2016

SUMMARY OF ADVANCES

in Autism Spectrum Disorder Research

IACC

INTERAGENCY AUTISM
COORDINATING COMMITTEE

OFFICE OF
AUTISM RESEARCH
COORDINATION
NATIONAL INSTITUTES OF HEALTH

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is a Federal advisory committee charged with coordinating all activities concerning autism spectrum disorder (ASD) within the U.S. Department of Health and Human Services (HHS) and providing advice to the Secretary of HHS on issues related to autism. It was established by Congress under the Children's Health Act of 2000, reconstituted under the Combating Autism Act (CAA) of 2006, and renewed under the Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014.

Membership of the Committee includes a wide array of Federal agencies involved in ASD research and services, as well as public stakeholders, including self-advocates, family members of children and adults with ASD, advocates, service providers, and researchers, who represent a variety of perspectives from within the autism community. This IACC membership is composed 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 and subsequent authorizations, 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.

Through these and other activities, the IACC provides guidance to HHS and partners with the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

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For more information about the IACC, see *http://www.iacc.hhs.gov*.

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THE 2016 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

Each year, the IACC releases a list of scientific advances that represent significant progress in the field. The 20 studies selected have provided new insight into characteristics of high-risk siblings of children with autism spectrum disorder (ASD), molecular changes underlying the biology of ASD, and risk factors for neurodevelopmental disorders. The advances also include studies that examined promising communication interventions, the effects of policy changes on ASD service delivery, health and employment outcomes for adults with ASD, and the latest data on ASD prevalence in the U.S. The *2016 Summary of Advances* provides short, plain language summaries of the top research breakthroughs selected by the IACC from a pool of research articles nominated by the members. Articles are grouped according to the topics represented by the questions of the *IACC Strategic Plan for ASD Research*. 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.

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- Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012

QUESTION 1

WHEN SHOULD I BE CONCERNED?

Reduced engagement with social stimuli in 6-month-old infants with later autism spectrum disorder: a longitudinal prospective study of infants at high familial risk

Jones EJ, Venema K, Earl R, Lowy R, Barnes K, Estes A, Dawson G, Webb SJ. *J Neurodev Disord.* 2016 Mar 15;8:7. [*PMID: 26981158*]

The average age of an ASD diagnosis in the U.S. is approximately 4 years old. Research has shown that up to 20% of infants who have an older sibling with ASD will also be diagnosed with ASD later in their lives. Parents may suspect ASD prior to a formal diagnosis, particularly if their infant has a sibling with an ASD diagnosis.

Early diagnosis is important for effective ASD intervention. It is therefore important to identify characteristics of ASD that may be measurable in infancy. Social attention, which is the ability to interact and orient eye contact with another person, is a common deficit in ASD, and may occur as early as at 6 to 12 months old. Furthermore, it is possible that there are measurable differences in brain activity that might be detectable even before the full manifestation of autism is present. The goal of this study was to determine whether 6- and 12-month-old infants who later develop ASD differ from typically developing infants in terms of their neural responses and attention patterns to social versus non-social stimuli.

In this study, the researchers first conducted experiments to determine patterns of social attention in typically developing infants. Children at 6 and 12 months old were shown colored images of non-social attention stimuli (age-appropriate objects) and social attention stimuli (different faces). Attention was measured using habituation (when the amount of "look time" at an image declines after consecutive looks) and event-related potential (ERP, which records brain activity simultaneous with the presentation of the images to correlate attention engagement in the brain). The results of this experiment confirmed that, in typically developing infants, a longer duration of attention was given to faces than to objects, as reflected in both habituation patterns and neural responses.

In the second part of the study, researchers examined the differences between infants with an older sibling diagnosed with ASD (high risk) and infants without an older sibling diagnosed with ASD (low risk). The same social attention experiments were conducted across both groups. At 24 months of age, the same infants were clinically assessed for ASD. The results of this experiment showed that 6-month-old high-risk infants who were later diagnosed with ASD at 24 months displayed a disruption in the ability to sustain attention in general—a finding both in habituation patterns and in neural response times. The 6-month-old infants at high risk for ASD and later diagnosed with ASD at 24 months showed disrupted habituation specifically to faces and showed a more robust (higher amplitude) neural response to objects than faces, a pattern not evident in the infants who did not develop ASD. At 12 months, the difference between the groups was less apparent. High-risk infants who did not develop ASD did not show reduced attention during these experiments.

These findings suggest that high-risk infants who are later diagnosed with ASD have disrupted or delayed attention engagement for social stimuli at 6 months old. Differences in neural responses to social versus non-social information in high-risk infants who later develop ASD are evident by 6 months of age and precede the development of the full behavioral syndrome. As the child ages and developmental milestones are passed, this early disruption in social attention may cascade into reduced social engagement.

School-age outcomes of infants at risk for autism spectrum disorder

Miller M, Iosif AM, Young GS, Hill M, Phelps Hanzel E, Hutman T, Johnson S, Ozonoff S. *Autism Res.* 2016 Jun;9(6):632-42. [*PMID: 26451968*]

ASD occurs at a significantly higher rate in children who have an older sibling with ASD compared with those who do not. Recent studies have investigated the developmental characteristics of such high-risk children from infancy to toddler age, but few of these studies have been extended to include school-age children. High-risk, school-age children sometimes may not meet diagnostic criteria for ASD, but still exhibit clinical concerns such as attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and learning issues, as well as a broader autism phenotype—a constellation of subclinical, ASD-related difficulties such as deficiencies in language, social skills, motor function, and behavior. Therefore, studies of non-ASD, high-risk children are critical to improve diagnosis and treatment of these ASD-related clinical concerns.

This study followed children from infancy to school-age (up to 9 years old) who were high-risk (younger siblings of children with ASD) and low-risk (younger siblings of typically developing children) to:

- Determine rates of dysfunction across assessment scores for cognition, language, psychopathology, and ASD symptoms
- Examine the rate of ASD-related clinical concerns
- Compare clinical concerns outcomes across time—at 36 months and school-age

When comparing assessment scores across groups, the researchers found that 43% of children in the high-risk group and 12% of children in the low-risk group had one or more clinically elevated assessment scores. The most pronounced deficiencies in the high-risk group were seen in the Social Responsiveness Scale (SRS, which measures social, communication, and repetitive/stereotyped behaviors) and the Child Behavior Checklist (CBCL, which measures mood, attention, behaviors, and social issues). The rate of ASD-related clinical concerns was 38% for children in the high-risk group as compared to 13% for children in the low-risk group. The most frequently observed clinical concerns were broader autism phenotype and ADHD.

There were some differences in outcomes across age, with almost 12% of high-risk children exhibiting clinical concerns at school-age but not earlier in infancy, and 17% of high-risk children exhibiting clinical concerns at infancy that seemed to have improved by school age. However, most high-risk children showed consistency in clinical concerns across time. Notably, the proportion of high-risk children who exhibited clinical concerns was consistent with the proportion of high-risk children who received elevated scores on the SRS and CBCL. This suggests that nonverbal cognitive and language impairment might not be a primary area of concern in school-age children—an important finding considering that schools focus on cognitive and language functioning and may miss the challenges that are more relevant to school-age children. These results suggest that clinical concerns associated with high-risk infants and toddlers may continue to school-age, and that these children would benefit from continued screening, specifically expanded into areas of social responsiveness and skills, ADHD, and mood disorders.

QUESTION 2

HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs
Orefice LL, Zimmerman AL, Chirila AM, Sleboda SJ, Head JP, Ginty DD. *Cell.* 2016 Jul 14;166(2):299-313. [*PMID: 27293187*]

Unusual or increased sensitivity to touch is a common symptom in individuals with ASD. The experience of touch in early childhood is important for the development of social behaviors and communication, and it is possible that hypersensitivity to touch can contribute to social and communication challenges later in a child's life.

The brain mechanisms that underlie this increased sensitivity to touch in individuals with ASD are not well understood, but they are thought to have a genetic component. In this study, researchers used several mouse models of ASD to examine genetic contributions to different behaviors and brain functions related to touch.

Mice with mutations in one of four genes that are linked to ASD in humans (*Mecp2*, *Gabrb3*, *Shank3*, and *Fmr1*) were compared to mice without mutations in those genes. First, the mice were permitted to explore an environment that contained smooth- and rough-textured objects. The control mice preferred to explore different textures, while the mice with ASD-related mutations showed aversion to exploring the differently textured objects. Next, the mice received a light puff of air against the hair on their backs followed by a brief noise to stimulate a startle response (an unconscious response or reflex to a perceived threat). Compared to control mice, mice with ASD-related mutations exhibited an increased startle response, indicating hypersensitivity to touch.

Next, the researchers examined the effect of deleting ASD-linked genes in different types of brain cells. They found that deletion of *Mecp2* or *Gabrb3* in sensory neurons caused abnormalities in identifying different textures and in touch sensitivity. By recording electrical activity in brain cells that lacked *Mecp2* or *Gabrb3*, the researchers determined that the abnormal touch sensitivity was due to abnormal electrical signals between sensory neurons. Surprisingly, when the researchers restored *Mecp2* in just the sensory neurons, the hypersensitivity to touch and aversion to texture was normalized.

Finally, the researchers observed behavioral changes after deleting *Mecp2* or *Gabrb3*. They found that mice lacking either gene displayed anxiety-like behavior, such as an aversion to exploring their environment. The mice also showed impaired social behavior with other mice in a social interaction test. Interestingly, deletion of these genes during developmental stages, but not during adulthood, resulted in increased anxiety and decreased social interactions. Again, restoring expression of *Mecp2* normalized the anxiety behaviors and social interactions.

Together, these results indicate that, in mice, the ASD-linked genes *Mecp2* and *Gabrb3* affect touch sensitivity, and that touch sensitivity may be linked to other ASD traits, such as anxiety and social interaction deficits.

Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism
Parikshak NN, Swarup V, Belgard TG, Irimia M, Ramaswami G, Gandal MJ, Hartl C, Leppa V, Ubieta LT, Huang J, Lowe JK, Blencowe BJ, Horvath S, Geschwind DH. *Nature*. 2016 Dec 15;540(7633):423-427. [*PMID: 27919067*]

Research shows that ASD is associated with non-typical genetic patterns (an ASD "genomic signature"), but exactly how genes influence biological and behavioral outcomes in ASD is not well understood. This study aimed to better understand how genetic expression—the instructions that determine an individual's unique traits and characteristics (also known as a person's phenotype)—is different in the brains of individuals with ASD. The study further investigated how RNA, which is an important molecule in the transcription and translation of genes, might also regulate genetic expression. Post-mortem studies were performed on 48 individuals with ASD and 49 control group individuals to find patterns of genetic expression specific to ASD.

First, the researchers found significant ASD-related differences in genetic expression in the cortex, the region of the brain important for higher functioning such as language, memory, and learning. In this region, 584 genes had higher expression and 558 genes had lower expression in individuals with ASD as compared to the controls. The degree of difference in genetic expression between individuals with ASD and the control group likely reflects how significantly a particular gene influences phenotype. The genes that had higher expression levels in subjects with ASD were largely present in microglia and astrocytes, which are non-neuronal cells in the central nervous system responsible for regulation and maintenance of neurons. The genes that had lower expression levels in individuals with ASD were largely genes that are specifically expressed in neurons, the brain cells responsible for transmitting and receiving information.

The researchers also determined differences in long noncoding RNAs (lncRNAs), which do not result in expression of a specific protein, but do affect how other genes are expressed. Interestingly, they found differences in 60 lncRNAs in individuals with ASD as compared to the controls. They further found that abnormal regulation of expression and function of lncRNAs is an important component of the ASD genomic signature. Two specific lncRNAs were identified that have decreased expression during development in controls, but increased expression in ASD.

Next, the researchers examined differences in alternative splicing, a regulatory process of gene expression that can result in one gene coding for multiple proteins based on how the RNA sequence is "trimmed." They found differences in alternative splicing in the cortex of subjects with ASD, which results in the removal of parts of genes that would normally be expressed in neurons.

Additionally, the researchers examined differences in gene expression between the frontal and temporal regions of the cortex. They found 523 genes with differences in expression between the two regions in the control group, but no significant expression differences between regions in the ASD group. This suggests that reduced differences in gene expression across brain regions contribute to the ASD genomic signature.

Together, these data improve our knowledge of the genetic pathways that underlie ASD and indicate that different genetic patterns and pathways may ultimately result in the complex effects of ASD.

Gene expression in human brain implicates sexually dimorphic pathways in autism spectrum disorders
Werling DM, Parikshak NN, Geschwind DH. *Nat Commun.* 2016 Feb 19;7:10717. [*PMID: 26892004*]

ASD is more common in males than females, and there are two theories that may provide a biological basis for the difference in prevalence. Given that many genes in the human genome are expressed differentially in males and females, one possibility is that genes associated with ASD (ASD-risk genes) are among the many genes that are differentially expressed based on sex. The other possibility is that the expression of ASD-risk genes is the same between males and females, but that ASD-risk genes interact with sex-specific genes or biological pathways to determine an ASD outcome. In this study, researchers investigated the interaction between ASD-risk genes and sex-specific genes to distinguish between these two possibilities.

First, the researchers analyzed pre-existing data of genomic expression in male and female adult and prenatal brain tissue. They focused specifically on the cerebral cortex, the region of the brain important for complex functions such as learning and language, as this brain region has been shown to have elevated expression levels of ASD-risk genes. Using both adult and prenatal tissue allowed the researchers to identify genes that are differentially expressed based on sex, as well as ASD-risk genes that are typically expressed during development.

When comparing gene expression between male and female adult tissue, the researchers found no known ASD-risk genes that are differentially expressed between males and females. They considered the possibility that a difference may be more evident during development, but when comparing gene expression from prenatal tissue samples, they again saw no difference between males and females. These results suggest that the increased risk of ASD in males is not due to differential expression of known ASD-risk genes between males and females.

Next, the researchers tested the possibility that genes that are abnormally regulated in ASD are differentially expressed in males and females. When comparing gene expression in adult cortex, they found that 67% of genes that are known to have increased expression in ASD are present at higher levels in males than in females. Among these are genes that regulate the function of astrocytes and microglia, which are involved in the development and maintenance of neurons. In contrast, they found that some genes that typically have lower expression in ASD were present at higher levels in females than in males. Among these are genes that are involved in regulation of neural synaptic function. That these genes, which are commonly down-regulated in ASD, are up-regulated in females, suggests that there may be ASD-protective mechanisms in the female genome.

The results from this study support the theory that the difference in prevalence of ASD in males and females is not due to sex-specific differences in ASD-risk genes, but instead due to differences in the way ASD-risk genes interact with sex-specific genes. These differences may ultimately affect the relationships among neurons, astrocytes, and microglia to skew prevalence of ASD towards males.

QUESTION 3

WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Effect of co-twin gender on neurodevelopmental symptoms: a twin register study

Eriksson JM, Lundström S, Lichtenstein P, Bejerot S, Eriksson E. *Mol Autism*. 2016 Jan 19;7:8. [*PMID: 26793297*]

There is a higher prevalence of ASD and attention-deficit/hyperactivity disorder (ADHD) in males than females. There is evidence of significant heritability in both ASD and ADHD, but there are also thought to be significant environmental factors involved in risk of diagnosis. For instance, past research suggests that exposure to high levels of testosterone in the womb may increase the risk for development of ASD and ADHD. Therefore, this study sought to better understand whether testosterone produced from a male twin fetus could lead to increased exposure to testosterone by the co-twin, theoretically increasing the other twin's risk for ASD or ADHD.

To investigate the role of exposure to elevated prenatal testosterone levels in the risk for ASD or ADHD, the researchers assessed ASD and ADHD traits in fraternal female-female, female-male, and male-male twin-paired children to determine whether the presence of a male co-twin increased the likelihood of development of ASD and ADHD. The researchers used data from the Child and Adolescent Twin Study in Sweden (CATSS). The population consisted of 4,219 male-female, 1,808 female-female, and 2,129 male-male twin pairs at either 9 or 12 years old. They assessed ASD and ADHD traits using the Autism-Tics, AD/HD, and other Comorbidities inventory (A-TAC), which is a parent interview conducted by telephone. The A-TAC tests for many traits related to ASD and ADHD, such as language, social interaction, behavioral flexibility, impulsiveness/activity, and concentration/attention.

In contrast to the hypothesis that having a male co-twin would increase the likelihood of developing ASD and ADHD, twins with a female co-twin actually had higher scores on the A-TAC, reflecting a greater number of ASD and ADHD traits than twins with a male co-twin. When breaking down the scores by trait, the scores were higher in twins with a female co-twin in attention/concentration for ADHD, and in flexibility in thought, social interaction, and abnormal sensory reactivity for ASD.

One interpretation of these results is that there may be an *in utero* protective effect for girls with a male co-twin. However, it is important to also consider reporting biases when interpreting these results. Since the scores were based on parent interviews, there may be underreporting of ASD and ADHD traits in female twins due to commonly existing differences between male-female twin pairs. However, the finding that having a female co-twin slightly increases the risk of displaying ASD and ADHD traits challenges our current understanding of these disorders.

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

Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders

Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, Suominen A, Gyllenberg D, Chudal R, Leivonen S, Gissler M, Brown AS, Sourander A. *JAMA Psychiatry.* 2016 Jun 1;73(6):622-9. [PMID: 27145529]

Research has shown that there is a "clustering" effect of diagnoses within families that have a child with ASD. For instance, a child with ASD is at greater risk for a co-existing psychiatric diagnosis such as schizophrenia, bipolar disorder, anxiety, and affective disorders, as well as other diagnoses such as intellectual disability or pervasive developmental disorder. Research has also shown increased risk of ASD in children whose parents have a psychiatric diagnosis. However, there had been no previous study comprehensively investigating the relationship between a diagnosis of ASD in one child and a sibling's diagnosis of a psychiatric or other neurodevelopmental disorder.

In this study, researchers used data from three Finnish nationwide registers (the Finnish Hospital Discharge Register, the Finnish Medical Birth Register, and the Finnish Population Register Centre) to determine the rates of psychiatric and neurodevelopmental disorders among individuals who have a sibling with ASD. They looked at data from two groups: 1) 3,578 children with ASD and their 6,022 siblings and 2) 11,775 typically developing children and their 22,127 siblings.

The researchers found that 36.9% of children with ASD had at least one sibling who had been diagnosed with at least one neurodevelopmental or psychiatric disorder, as compared to only 17.4% of typically developing children. This association was strongest for childhood-onset disorders, with 29.7% of children with ASD having a sibling with at least one childhood-onset disorder, as compared to 11.6% of typically developing children. The most common childhood-onset disorders in siblings of children with ASD were ASD (10.5% versus 1.1% of typically developing children), learning and coordination disorders (15.7% versus 5.9%), attention-deficit/hyperactivity disorder (5.3% versus 1.5%), and conduct and oppositional disorders (5.0% versus 1.9%). Of the children diagnosed with a disorder, siblings of children with ASD were in general more likely to be diagnosed with a neurodevelopmental or psychiatric disorder at a younger age than siblings of typically developing children. There was no difference in this increased risk between male and female siblings.

These results show that a sibling of a child with ASD is more likely to be diagnosed with a psychiatric or neurodevelopmental disorder than a sibling of a typically developing child. One interpretation is that parents of a child with ASD may be more aware of signs and symptoms of these disorders. They may also be more likely to seek help for their other children, and seek it earlier, than parents without experience with ASD.

These results also suggest there may be a significant hereditary component to ASD, psychiatric, and neurodevelopmental disorders. However, there may also be shared environmental risk factors such as psychological stress within the family due to the challenges associated with ASD. Professionals who work with families of children with ASD should be aware of this increased risk and educate towards earlier diagnosis and intervention.

Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder

Zerbo O, Qian Y, Yoshida C, Fireman BH, Klein NP, Croen LA. *JAMA Pediatr.* 2017 Jan 2;171(1):e163609. [Available online November 28, 2016] [*PMID: 27893896*]

Maternal infection and fever during pregnancy activates an immune system response that may be associated with complications or abnormalities in offspring, such as preterm birth and low birth weight. Accordingly, pregnant women are encouraged to get vaccinated against influenza, a common infection, to decrease the risk of these complications. Despite numerous investigations of maternal infection and ASD, there has been no conclusive evidence of an association. However, no studies had been previously conducted on maternal influenza vaccination during pregnancy and risk for ASD.

The goal of this study was to better understand whether or not there is a relationship between maternal influenza vaccination and development of ASD. The population for the study was 196,929 children born at Kaiser Permanente Northern California from January 1, 2000 to December 31, 2010, from a gestational age of at least 24 weeks to a follow-up time between 2 and 15 years of age. Data on maternal vaccination, maternal influenza infection, and pediatric ASD diagnoses were obtained from electronic medical records. The researchers accounted for confounding variables (variables that researchers are unable to control) such as gestational age, maternal age, maternal pre-pregnancy body mass index, maternal race/ethnicity, and other maternal health conditions. Four time periods were investigated: first trimester, second trimester, third trimester, and anytime in the pregnancy.

The researchers found no association between risk of ASD and maternal influenza vaccination or maternal influenza infection across the entire pregnancy. When considering each trimester separately, there was a weak association between maternal influenza vaccination during the first trimester and ASD risk—a finding likely due to chance, but potentially warranting future study. Since this study found no significant increased risk of ASD with influenza vaccination, the researchers suggest that no changes to influenza vaccination recommendations should be made at this time.

QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Studies estimate that 25-30% of children with ASD who engage in communication interventions will not achieve spoken communication. Failure to develop spoken language by school-age increases the likelihood of poor long-term outcomes in social functioning. Timing of effective communication intervention is also critical, as there is a developmental window for children to develop communication skills.

Because there is high variability between minimally verbal children with ASD, the progress that each child makes in response to treatment will be different. Treatment that can be adjusted based on the progress of the child is critical for maximizing the effectiveness of the intervention. Therefore, it is important to determine long-term outcomes across different combinations of communication interventions.

In this randomized study of 61 minimally verbal 5- to 8-year-old children with ASD, researchers compared the effectiveness of three adaptive communication interventions over time. All children received joint attention, symbolic play, engagement, and regulation (JASP—a naturalistic developmental behavioral intervention that has been shown to improve social communication outcomes) with enhanced milieu training (EMT—a spoken-language intervention).

A major concern in this field is whether speech generating devices (SGDs) help or hinder progress in communication in this population. Therefore, one component of this study tested JASP+EMT with and without the use of SGDs. To better understand how to accommodate differences in treatment response, another component of this study tested an intensified intervention for children who show a slower response to the treatment.

Each intervention was 24 weeks long and occurred in two stages, as follows:

Intervention 1 (No SGD, No SGD):

    Stage 1 – JASP+EMT

    Stage 2 – (Responders) Continued JASP + EMT

        – (Slow Responders) Intensified JASP+EMT

Intervention 2 (No SGD, SGD):

    Stage 1 – JASP+EMT

    Stage 2 – (Responders) Continued JASP+EMT+SGD

        – (Slow Responders) Intensified JASP+EMT+SGD

Intervention 3 (SGD, SGD):

    Stage 1 – JASP+EMT+SGD

    Stage 2 – (Responders) Continued JASP+EMT+SGD

        – (Slow Responders) Intensified JASP+EMT+SGD

The researchers measured communication skills by verbal outcomes (the total number of spontaneous communicative utterances and the number of different word roots) and nonverbal outcomes (using eye contact or gestures to alert another child to pay attention to an object or request something). For each intervention, all children participated in Stage 1 for the first 12 weeks. If a participant was responsive (improved by 25% or more from baseline scores on verbal and nonverbal communication tests) in the first 12 weeks, they continued with the intervention through Stage 2. If a participant was slow to respond to the Stage 1 intervention, they progressed to an "intensified" treatment (one additional treatment session per week) for Stage 2.

The third intervention, which included SGD in both stages, proved to be the most effective intervention across all outcome measures, showing significant improvement in spontaneous spoken and non-spoken communication. The enhanced effect of adding SGD to the intervention was seen in both the early-responding and the slower-responding groups of children. In addition to improved communication outcomes, the children demonstrated an increased desire to engage in communication during intervention sessions.

These data indicate that SGDs in combination with a development-based behavioral intervention can significantly improve social communication skills in minimally verbal children with ASD. Over time, this improved outcome may positively impact further gains in social functioning.

Early intervention for social and communication skills is important for children with ASD. Most preschool-age children with ASD are taught in public preschools, where they can receive educational and small group support. Although public preschool teachers are provided with strategies to support children with ASD, they often lack specific training for social communication skills, and may have inadequate skills for this developmentally critical intervention.

Social communication skills include joint attention and engagement (the ability to draw another person's attention to and engage them in an object of shared interest), language skills, and play skills. There has been some evidence that social communication can improve with one-on-one programs, in which the teacher engages directly with only one student. However, one-on-one programs may not be feasible in a public classroom setting, where teachers are typically able to support children with ASD in small groups only.

This study tested the effectiveness of a modified training program for the small group social communication program called JASPER (Joint Attention Symbolic Play Engagement and Regulation). Sixty-six 3- to 5-year-old children with ASD were divided into 12 classrooms. Classrooms were randomized across two groups of children: 1) a group that received an immediate treatment (IT) of JASPER upon entry to the classroom, and 2) a control group that was waitlisted (WL), placed in the usual preschool curriculum, and received JASPER 4 months later. Outcome measures were taken on teachers and students at three time points (at entry into the program, after 2 months of use, and at a 1-month follow-up). Student assessments measured standard social communication, interaction, and play. Teacher assessment included measures to ensure that they were correctly implementing the interventions.

The researchers had three goals: 1) to determine whether children in the IT group showed greater improvement in social communication and engagement skills than children in the WL group; 2) to determine whether children in the IT group would show greater improvement in cognitive and language tests than children in the WL group; and 3) to determine if the modified small group program could be effectively implemented in a classroom setting.

As compared to children in the WL group, children in the IT group showed improvement in initiating social communication and making requests to engage with teachers and children, as measured by the number of times children used phrases such as "Let's play" or "I want block." Children in the IT group also showed improvement in use of spontaneous words or phrases, engaged in more complicated forms of play, and increased their use of two- to three-word utterances, as compared to the WL group. Teacher outcomes indicated that trained teachers maintained reliable and effective delivery of JASPER over time.

The results of this study indicate that social engagement interventions such as JASPER can be successfully adapted for small groups within a public school setting. Teachers who are provided with the proper training can effectively implement JASPER so that children with ASD in public preschools can receive much-needed social communication intervention.

Intervention effects on spoken-language outcomes for children with autism: a systematic review and meta-analysis

Hampton LH, Kaiser AP. *J Intellect Disabil Res*. 2016 May;60(5):444-63. [*PMID: 27120988*]

Spoken-language delays are common in children with ASD, but studies that investigate the effect of early intervention on ASD symptoms often do not address the effect of intervention on language deficits. However, some research has indicated that early interventions that target play and joint attention skills can improve language outcomes.

The two main types of spoken-language interventions are "targeted" and "comprehensive." Targeted interventions focus on teaching pre-linguistic and communication skills, while comprehensive interventions teach a broad set of skills that are related to the development of spoken-language skills. Both targeted and comprehensive interventions may include parent training, and studies suggest that parent intervention may be just as effective in spoken-language development as clinician-based intervention.

This comprehensive review of 26 original research studies of children with ASD who participated in early intervention was conducted to determine if 1) early interventions improve spoken language in young children with ASD, as compared to usual treatments, 2) the amount of intervention affects spoken-language outcome, 3) adding parent training helps improve spoken-language outcome, and 4) spoken-language outcome is affected by other variables such as the age of the participant or the type of intervention (targeted versus comprehensive).

The studies included in this review met the following criteria: all subjects were English-speaking children that were 8 years old or younger, all studies included behavioral interventions but did not include pharmacological interventions, the outcomes of the studies were determined using standardized spoken-language measures, and the studies included a comparison group that did not receive intervention. The review included data from a total of 1,738 participants with ASD. The average age of the participants was 3.33 years old, and 81% of children were male. Most participants had cognitive scores that indicated comorbid intellectual disabilities. Interventions included direct teaching components and naturalistic teaching components.

Overall, children with ASD improved in spoken-language skills after intervention for ASD symptoms. Of the interventions included, 38% of the studies used parent-guided treatment, 15% of the studies used clinician-guided treatment, and 47% of the studies used treatment that involved both parents and clinicians. Interventions that included both clinicians and parents were more effective than interventions that included only clinician or only parent.

Analyzed together, these studies indicate an improvement equivalent to a 4-point increase on a standard language measure immediately following intervention, and an additional 6-point increase for children that received intervention from both the parent and the clinician, compared to children that received a community intervention.

It is important to note that improvement across these studies is demonstrated for single-word language use but has not been demonstrated for more complex language. In addition, the studies included in this analysis did not

include a long-term follow-up, so it is not known whether these effects can be sustained. Improvements in spoken language did not seem to increase with dose of therapy, nor were they dependent on the type of therapy (targeted versus comprehensive).

The main limitation of this comprehensive review is there was not a lot of variability in the degree of intellectual disabilities among the children included in the studies. Therefore, no conclusion can be made about the effect of intervention on spoken-language skills across a range of intellectual disabilities. As a result of the analysis across studies, the researchers propose that 1) both parents and clinicians should be involved in interventions for the greatest benefit, 2) long-term intervention may be needed to maintain the benefit in spoken-language skills, and 3) targeted and comprehensive interventions are equally effective and both can be used to improve spoken language in children with ASD.

Children with autism spectrum disorder and social skills groups at school: a randomized trial comparing intervention approach and peer composition

Kasari C, Dean M, Kretzmann M, Shih W, Orlich F, Whitney R, Landa R, Lord C, King B. *J Child Psychol Psychiatry*. 2016 Feb;57(2):171-9. [*PMID: 26391889*]

Children with ASD often struggle to form relationships with their peers, which can impede their ability to form and interact within social networks. Typically developing children form relationships based on propinquity (the tendency to develop friendships with those in close proximity) and homophily (the connection made from shared characteristics such as gender, cultural background, and common interests). Children with ASD, though close in proximity to their classmates, are often isolated as being the only child with ASD. Therefore, even with propinquity acting in their favor, the lack of homophily can present challenges for the development of peer relationships. To address this social development challenge, children with ASD are often enrolled in clinic-based social skills intervention groups, which help children navigate skills such as starting and maintaining a conversation and choosing appropriate friends. However, the clinic-based group setting is not often generalizable to the real world, and the social skills they develop in the clinic may not translate to the school setting, where those skills would have the most impact. Therefore, social skills interventions performed in a school setting may be the most effective way to help children with ASD develop peer relationships.

The goal of this randomized study was to compare two social skills interventions adapted for a school setting, and to compare group composition (children with ASD only versus children with ASD and typically developing children combined). Children ranging from kindergarten to fifth grade participated in either a SKILLS or an ENGAGE intervention program over an 8-week period. The SKILLS intervention was made up of only children with ASD. The SKILLS intervention (a lesson-based approach most likely to be used in a clinical setting) was led by an adult instructor at the school. Children with ASD received a set of interactive lessons on social skills, such as how to handle teasing, nonverbal language, conversation, and friendship tips. The children also received weekly homework assignments. The ENGAGE intervention was randomized to include both children with ASD and typically developing children from the same classroom, and was designed to help children with ASD model friendship-promoting behaviors. In this child-led intervention, the children worked together to set up a daily schedule and engaged in activities that included conversational exercise, structured games, free play, storytelling, and music. Both interventions were evaluated using The Friendship Survey, a questionnaire that students completed before the intervention, at the end of treatment, and 6-8 weeks after the intervention, to assess the children's friendships and social networks. The researchers also recorded playground observations using the Playground Observation of Peer Engagement tool and "friendship nominations" (the number of times a child with ASD nominated friends and the number of times a classmate nominated a child with ASD as a friend) to determine the extent of their social networks.

The researchers found that on average, both groups showed increased amounts of time spent engaging with other children on the playground. Surprisingly, the SKILLS group more significantly increased time spent with other children and decreased time spent in isolation than the ENGAGE group. The researchers also found that the two interventions benefitted children differently based on their level of behavioral problems and their closeness with their teacher. The SKILLS intervention more greatly benefited children with high behavioral problems and low teacher-child closeness, while the ENGAGE intervention benefitted children with high teacher-child closeness. There was no significant change in friendship nominations as a result of these interventions, suggesting no change in social networks. However, this could be due to the fact that both interventions brought together children from different classrooms, but friendship nominations were only allowed to be made between children of the same classroom.

These results suggest that an adult instructor-based intervention may be most effective in a school setting. This is likely because the SKILLS intervention provided more concrete and direct instruction than the indirect activities in the ENGAGE intervention. Also, by bringing children from different classrooms together and by including only children with ASD in the intervention groups, the SKILLS intervention better met both the propinquity and homophily criteria for relationship development. However, a child with ASD who has fewer behavioral issues and higher closeness to the teacher may benefit from an ENGAGE approach to building social skills.

Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial
Pickles A, Le Couteur A, Leadbitter K, Salomone E, Cole-Fletcher R, Tobin H, Gammer I, Lowry J, Vamvakas G, Byford S, Aldred C, Slonims V, McConachie H, Howlin P, Parr JR, Charman T, Green J. *Lancet.* 2016 Nov 19;388(10059):2501-2509. [*PMID: 27793431*]

Early intervention is important for reduction of symptoms in children with ASD. Previous studies of early interventions have been limited to short-term follow-up periods, and it is not known if the effect of early intervention is maintained throughout childhood. It is therefore important to study the long-term effectiveness of a parent-mediated social intervention for children with ASD.

PACT (Preschool Autism Communication Trial) is a 1-year social communication intervention for preschool-age children with ASD. PACT consists of 12, 2-hour therapy sessions over 6 months, followed by 6 months of monthly support sessions. In addition, the program includes 20-30-minute parent-led daily activity sessions. In this randomized controlled study, researchers compared outcomes of children with ASD who participated in the PACT program against children with ASD who received treatment as usual.

The children were assessed for the severity of ASD symptoms, parent-child communication, and language skills at three time periods: before the intervention, at the end of the intervention, and at a 6-year follow-up. At the end of the intervention, children who participated in PACT showed significantly greater improvement in ASD symptom severity than the children who received treatment as usual. In addition, children who participated in PACT also showed a greater tendency to initiate parent-child communication, which led to improved communication in general. Notably, this improvement in ASD symptom severity and parent-child communication was sustained over the long-term through the 6-year follow-up. There was no difference in language skills between the two groups.

This is the first study to show long-term effects of a naturalistic developmental intervention for social communication. The researchers proposed that the long-term effect of PACT was due in part to the promotion of parent-child social communication at home, a setting where much of social learning occurs.

Brain responses to biological motion predict treatment outcome in young children with autism
Yang D, Pelphrey KA, Sukhodolsky DG, Crowley MJ, Dayan E, Dvornek NC, Venkataraman A, Duncan J, Staib L, Ventola P. *Transl Psychiatry.* 2016 Nov 15;6(11):e948. [PMID: 27845779]

Early intervention is critical for improvement of ASD symptoms. However, the constellation of ASD symptoms is complex and diverse across individuals, therefore an intervention that is effective for one person may not be effective for another. Time invested in the wrong treatment may be time wasted, especially during developmentally critical periods. A theoretical solution would be to identify unique markers of biological activity that could predict whether a child would likely respond to a given treatment. This would allow clinicians to identify effective treatments more accurately and efficiently.

Neuroimaging techniques, which allow for visualization of brain activity, have identified brain circuits involved in the social processes that are often altered in ASD. For example, previous studies have identified neural circuits involved in social reward and motivation, social attention and action observation, and social perception. In this study, researchers used a neuroimaging technique called functional magnetic resonance imaging (fMRI), a technique that measures blood oxygen level-dependent (BOLD) response to behavior. The BOLD response is measured on the premise that blood oxygen levels are higher in active parts of the brain. The researchers measured the BOLD response to identify brain areas that are active while observing a filmed presentation of social situations to predict how children with ASD would respond to behavioral intervention. The average age of the children with ASD was 6 years old.

The behavioral intervention used in this study was a 16-week pivotal response treatment (PRT)—a naturalistic, behavior-based approach designed to increase social motivation. The treatment consisted of 7 hours of treatment per week, 5 of which involved direct work with the child and 2 of which consisted of parent training. Tasks involved play-based activities between parent and child to reinforce social behaviors such as social initiation and responsiveness to social cues.

The researchers used a battery of clinical assessments and an fMRI task to determine a baseline before the intervention and any change after the treatment. The battery of clinical assessments included the parent-reported Social Responsiveness Scale (SRS), the Clinical Evaluation of Language Fundamentals (CELF), and the clinician-administered Vineland-II, which is a scale that assesses adaptive behavior. During the fMRI scan, the children observed a series of filmed motion displays. These displays consisted of a "point-light stimulus," which is a recording of an adult male actor with lights attached to his major joints, filmed in the dark performing common movements. This motion display paradigm has been well-established in research to engage the brain regions involved in social motivation.

The results of this study show that PRT reduced the severity of ASD symptoms, as measured by the parent-reported SRS. Importantly, the researchers identified key brain areas that showed activity correlated with improvement in ASD symptoms in response to PRT. The researchers also conducted an analysis to identify patterns across different

brain areas that could predict response to the PRT. The patterns of brain activity they found were precise enough to predict response to PRT for the children with ASD.

The key brain areas involved in social information processing were the right posterior superior temporal sulcus (involved in perception of eye gaze, emotion, and biological motion), the fusiform gyrus (face perception), and the right superior parietal lobule (distribution of spatial attention). The brain areas involved in social motivation were the orbital frontal cortex (emotion and memory), putamen (social learning), and ventral striatum (part of the brain's reward system).

These results are important because they suggest that clinicians could potentially pre-screen children with ASD to predict whether a treatment such as PRT would be effective in reducing ASD symptoms before treatment occurs. This would allow for more efficient intervention during the critical time window in early childhood to reduce symptoms related to ASD. Moreover, the results provide a roadmap forward to help researchers develop novel ways to help children respond to evidence-based behavioral interventions who otherwise would not respond.

WHERE CAN I TURN FOR SERVICES?

The effects of Medicaid home and community-based services waivers on unmet needs among children with autism spectrum disorder
Leslie DL, Iskandarani K, Dick AW, Mandell DS, Yu H, Velott D, Agbese E, Stein BD. *Med Care.* 2017 Jan;55(1):57-63. [Available online 2016] [*PMID: 27547947*]

Health services for children with ASD can be a significant financial burden on families. Until recently, most ASD intervention and treatment programs were not included in insurance benefits, making it more difficult for children with ASD to access the care they need. To address this service gap, many states provide Medicaid Home and Community-Based Services (HCBS) waivers to expand health service coverage and eligibility for children with ASD. There is considerable variation among states in their eligibility criteria, services covered, and spending limits related to these waivers. It is not well understood whether Medicaid HCBS waivers and their characteristics are associated with reducing this service gap.

The goal of this study was to determine whether HCBS waivers reduced unmet healthcare needs for children with ASD. The researchers obtained data from the 2003, 2007, and 2011 versions of the National Survey of Children's Health (NSCH), which is a telephone-based health survey. The researchers used data from parents with a child age 2 or older and divided this group into those with and without a child with ASD. They also used the survey questions that determined whether the parent felt that the child's medical, dental, and mental health needs were being met. The researchers then obtained information on HCBS waiver programs for each state. The information included the average estimated costs of waiver services per individual, cost limit (maximum cost of services allowed for each person enrolled in the waiver program), and enrollment limit (number of people a waiver would serve).

The study included data from 35 states—11 states that provided HCBS waiver programs specifically for children with ASD and 24 states that did not. Analysis of waiver use from 2003 to 2011 showed that the average estimated cost of services provided through a waiver decreased from $49K to $38K. Across states that provided HCBS waiver programs, the average waiver cost limit increased from $81K to $121K, and the average maximum number of children who could be covered by a waiver decreased from 969 to 907.

The researchers found that children with ASD were significantly more likely than children without ASD to have unmet medical, dental, or mental health needs. The researchers found that access to HCBS waivers was associated with a significant decrease in the rate of unmet health needs for children with ASD in general. However, simply providing a waiver was not enough to reduce unmet health needs. Specific features of the waivers such as higher enrollment limits, lower cost, and higher cost limits significantly reduced the odds of having unmet health needs. The effect of these waiver characteristics on unmet needs was amplified as household income increased. There are some possible explanations for why HCBS waiver use provides a greater benefit to higher income households than lower income households. One possible reason is that children from lower income households are eligible for and covered under standard Medicaid, and the benefits of Medicaid are greater than that which is provided for in HCBS waivers. Another reason is that households with greater income may also have the resources needed to navigate the lengthy process of applying for HCBS waivers. Finally, children with ASD who live in higher income households may more often use private health insurance, which often does not adequately cover ASD services, requiring these families to bridge the service gap with waivers.

This study found that HCBS waivers significantly decreased unmet health needs for children with ASD, especially for children whose families had higher incomes and were less likely to use other Medicaid benefits. HCBS waivers can therefore be an effective strategy for meeting the unmet health needs of children with ASD, but additional efforts are needed to develop resources and supports that will enable lower income families of children with ASD to fully benefit from the waivers.

Effects of autism spectrum disorder insurance mandates on the treated prevalence of autism spectrum disorder
Mandell DS, Barry CL, Marcus SC, Xie M, Shea K, Mullan K, Epstein AJ. *JAMA Pediatr*. 2016 Sep 1;170(9):887-93. [*PMID: 27399053*]

The cost of healthcare for children with ASD is significantly higher than that for typically developing children. In the past decade, many states have enacted mandates that require commercial insurance plans to cover ASD-related treatments. Insurance companies have argued that the treated prevalence of ASD—the number of individuals diagnosed with ASD being treated in the healthcare system—will increase with this mandated coverage, thereby increasing cost to the insurance company.

The goal of this study was to determine whether insurance mandates to cover ASD did in fact increase the number of children diagnosed with ASD. This study used observational data from health insurance claims for children 21 years old and younger from UnitedHealthcare, Aetna, and Humana to determine if insurance mandates for ASD increased the number of individuals who had at least one healthcare service claim associated with a diagnosis of ASD. Additionally, the researchers gathered detailed information about state-specific insurance mandates from the advocacy organization Autism Speaks, as well as original state mandate laws to verify when the mandate was enacted and its specific provisions for ASD services.

The researchers found that the treated prevalence of ASD did increase in states that had enacted ASD insurance mandates. The monthly treated prevalence of ASD was 1.8 per 1,000 children in states with ASD mandates, compared with 1.6 per 1,000 children in states without ASD mandates. The treated prevalence increased by approximately 10% at the beginning of insurance mandate use and increased to 18% after mandates had been in effect for 3 years, suggesting that there was some lag time between policy implementation and its active use.

During this study period, implementation of insurance mandates for ASD services was associated with an increased prevalence of children with ASD receiving treatment through private insurance. However, the increased treated prevalence was still well below the estimated community prevalence of ASD, suggesting that some children with ASD are still not getting the services they need. The implementation of insurance mandates for ASD may not have raised cost of ASD services as significantly as feared by insurance companies. But this study suggests that additional efforts are needed to further improve the ability for all children with ASD to access the services they need.

Sociodemographic disparities in intervention service utilization in families of children with autism spectrum disorder
Nguyen CT, Krakowiak P, Hansen R, Hertz-Picciotto I, Angkustsiri K. *J Autism Dev Disord*. 2016 Dec;46(12):3729-3738. [*PMID: 27639855*]

Between the years 2000 and 2012, the prevalence of ASD has increased from 1 in 150 to 1 in 68 children. Research indicates that early intervention leads to better outcomes, but 9 in 10 children are not fully utilizing intervention services, even though provision of these services is mandated by the Individuals with Disabilities Education Act (IDEA). Children with ASD who do receive intervention access these services either through classroom-based or individual programs. However, the barriers that families face in fully utilizing these services are not well understood. In this study, researchers sought to understand whether certain sociodemographic factors contribute to how families use ASD intervention services.

The researchers investigated the following demographic factors: maternal race/ethnicity, maternal education, primary language spoken at home, and insurance type. Data was collected about families from the Child Autism Risks from Genetics and the Environment (CHARGE) Study, an ongoing study in California that aims to identify genetic and environmental contributions to ASD. In the CHARGE study, participants were interviewed over the phone to gather demographic information. In a follow-up in-person visit, the CHARGE researchers assessed children to confirm an ASD diagnosis, and administered a language questionnaire to determine the primary language spoken at home. Physicians also administered an in-person interview to determine intervention and service utilization for the child.

The researchers found that all of the studied demographic factors were associated with differences in ASD intervention use. One significant finding was that black mothers enrolled their children with ASD into a classroom-based program about a half-year earlier than white mothers. There are a few possible explanations for this difference. First, children of white mothers may have received individual services at an earlier age, thus delaying entry into a classroom program. Second, black mothers may have sought classroom-based programs earlier to better manage their employment situations. Third, children of black mothers may have received a developmental delay or behavioral disorder diagnosis at an earlier age, allowing their children to access classroom-based services sooner.

Language was also a factor in accessing ASD services. Children with ASD whose primary language at home was not English entered a classroom-based program at an age of about 3 months older than children whose primary language was English. Three months represents a significant one-third of a school year, suggesting that children whose primary language is not English may fall significantly behind in school due to lack of service support. Additionally, Hispanic families were more likely to not receive individual ASD services at all—a finding that may also be a result of language barrier implications.

Finally, insurance type was a significant factor in how ASD services were used. The researchers found that children of families with public insurance used significantly fewer hours per week in individual services than children in families with private insurance. This finding aligns with past research showing that families in lower income brackets are less likely to use specialized health services, even when those services are made available to families with public insurance. This disparity may result from not being aware that these services are available to them or because their access to these services would result in lost wages and other costs.

This study found that certain demographic factors can negatively impact how families access ASD services. To address these disparities, programs can increase their education and outreach efforts to target families who use public insurance or who have lower household incomes. Outreach efforts can also focus on cultural diversity to promote community support and increase awareness about available services. In addition to outreach and education, case management support can be increased to support families who have language barriers and may be unaware of available programs.

QUESTION 6

WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

Premature mortality in autism spectrum disorder
Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S. *Br J Psychiatry*. 2016 Mar;208(3):232-8. [*PMID: 26541693*]

Past research suggests that individuals with ASD have a higher risk of premature mortality, but the specific factors that impact this risk are unclear. Individuals with ASD often have co-occurring medical conditions, such as seizures and intellectual disabilities, which may be associated with increased risk of premature mortality. Further, previous studies have found that females with ASD have a higher risk of mortality than males with ASD. The goal of this study was to understand the causes of mortality in individuals with ASD and determine the impact of gender and intellectual ability on mortality rate.

To conduct this study, the researchers compared causes of mortality in both the general population and in the ASD population. They also compared mortality in high- and low-functioning ASD to assess the effect of intellectual disability. Their data sources were Swedish population-based registers (the National Patient Register and the Cause of Death Register), which included 2,672,185 individuals from the general population and 27,122 individuals with ASD.

The researchers found that the death rate in the ASD population was greater than in the general population. In the time period studied, 0.9% of people in the general population had died, compared to 2.6% of people in the ASD population. The average age of death for the ASD population was 53.87 years, compared to 70.20 years in the general population. When comparing low- and high-functioning individuals with ASD, the researchers found that the age of death was significantly different between the two (39.5 years of age for low-functioning ASD, compared to 58.39 years for high-functioning ASD).

Compared to the general population, the death rate for individuals with ASD was significantly elevated for all categories of cause of death except for infections. The largest differences between the two groups were deaths caused by diseases of the nervous system and suicide. Low-functioning individuals with ASD had higher mortality rates than did high-functioning individuals with ASD for all causes of death, except for suicide. This result was

consistent with previous data that suggest that individuals with high-functioning ASD have a high rate of suicide. In low-functioning individuals with ASD the most common cause of death was epilepsy.

When comparing across gender, the researchers found that the rates of death were comparable between males and females with ASD for most causes of death; however, there were some differences. The risk of dying from diseases of nervous and circulatory systems was higher in males with ASD than in females with ASD. Endocrine diseases, congenital malformations, and suicide were more common in females with ASD. When comparing differences between gender across low- and high-functioning groups, the mortality rate for low-functioning females with ASD was particularly high.

Together, these results indicate that biological health and medical care access may make individuals with ASD more vulnerable to premature death. Education and awareness programs to help individuals with ASD identify and seek help for co-occurring medical conditions and suicide risk are warranted.

Effects of an employer-based intervention on employment outcomes for youth with significant support needs due to autism
Wehman P, Schall CM, McDonough J, Graham C, Brooke V, Riehle JE, Brooke A, Ham W, Lau S, Allen J, Avellone L. *Autism*. 2016 May 5. [Epub ahead of print] [*PMID: 27154907*]

High school graduates with ASD often have difficulty finding and keeping employment, which can have a significant impact on quality of life and independence. Additionally, individuals with ASD have higher rates of underemployment and unemployment than similar disability populations. The goal of this study was to develop and test an employment training intervention to help high school graduates with ASD succeed in post-graduate employment.

The training model used in this study was a modified version of Project SEARCH (Project SEARCH plus Autism Spectrum Disorder Supports; PS-ASD), an intensive job training program for young adults with developmental disabilities. To modify Project SEARCH to PS-ASD, the researchers embedded applied behavior analytic (ABA) techniques. These included teaching multistep tasks, demonstrating self-management for behavioral challenges, and increasing training for specific communication skills. The trainers also helped students with understanding statements that are common in the workplace, but may not be intuitive for individuals with ASD, such as "act professional" and "take the high road" by first defining and then demonstrating their meanings.

The researchers compared the ability to find and keep a job across high school students with ASD enrolled in PS-ASD and high school students with ASD enrolled in typical special education services. The study included 49 students with ASD at ages 18-21. The main outcome measure in this study was the Support Intensity Scale (SIS), an interview that measures the amount of support an individual needs across home living, community living, lifelong living, employment, health and safety, and social skills. The SIS interview was conducted at four times throughout the study (at the start of the program, at graduation, at 3 months, and at 12 months following graduation), from which researchers compiled a Support Needs Index (SNI) score for each student.

At 3 months after graduation, 90% of the students who participated in the PS-ASD program had acquired part-time jobs and 87% of those students kept their jobs for 12 months after graduation. In contrast, at 3 months after graduation, only 6% of the students who participated in the special education program acquired jobs and only 12% had found jobs at 12 months after graduation. In addition, students in the PS-ASD group acquired more independence than the students in the special education program, as evidenced by SNI scores as the study progressed.

The results of this study show promising evidence in support of an employment training intervention tailored to the unique needs of students with ASD. Improved employment outcomes and independence would provide a significant positive impact to young adults with ASD as they transition from high school.

QUESTION 7

WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012
Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Lee LC, Pettygrove S, Robinson C, Schulz E, Wells C, Wingate MS, Zahorodny W, Yeargin-Allsopp M. *MMWR Surveill Summ.* 2016 Apr 1;65(3):1-23. [*PMID: 27031587*]

Ongoing efforts to monitor the prevalence of ASD are important to substantiate the need for service and treatment programs, identify vulnerable populations, justify increased funding, and support new policies. The Autism and Developmental Disabilities Monitoring (ADDM) Network is a group of programs funded by the Centers for Disease Control and Prevention (CDC) to monitor the prevalence and characteristics of ASD in 8-year-old children (the age by which most children have been diagnosed). The ADDM Network tracks data from 11 communities in the United States that represent the diversity of children with ASD across the country. The ADDM Network recently published their 2012 report, which describes the number and characteristics of children with ASD, including the specific types of ASD diagnoses, the number of children with ASD who have intellectual disabilities based on standardized tests, and the frequency of early ASD diagnoses. To identify the population, the ADDM researchers first reviewed records to assess whether children had received education or healthcare services related to developmental disabilities. Then, clinical experts evaluated those records to determine if children met ASD diagnostic criteria. ASD criteria for this report was established using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).

Across the ADDM Network in 2012, 5,063 children met DSM-IV-TR criteria for autistic disorder, pervasive developmental disorder–not otherwise specified (PDD-NOS), or Asperger disorder. The overall estimated ASD prevalence in 8-year-old children was 14.6 children per 1,000 children (1 in 68 children). Prevalence was 4.5 times higher in boys (23.6 per 1,000) than in girls (5.3 per 1,000). The prevalence of ASD was higher for non-Hispanic white children (15.5 per 1,000) than for non-Hispanic black children (13.2 per 1,000), Asian/Pacific Islander children (11.3 per 1,000), and Hispanic children (10.1 per 1,000). The estimated prevalence varied among study sites, with significantly higher prevalence at sites that reviewed both health and education records. The prevalence of ASD

with intellectual disability was 4 in 1,000 and it was 8.7 per 1,000 for ASD without intellectual disability. Combined data across the ADDM Network showed that 74% of children with ASD had records of receiving special education, and 82% of children had a previous ASD diagnosis or a documented eligibility classification of ASD for special education. Forty-three percent of children received a first comprehensive evaluation for early developmental concerns by 36 months of age, while 20% of children were evaluated between 37-48 months of age, and 38% were not evaluated until after 48 months of age. Children with ASD and intellectual disabilities were more likely to receive a comprehensive evaluation by 36 months of age. Non-Hispanic black children and Hispanic children were less likely to have a comprehensive evaluation by 36 months of age than non-Hispanic white children.

CDC suggested several approaches based on the results of this study and in accordance with the U.S. government's *Healthy People 2020* goals for children with ASD. They suggest that efforts be continued to increase the percentage of children with ASD who receive a first evaluation by 36 months and delivery of support services by 48 months. Given that non-Hispanic black and Hispanic children were less likely than non-Hispanic white children to have a first evaluation by age 36 months, the authors encouraged development of targeted strategies to increase awareness and identification of ASD in minority communities. Additionally, there may be differences in the presentation of ASD in girls that require further attention to ensure that all girls with ASD are identified. Given that the estimated prevalence of ASD was higher in areas where both education and health records were used, and that a significant number of children with ASD classification received special education, the researchers also emphasize the important role of schools in enabling early detection. Finally, the authors advise that future evaluation occur to assess for any impact to prevalence of ASD as a result of the revised diagnostic criteria in the fifth edition of the DSM (DSM-5). Continued surveillance of ASD prevalence across the ADDM Network is required to better understand the needs of children with ASD and to target education, outreach, and policy efforts.

ARTICLES SELECTED FOR THE 2016 SUMMARY OF ADVANCES

QUESTION 1: WHEN SHOULD I BE CONCERNED?

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QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Orefice LL, Zimmerman AL, Chirila AM, Sleboda SJ, Head JP, Ginty DD. Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs. *Cell.* 2016 Jul 14;166(2):299-313. [*PMID: 27293187*]

Parikshak NN, Swarup V, Belgard TG, Irimia M, Ramaswami G, Gandal MJ, Hartl C, Leppa V, Ubieta LT, Huang J, Lowe JK, Blencowe BJ, Horvath S, Geschwind DH. Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature.* 2016 Dec 15;540(7633):423-427. [*PMID: 27919067*]

Werling DM, Parikshak NN, Geschwind DH. Gene expression in human brain implicates sexually dimorphic pathways in autism spectrum disorders. *Nat Commun.* 2016 Feb 19;7:10717. [*PMID: 26892004*]

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

Eriksson JM, Lundström S, Lichtenstein P, Bejerot S, Eriksson E. Effect of co-twin gender on neurodevelopmental symptoms: a twin register study. *Mol Autism.* 2016 Jan 19;7:8. [*PMID: 26793297*]

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QUESTION 5: WHERE CAN I TURN FOR SERVICES?

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

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FULL LISTING OF NOMINATED ARTICLES
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