing new treatments.

Protein interactome reveals converging molecular pathways – Sakai Y, Shaw CA, Dawson BC, Dugas DV, Al-Mohtaseb Z, Hill DE, Zoghbi HY. *Sci. Transl. Med.* 2011 Jun 8;3(86):86ra49.

A recent study sheds light on how a variety of different mutations in genes that seemingly have little in common can each result in the symptoms of autism. To answer this question, researchers developed a molecular map of protein networks or “interactome” to identify how proteins associated with ASD interact with hundreds of other proteins. Researchers used genes known to be associated with syndromic autism as a starting point for building the interactome. Syndromic autism occurs as part of a broader genetic disorder such as fragile X, Angelman syndrome, and Rett syndrome — understanding protein interactions with syndromic autism may give insight into idiopathic autism, or autism with no known cause. Using 26 genes associated with syndromic autism, researchers hypothesized that the seemingly dissimilar genes might interact with shared partners in common molecular pathways, leading to the symptoms of autism. Indeed, researchers identified a complex network of 539 proteins that interacted with the autism-related proteins, successfully demonstrating that all of the proteins linked to autism are connected by interactions with common partners. The interactome confirmed previously suspected gene relationships and several new pairings, such as the connection between SHANK3 and TSC1, which share 21 common protein partners. Researchers then performed a microarray analysis on 288 individuals with idiopathic autism in a search for genes within the interactome. They identified three novel copy number variations — chromosomal deletions and duplications — on genes found in the network, demonstrating that the interactome may help to identify new genes related to ASD and understand complicated genetic variation.

Transcriptomic analysis of autistic brain reveals convergent molecular pathways – Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH. *Nature.* 2011 May 25;474(7351):380-4.

A study found surprising consistency in molecular changes seen in the brains of people with autism across the spectrum, suggesting a common biological basis that may span multiple subtypes. Researchers analyzed postmortem brain tissue and found atypical patterns of gene expression common to many of the individuals with ASD. These findings may provide clues about how autism changes the brain at the molecular level, and lead to new avenues for developing treatments. In the study researchers focused on gene expression — the way information from the gene is used in the synthesis of functional gene products, often proteins. These proteins then perform specific tasks in the cell. In brains affected by autism, genes involved in neuron function and communication were expressed at much lower levels than in typically developing individuals, and the expression of genes involved in certain immune functions was abnormally high. The authors note that many of these genes are active during fetal development, supporting the theory that abnormal brain development may start very early in the womb. The findings also provide evidence that molecular changes in neuron function and communication are probably a cause of autism, rather than a result of the disorder. To identify common patterns of gene expression among people with autism, the researchers compared the frontal and temporal lobes of the brain — the frontal lobe is responsible for higher-level thinking including judgment and social response, while the temporal lobe plays a key role in hearing and language and is also

involved in sensory integration. They found that more than 500 genes were expressed at different levels in the frontal and temporal lobes of typically developing individuals, as would be expected in separate brain regions with differing functions. However, there was almost no difference in the levels of gene expression between the two regions in the brains of those with ASD. This blurring suggests a failure to differentiate regions in early brain development.

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

Genetic heritability and shared environmental factors among twin pairs with autism – Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C, Grether JK, Risch N. *Arch Gen Psychiatry*. 2011 Nov;68(11):1095-102.

Recent research suggests that environmental factors may play a much greater role in autism risk than previously suspected and could even be more influential than genetic factors. These findings stem from a study of autism in twins, the largest of its kind, designed to model the genetic and environmental factors that contribute to the development of autism. Because identical twins share 100 percent of their DNA, researchers can assess the degree to which a disorder is genetic by studying the number of cases where both twins are affected (called concordance). Fraternal twins share 50 percent of their DNA, similar to siblings, so by comparing concordance rates among fraternal twins and siblings, researchers can study the influence of environmental factors, particularly those in the womb. In the study, researchers looked at concordance among 192 pairs of identical and fraternal twins and found that 77 percent of male identical twins and 50 percent of female twins were both affected by autism. Previous studies with smaller numbers of twins suggested a much greater genetic contribution, as high as 90 percent. The fraternal twins in the study had a 35 percent concordance rate – much lower than rates among identical twins but higher than rates among siblings, estimated to range from 3 to 19 percent. Using mathematical modeling, the researchers propose that environmental factors accounted for 55 percent of autism risk, while genetic heritability contributed less than 40 percent. The difference in rates among fraternal twins and siblings, who share similar amounts of DNA, suggests that environmental factors in the womb may be an important area of future study.

Rare de novo and transmitted copy-number variation in autistic spectrum disorders – Levy D, Ronemus M, Yamrom B, Lee YH, Leotta A, Kendall J, Marks S, Lakshmi B, Pai D, Ye K, Buja A, Krieger A, Yoon S, Troge J, Rodgers L, Iossifov I, Wigler M. *Neuron*. 2011 Jun 9;70(5):886-97.

A study of the genetic causes of autism confirmed that spontaneous or *de novo* mutations are present in a substantial number of families with only one child on the spectrum. These *de novo* mutations are not inherited from parents' DNA, arising instead in their egg or sperm or very early in embryonic development. Researchers compared the DNA of children with ASD to that of their unaffected sibling(s) and identified a diverse array of rare genetic abnormalities that may contribute to autism. Recent advances in technology have allowed researchers to identify genetic mutations on a finer scale than was

previously possible. Some of the *de novo* mutations, known as copy number variations (CNVs) because they contain deleted or duplicated sections of DNA, were located in regions known to be associated with ASD, while others implicate new regions. Many of the mutations are thought to affect genes or gene networks involved in brain development. The study confirmed that these non-inherited CNVs are more common in children with ASD compared to their non-affected siblings; however, each unique variant is exceedingly rare, some found in only one family. In addition, researchers found evidence that inherited “ultrarare” genetic duplications may also contribute to autism. Based on the results of the study, the authors note that females have a greater resistance to autism from genetic causes, raising questions about the fate of female carriers. The study findings emphasize the diversity of rare genetic variations that contribute to ASD and suggest the possibility that a treatment for one form of autism may not have value for the majority of cases. The DNA samples analyzed in the study were part of the Simons Simplex Collection, a repository of over 1,000 families in the U.S. and Canada with only one child on the spectrum.

Exome sequencing in sporadic autism spectrum disorders identifies severe *de novo* mutations –

O’Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, Karakoc E, Mackenzie AP, Ng SB, Baker C, Rieder MJ, Nickerson DA, Bernier R, Fisher SE, Shendure J, Eichler EE. *Nat Genet.* 2011 Jun;43(6):585-9.

Another study of spontaneous mutations identified four genes that are likely to play a causal role in the development of autism. Instead of searching more broadly for copy number variants throughout the genome, researchers focused exclusively on the protein-coding region of the genome called the exome. This approach has a greater potential to identify single candidate genes for ASD. The study sequenced the exomes of 20 people with autism and their parents and identified 21 spontaneous or *de novo* mutations. Of the 21 mutations, four were determined to be potentially causative (FOXP1, GRIN2B, SCN1A, and LAMC3). Of note, the four participants carrying these mutations were profoundly affected by autism. Three of the four genes identified in the study had previously been associated with autism, intellectual disability without autism, and epilepsy. The fourth mutation, LAMC3, had never before been linked to autism and represents a potential new avenue of research. Within the study, two of the four children had been hit with a “genetic double-whammy” – both inheriting a harmful gene mutation from his parent and having a *de novo* mutation. For example, the child with a FOXP1 mutation also inherited a defective copy of CNTNAP2, believed to be involved in language development. This child had severe autism and the most profound language deficits of any participant. Another child with autism and epilepsy had both an inherited deletion putting him at risk for epilepsy and a *de novo* mutation of a gene associated with epilepsy, SCN1A. These two cases support the ‘multi-hit’ theory of autism – that a combination of mutations in the same pathway is necessary to cause severe autism or related disorders. The authors note that the study supports the role of *de novo* mutations as a major genetic contributor to autism and demonstrates the great potential of whole exome sequencing to identify candidate genes.

Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study – Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, Hutman T, Iverson JM, Landa R, Rogers SJ, Sigman M, Stone WL. *Pediatrics*. 2011 Sep; 128 (3) e488-95.

For parents with an autistic child, the risk of having another child with autism may be greater than previously thought, according to findings from the largest prospective study of baby siblings conducted to date. Earlier studies suggested that 3 to 10 percent of infants who had an older sibling with autism would go on to develop the disorder themselves – new findings suggest that the risk of recurrence is substantially higher, at approximately 19 percent. This risk is even greater if the younger sibling is a boy or if he or she has more than one older sibling with ASD – male siblings have a 1 in 4 chance of developing autism while those from multiplex families have almost a 1 in 3 chance. Other factors, such as the severity of symptoms in the older sibling, older sibling's gender, parental age, or birth order were not shown to have any effect on recurrence risk. In this study, researchers recruited 664 infants and tracked them from around 8 months of age to 36 months when they were tested for autism. Ultimately, 132 children were diagnosed with autism spectrum disorder using gold-standard direct assessment methods. The research was conducted through the Baby Siblings Research Consortium, an international network that pools data to learn more about children at high risk for developing autism. The researchers note that the increased risk of autism recurrence for siblings suggests that families and pediatricians should take special care tracking their development and refer them for early intervention should concerns arise. These findings also have important implications for genetic counseling and family planning purposes.

Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism – Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA, Mason CE, Bilguvar K, Celestino-Soper PB, Choi M, Crawford EL, Davis L, Davis Wright NR, Dhodapkar RM, Dicola M, Dilullo NM, Fernandez TV, Fielding-Singh V, Fishman DO, Frahm S, Garagaloyan R, Goh GS, Kammela S, Klei L, Lowe JK, Lund SC, McGrew AD, Meyer KA, Moffat WJ, Murdoch JD, O'Roak BJ, Ober GT, Pottenger RS, Raubeson MJ, Song Y, Wang Q, Yaspan BL, Yu TW, Yurkiewicz IR, Beaudet AL, Cantor RM, Curland M, Grice DE, Günel M, Lifton RP, Mane SM, Martin DM, Shaw CA, Sheldon M, Tischfield JA, Walsh CA, Morrow EM, Ledbetter DH, Fombonne E, Lord C, Martin CL, Brooks AI, Sutcliffe JS, Cook EH Jr, Geschwind D, Roeder K, Devlin B, State MW. *Neuron*. 2011 Jun 9;70(5):863-85.

A recent collaborative study identified six genetic mutations that are strongly associated with autism spectrum disorder, including an area of DNA that likely holds clues to understanding the nature of human social behavior. The researchers estimate that these mutations represent only a few of the hundreds of spontaneously arising variants that are likely to increase autism risk. Using gene chip or microarray technology, the researchers analyzed the genomes of over 1,100 families with a single child on the autism spectrum, and compared the results of affected and unaffected siblings. The DNA samples analyzed in the study were part of the Simons Simplex Collection. The scan revealed a variety of copy

number variants (CNVs) — genetic mutations that can range from micro-deletions and duplications to large sequences of missing or additional DNA. Notably, one of the non-inherited or *de novo* CNVs was located on a genetic region linked to Williams-Beuren syndrome, a rare disorder that causes people to be extremely social, overly trusting, and highly empathetic. While loss of DNA from the area results in Williams-Beuren syndrome, gain of extra DNA in this area is associated with autism, which is marked by difficulty with social interaction and lack of empathy. This region's connection with both disorders suggests its importance in understanding the nature of the social brain. The study also supports earlier findings of higher rates of *de novo* CNVs in people with autism compared to their unaffected siblings. Uncovering the genetic basis of autism is critical to understanding the neurobiology underlying the disorder and may aid in developing targeted treatment approaches for different subtypes.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

A systematic review of medical treatments for children with autism spectrum disorders – McPheeters ML, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, Veenstra-Vanderweele J. *Pediatrics*. 2011 May;127(5):e1312-21.

Researchers conducted a systematic literature review to evaluate the effectiveness of drug treatments for children with autism spectrum disorder, age 12 and younger. While there was strikingly little evidence to support the benefits of most medications prescribed for children with ASD, the antipsychotics risperidone and aripiprazole showed clear benefit for managing challenging and repetitive behavior. Both drugs had at least one randomized controlled trial, considered the gold standard for intervention studies, conducted by the pharmaceutical company that produces each drug and at least two randomized controlled trials showing parent-reported benefits. The strength of the evidence for aripiprazole was considered to be high, while risperidone was deemed moderate. Despite benefits, both drugs cause significant side effects including marked weight gain, sedation, and a number of movement disorders; as a result, they are generally limited to patients with severe impairment or risk of injury. The systematic review also examined antidepressants and stimulants and found insufficient evidence to evaluate the effectiveness of either type of drug in reducing challenging and repetitive behavior in children with ASD. A widespread search across multiple databases identified only one good-quality and one fair-quality randomized controlled trial of serotonin reuptake inhibitors (SRIs) and one good-quality randomized controlled trial of stimulants. Study quality was determined by two reviewers who independently assessed the studies based on factors such as study design, participant characterization, diagnostic approach, outcome measurement, and statistical analysis. The authors note the need for more publicly funded studies to evaluate the potential benefits and risks of medications currently being prescribed for children on the spectrum.

Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial – Landa RJ, Holman KC, O'Neill AH, Stuart EA. *J Child Psychol Psychiatry*. 2011 Jan;52(1):13-21.

Two-year-olds with ASD showed improved social skills after completing an intervention targeting core social deficits in autism. It is the first randomized controlled trial to test such an intervention in toddlers and gives promise that a supplementary curriculum could improve social and communication skills in very young children. The researchers randomly assigned 50 toddlers with ASD, aged 21 to 33 months, to receive either an intervention called Interpersonal Synchrony — which targets social imitation, joint attention skills, and sharing of emotions — or a comparison intervention that does not target these specific social skills. Both six-month interventions were used for 10 hours per week in the classroom, and parents in both groups were given similar levels of training to continue the intervention at home. While toddlers in both groups showed gains in social, cognitive, and language skills during the study, children who received the Interpersonal Synchrony intervention, which encouraged them to communicate and play with others, had the greatest progress. At the end of the six months, these children had more than doubled the instances in which they engaged in social imitation (such as imitating the way a parent plays with a toy or mimicking a facial expression), while also making eye contact. Social imitation is believed to be critical in developing social communication skills — deficits in such core social skills are a defining characteristic of autism. Importantly, children in the Interpersonal Synchrony group were able to generalize their newly developed skills to new people and settings. While their progress slowed in the six months following the end of the intervention, they did not lose any of the skills gained, unlike children in the comparison group who showed poorer social communication skills at the six-month follow-up.

Randomized, controlled trial of the LEAP model of early intervention for young children with autism spectrum disorders – Strain PS and Bovey EH. *Topics in Early Childhood Special Education*. 2011 Nov;31(3):133-154.

A 2011 study supports the effectiveness of an early intervention model for autism spectrum disorder designed to be used in an integrated classroom. Randomized controlled trials are considered to be the gold standard of evidence; however, due to their complexity and cost, only four other RCTs of comprehensive interventions for young children with autism had been completed at the time this article was published. Of these four, all were tested in segregated environments and involved one-on-one instruction at the beginning of the intervention. In contrast, the LEAP (Learning Experiences and Alternative Program for Preschoolers and Their Parents) preschool model uses teaching opportunities that arise naturally in an integrated setting and incorporates typically developing students by training them to support the social skills development of their peers with ASD. The LEAP model is also the first evidence-based intervention for ASD to be tested in a public school setting. In the study, researchers compared the performance of students in 28 classrooms where teachers received personal training and coaching support in the LEAP model over two years to the performance of teachers in 28 classrooms who received only training manuals and written materials. While all children had equivalent skill levels

at the start of the intervention, after two years the students in the coached classrooms showed marked improvement in symptoms of autism, cognitive scores, language development, social skills, and a reduction in problem behavior. The teachers' fidelity to the LEAP strategies predicted the students' level of improvement. These findings suggest that successfully adhering to LEAP strategies produces broad developmental improvements. It costs much less than other commonly used one-on-one strategies — an estimated \$20,000 per child annually compared to \$45,000 — \$69,000.

QUESTION 5: WHERE CAN I TURN FOR SERVICES?

Post-high school service use among young adults with an autism spectrum disorder – Shattuck PT, Wagner M, Narendorf S, Sterzing P, Hensley M. *Arch Pediatr Adolesc Med.* 2011 Feb;165(2):141-6.

A study of service use among young adults with autism showed a dramatic decline in the use of services after leaving high school. Use of medical, mental health, and case management services decreased, with nearly two-fifths (39%) of young adults reportedly receiving no services at all. The loss of school-based services comes at a critical juncture when young adults with autism may be transitioning into a new living situation, forming new types of relationships, or adjusting to the demands of work or vocational training. Researchers analyzed data about service use provided by 410 families of young adults with ASD, 19 to 23 years of age, who had recently left high school. This information was compared to data collected from most of the families six years earlier. While in school, 46 percent of the adolescents received mental health services, 47 percent received medical services, and 64 percent had a case manager. Six years later, these figures fell to 35 percent receiving mental health services, 24 percent receiving medical services, and 42 percent with a case manager. The greatest decline was seen in speech therapy, with a drop from 75 percent to 9 percent in the years following high school. Race and socioeconomic status played a strong role in predicting levels of service engagement, with African-American youths more than three times as likely to become completely disengaged after leaving school compared to white youths. Young adults from families making less than \$25,000 annually were almost six times more likely to be disengaged than those from more affluent families making \$75,000 a year or more. The authors note that these disparities indicate a need for targeted outreach and services.

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

Epidemiology of autism spectrum disorders in adults in the community in England – Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J, Bettington P, Jenkins R, Meltzer H. *Arch Gen Psychiatry*. 2011 May;68(5):459-65.

Approximately 1 percent of adults in England have autism spectrum disorder, based on one of the first studies of adult prevalence in the country. Previous studies have relied primarily on self-report which can be unreliable. To determine what proportion of the English population age 16 years and older is affected by autism, researchers conducted a multiphase study to screen adults in the community. They hypothesized that the rate of autism would be much lower in older adults than in children and that adults on the spectrum would be predominately male and socially disadvantaged. In the first phase of the study, participants selected from the 2007 Adult Psychiatric Morbidity Survey in England completed the Autism-Spectrum Quotient self-questionnaire. The answers to this and other self-assessments helped the investigators select 618 individuals from the initial 7,461 respondents to interview using the Autism Diagnostic Observation Schedule (ADOS-4). Based on the results of screening using the tool, 19 people met the criteria for autism spectrum disorder representing a prevalence rate of 9.8 per 1,000 individuals, or nearly 1 percent. While only a small number of individuals were identified, many were living in social housing and had the lowest levels of education, reinforcing the authors' hypothesis that those with autism are more likely to be socially disadvantaged. None of these associations, however, were statistically significant. The authors note that the prevalence rate identified in this study is similar to the rate reported among children, supporting the idea that autism rates have not changed significantly over time. Due to the small sample of adults with ASD, they were unable to examine differences in adult prevalence by age. The findings suggest that adults with ASD may be undiagnosed and socially disadvantaged, which has significant public health implications.

Autism spectrum disorders in older adults: toward defining a research agenda – Piven J, Rabins P. Autism-in-Older Adults Working Group. *J Am Geriatr Soc*. 2011 Nov;59(11):2151-55.

Relatively little is known about older adults with autism spectrum disorder – few studies have been done to determine how behaviors and symptoms change over time, how aging may impact people with ASD differently, and whether findings in children and young adults with ASD generalize to the older adult population. Based on current estimates, by 2030 there will be approximately 700,000 adults with ASD over the age of 65. Much work must be done to identify the unique service needs of this group and ensure that adequate long-term care options exist. To address the lack of knowledge about older adults with ASD, a multidisciplinary group convened in March 2010 to begin defining a research agenda to address the needs of the population. The group defined six research priorities, the first of which was the need for diagnostic criteria and instruments to identify individuals based on adult symptom profiles. Based on findings from a recent study in England, rates of autism appear to be relatively similar across generations suggesting that there is a large group of older adults with ASD who have gone undiagnosed.

Second, the group noted the need for studies characterizing symptoms, behaviors, and co-occurring conditions in adults, as well as available services and supports. Other priorities include the need for longitudinal research to study lifespan trajectories, neurobiological research to study how the autistic brain ages, and studies of different types of interventions for use with older adults on the spectrum. Finally, the group identified the need to support training that would attract young researchers and clinicians to the emerging field of aging and autism. These proposed priorities should begin to answer questions about autism and aging in an effort to address individual needs and gauge its potential impact on the healthcare system and society.

Emerging new practices in technology to support independent community access for people with intellectual and cognitive disabilities – Stock SE, Davies DK, Wehmeyer ML, Lachapelle Y.

NeuroRehabilitation. 2011; 28(3):261-9.

New technology holds promise for helping people with cognitive disabilities access their community. A recent paper describes the various electronic devices and software applications currently on the market to help individuals navigate their community on foot and by public transit. While being unable to navigate one's community without assistance is a major barrier to community inclusion, little research has been devoted to exploring technologies that could promote community access. The authors review some of the advantages and drawbacks of emerging technologies for community access, and report results from a case study of a smartphone application in use. Of the technologies discussed, computer based video instruction (CBVI) has shown promise in small trials. Using CBVI, individuals are able to rehearse their routes using video shot from a first-person perspective while a voice-over gives instructions such as "push the request for stop signal when you see the Chick-Fil-A and Target sign." A three-person trial of CBVI found that two of the three participants were able to successfully generalize the skills they had rehearsed while on a public bus. Global Positioning System (GPS) technology used together with pictures of landmarks and audio cues has also been shown to be effective — 24 out of 26 participants successfully traveled to a new destination unaccompanied using the system. A case study of a 19-year-old man with Down syndrome documented his use of a similar smartphone application to complete routes to four new destinations. Both he and his parents were extremely positive about the technology. In addition to enhancing self-determination and community integration, enabling people with cognitive disabilities to use public transit offers cost-savings. For example, a mid-size city would save more than \$4,500 annually for each individual with cognitive disabilities who took a standard bus rather than specialized para-transit services.

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

Trends in the prevalence of developmental disabilities in US children 1997-2008 – Boyle C, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeagrín-Allsopp M, Visser S, Kogan MD. *Pediatrics*. 2011 Jun;127(6):1034-42.

Developmental disorders among children in the U.S. increased in prevalence by 17.1 percent from 1997 to 2008, affecting an estimated 1.8 million more children than a decade before. Of all developmental disorders, autism showed the most growth, increasing 289 percent over the twelve-year time frame. During the same period, attention deficit hyperactivity disorder (ADHD) increased by 33 percent, while moderate to profound hearing loss, the only developmental disability to show improvement, decreased by 30.9 percent. In total, 15 percent of all children in the U.S. had some sort of developmental disability when last measured in 2008. Boys were more likely than girls to have a developmental disability and Hispanic children had a lower prevalence than other racial groups. The prevalence of developmental disabilities increased in all groups regardless of race or socio-economic status. Children from low-income families were more likely to have a developmental disability and those on Medicaid were nearly twice as likely to have a diagnosis. The study, conducted by the Centers for Disease Control and Prevention, analyzes data from 119,367 children ages 3 to 17 collected during National Health Survey Interviews. Parents or legal guardians were asked if their children had any of the following conditions: ADHD, autism, blindness, cerebral palsy, moderate to profound hearing loss, intellectual disability, learning disorders, seizures, stuttering/stammering, or any other developmental delay. The study authors conclude that the increased prevalence of developmental disorders demonstrated by the study underscores the heightened need for targeted health, education, and social services.

Prevalence of autism spectrum disorders in a total population sample – Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Cheon KA, Kim SJ, Kim YK, Lee H, Song DH, Grinker RR. *Am J Psychiatry*. 2011 Sep;168(9):904-12.

A comprehensive study of school children in a region of South Korea revealed that approximately 1 in 38 children, or 2.6 percent, are on the autism spectrum. This study was the first of its kind to use total population sampling, and the findings suggest that using this technique might increase prevalence estimates in other countries. Researchers assessed more than 55,000 children between the ages of 5 and 12 living in the middle-class city of Goyang and found that two-thirds of the students with ASD were undiagnosed and had never received services. Only one third of the students with ASD were in the study's "high probability group" of 294 children enrolled in special education or listed on a disability registry. The rest of the children diagnosed with ASD were among the general population enrolled in mainstream classrooms. The authors note that if only the high probability group had been used to calculate prevalence, they would have arrived at a 0.7 percent prevalence rate — similar to the 0.9 percent in the United States. They hypothesize that the low level of awareness about autism and the high degree of stigma surrounding the disorder in South Korea could partially explain the large number

of undiagnosed children. To identify autism among children enrolled in mainstream classrooms, researchers asked parents and teachers to complete a 27-item questionnaire – children who screened positive for autism on the assessment were individually evaluated using gold-standard diagnostic methods. The study findings suggest that total population studies may be necessary to produce more accurate ASD prevalence estimates. Further work will need to be done to determine whether the South Korean findings can be generalized to other countries.

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QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Auerbach BD, Osterweil EK, Bear MF. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature*. 2011 Nov 23;480(7375):63-8.

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

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

Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J, Bettington P, Jenkins R, Meltzer, H. Epidemiology of autism spectrum disorders in adults in the community in England. *Arch Gen Psychiatry*. 2011 May; Vol 68(5):459-65.

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