INTERAGENCY AUTISM COORDINATING COMMITTEE

2013

SUMMARY OF ADVANCES

in Autism Spectrum Disorder Research

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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 Combating Autism Reauthorization Act (CARA) of 2011.

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, parents of children and adults with ASD, advocates, service providers, and researchers, 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.

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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INTRODUCTION

THE 2013 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

Each year, the IACC releases its annual list of scientific advances that represent significant progress in the field. The 20 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 United States and internationally, as well as the service needs of people with ASD across the lifespan. The *2013 Summary of Advances* provides short, plain language synopses of the top research breakthroughs selected by the IACC 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*. 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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- Evaluating changes in the prevalence of the autism spectrum disorders (ASDs)

QUESTION 1

WHEN SHOULD I BE CONCERNED?

Effectiveness of developmental screening in an urban setting

Guevara JP, Gerdes M, Localio R, Huang YV, Pinto-Martin J, Minkovitz CS, Hsu D, Kyriakou L, Baglivo S, Kavanagh J, Pati S. *Pediatrics.* 2013 Jan;131(1):30–37. [*PMID: 23248223*]

Research suggests that early identification paired with early intervention leads to better outcomes in children with ASD. Currently, the number of children receiving early intervention (EI) services falls short of the number estimated to need them, suggesting that developmental issues are often not being identified in a timely manner. In the pediatrician's office, general developmental delays and specific conditions such as ASD can be caught either by developmental screening tools or by the general observations of parents and physicians. This study examined whether using developmental screening tools enabled quicker and more efficient identification of developmentally delayed children, and led to faster referral to EI services. The 2,092 children enrolled in this study belonged to four urban pediatric practices in the Philadelphia area, were mostly African-American, and were from households with an annual income of less than $30,000. Each child was randomly assigned to one of three treatment groups. In the first treatment group, parents filled out the Ages and Stages Questionnaire-II (ASQ-II) at the child's 9-, 13-, and 30-month well-baby visits, and the Modified Checklist for Autism in Toddlers (M-CHAT) at the 18- and 24-month visits. Both the ASQ-II and M-CHAT are questionnaires filled out by the parent to check for normal physical and social development, and the M-CHAT also contains questions that help screen specifically for ASD. The second treatment group was identical to the first, with the addition of assistance from the doctor's office staff in completing the questionnaires. The third group of children attended the same well-baby visits, but no specific screening tools were used, so identification relied upon the interactions and observations of the parent and physician. Results showed that developmentally delayed children who were screened using the ASQ-II and M-CHAT were about twice as likely to be identified, referred and found eligible for EI services as children who were not specifically screened. The study also found that screening did not over-identify, or create false positives among normally developing children when compared with surveillance alone. There were no significant differences between the outcomes for the children whose parents did or did not receive help on the surveys. These findings suggest that the use of specific screening tools greatly enhances the identification and referral of children for EI services. This study shows that use of these screening tools is effective in an urban, low-income population and suggests that more widespread use could ensure that children with developmental delays and specific conditions such as ASD have the best chance of early intervention.

QUESTION 1: WHEN SHOULD I BE CONCERNED?

Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism

Jones W, Klin A. *Nature*. 2013 Dec 19;504(7480):427-31. [*PMID: 24196715*]

A new study identifies signs of ASD that emerge in the first months of life. Within a few hours of being born, babies begin to focus their gaze on human faces, learning to pick up social cues by paying special attention to other people's eyes. Since ASD was first described, a disruption in this eye contact has been one of the key predictors that a child might have the condition, making this feature a strong component of many screeners and diagnostic tests. The question that arises is whether those with ASD are born with this lack of interest in looking at others' eyes, or if it is something that develops gradually over the first 2 years of life. Researchers prospectively studied high-risk infant siblings of children with ASD from birth until 3 years of age, using eye-tracking technology to measure the way they looked at and responded to videos of the faces of caregivers socially interacting with them. At 2 months of age, babies who were later diagnosed with ASD showed no difference in eye-looking compared to those who did not receive an ASD diagnosis. However, from 2 to 6 months of age, these babies showed an abrupt decline in attention to eyes, whereas those who did not go on to be diagnosed showed no such drop. This decrease in eye-looking continued throughout the course of the study, and by 24 months these children focused on the caregiver's eyes half as long as did their typically developing peers. This measurable difference, emerging from 2 months of age onwards, is the earliest sign of ASD ever observed in an ASD research study, and holds promise for the development of tools for early identification. Interestingly, since the difference only begins to develop after the 2-month mark, this finding disproves the hypothesis that eye contact in those with ASD is diminished from birth; it appears, instead, that social eye gaze starts out at normal levels and then declines. The timing of this decrease in eye contact highlights a developmental window that is central to the development of brain circuits involved in social cognition, and presents a potential target for early intervention strategies for ASD. If infants are identified before this decline in attention to social cues, interventions could build on the levels of eye contact that are still intact, which is a more promising proposition than trying to induce the development of a function that was absent from birth.

Developmental trajectories in children with and without autism spectrum disorders: the first 3 years

Landa RJ, Gross AL, Stuart EA, Faherty A. *Child Dev*. 2013 Mar-Apr;84(2):429–442. [*PMID: 23110514*]

With little known about the onset and early behavioral developmental courses of children with ASD, previous studies have suggested that two main patterns of symptom onset may exist for children with ASD. In some cases, studies have described an early period of apparently typical development with achievement of expected milestones followed by regression, involving loss of language and/or social skills and the emergence of ASD-related behaviors such as repetitive and stereotypical behaviors/interests. In other cases, studies have noted an early onset of ASD-related signs and impairments that results in failure to meet expected developmental milestones and a plateau in skills, but without regression. Retrospective studies examining these two patterns of ASD symptom onset have developed conflicting assessments regarding the relationship between regression and severity of developmental outcomes. To avoid the limitations of retrospective studies, researchers designed a prospective, longitudinal study that examined social, language, and motor trajectories in a high-risk group consisting of 204 infant siblings of children with ASD, and a low-risk group composed of 31 infants with no family history of ASD. Children were assessed from 6 months to 36 months of age, and classified into one of three groups: the Early-ASD group who received a tentative diagnosis by 14 months (confirmed at the outcome of the study), the Later-ASD group who received a diagnosis after 14 months, and the Non-ASD group. Investigators observed similar patterns of initial development at 6 months among all three groups. However, between 14 and 24 months, the Early-ASD group exhibited greater delays in language development compared with the Later-ASD group. At 36 months, the Later-ASD group indicated impairments of comparable severity to the Early-ASD group, suggesting that an earlier or later diagnosis is not predictive of symptom severity. In addition, the timing of ASD diagnosis did not correlate with a specific developmental pattern—either plateau of skills or regression. With these findings, the researchers who conducted this study suggest that screening practices be amended to account for the fact that children may demonstrate variable ASD-related symptoms at different time points in development. Clinical implications of the study include the need for implementation of general developmental assessments before 1 year of age and continued screening at regular intervals through preschool years.

Pediatrician identification of Latino children at risk for autism spectrum disorder

Zuckerman KE, Mattox K, Donelan K, Batbayar O, Baghaee A, Bethell C. *Pediatrics*. 2013 Sep;132(3): 445-453. [*PMID*: 23958770]

A recent survey of primary care physicians (PCPs) suggests that language, access, and cultural barriers all contribute to poor early diagnosis of ASD among Latino families. Previous research has indicated that Latino children are diagnosed with ASD less often compared with white children, and those diagnosed are identified later and exhibit more severe symptoms. While many factors, including family access to healthcare and parent knowledge of ASD may influence diagnosis of ASD among Latino children, this study examines the potential role that PCPs play in disparities in diagnosis. Through the examination of a sample of 267 PCPs in California via a mail-based survey, researchers assessed their bilingual ASD developmental screening practices, perceptions of parent ASD knowledge among Latino and white families, difficulties in evaluating for ASD in Latino and white children, and other issues that are potential barriers to early ASD identification for Latino children. Results from the study indicated that while 81% of the PCPs surveyed conducted developmental screening for ASD, only 29% of all PCPs provided screening in Spanish for ASD (and an even smaller fraction of PCPs, 10%, offered both general developmental and ASD screening in Spanish). In addition, a majority of PCPs cited that they felt that Latino parents were less informed of ASD compared to white parents, and had more difficulty evaluating risk for ASD in Latino children. Nearly 75% of PCPs experienced barriers to diagnosing Latino children for ASD with the chief barriers consisting of long waits for appointments at their practices due to a shortage of PCPs, limited access to ASD or developmental specialists to whom they could refer patients, limited access to primary care due to the prevalence of uninsurance or underinsurance among Latino children, and language differences between providers and families. Researchers in this study concluded that several factors contribute to delayed identification of ASD in Latino children, and suggested key steps toward closing this gap: the promotion of language-appropriate screening, dissemination of culturally relevant informational materials to Latino families, and increased support to PCPs for ASD screening and specialist referral.

QUESTION 2

HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Gastrointestinal problems in children with autism, developmental delays or typical development

Chaidez V, Hansen RL, Hertz-Picciotto I. *J Autism Dev Disord*. 2013 Nov. [Epub ahead of print] [*PMID: 24193577*]

Gastrointestinal (GI) problems associated with ASD are a common concern among many families who have a child with ASD. Though recently a number of studies have been undertaken to better understand the prevalence and characteristics of GI disruption, limitations posed by factors such as methodology, study population characteristics, and definitions of GI symptoms have presented some challenges in determining the scope of the issue. Researchers involved in the ongoing Childhood Autism Risks from Genetics and Environment (CHARGE) study examined this issue using their ethnically-diverse cohort. The aim was to learn more about not only the prevalence of GI disturbances (including abdominal pain, diarrhea, constipation, and food sensitivity), but to also gain a better understanding of the relationship between GI issues and maladaptive behaviors such as irritability, lethargy/social withdrawal, stereotypical behaviors, hyperactivity, and inappropriate speech. The researchers compared GI symptoms and maladaptive behaviors in 960 children who were age, gender, and ethnically-matched among three categories: children with ASD, children with developmental delay (DD), and typically developing (TD) children. Data was gathered using self-administered standardized questionnaires including the CHARGE gastrointestinal history (GIH) questionnaire and the Aberrant Behavior Checklist (ABC), as well as through clinician-administered standardized instruments such as the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales. Results indicated that children with ASD are approximately six to eight times more likely to report frequent gaseousness/bloating, constipation, diarrhea, and sensitivity to foods than TD children, with constipation, diarrhea, and food sensitivities or dislikes being the most common GI symptoms. The researchers suggested that their data support the possibility that some GI issues in children with ASD could be related to or exacerbated by food selectivity and restricted diets that may result from sensory issues or insistence on sameness, but further research would be needed to determine if this is the case. The data also indicated that children with ASD who experienced GI problems exhibited greater severity in certain maladaptive behaviors (irritability, social withdrawal, repetition, and hyperactivity). The researchers suggested that chronic GI symptoms causing pain, discomfort and anxiety, could potentially contribute to increased irritability and social withdrawal, particularly in someone with

deficits in social and communicative skills, and that stereotypy and hyperactivity may represent coping mechanisms for the discomfort associated with GI conditions. The study results suggest that it is important for providers to consider GI issues that may be present when planning ASD therapy approaches, as addressing these issues could potentially help children with ASD address not only the discomforts associated with GI dysfunction, but also could result in improvement in behavioral symptoms. In addition, further research on GI issues in ASD may be helpful in determining the roles of the microbiome, the immune system, and the functioning of neurons in both the brain and gut in ASD.

Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis
Doshi-Velez F, Ge Y, Kohane I. *Pediatrics.* 2014 Jan;133(1):e54-63. [*PMID: 24323995*]

ASD is sometimes accompanied by one or more comorbid health condition, such as gastrointestinal (GI) issues, seizures, sleep disorders and psychiatric disorders. However, the relationship between ASD and comorbidity is poorly understood, and although previous research has quantified the prevalence of various comorbidities, they do not occur evenly across the ASD population. The current study investigated the patterns of co-occurrence of these comorbid health conditions in those with ASD, identifying ASD subgroups with different sets (clusters) of co-occurring conditions. Researchers analyzed electronic health records from 4,927 individuals at least 15 years of age with a diagnosis of ASD, aggregating the standard international diagnostic classification codes found in the records (representing diagnoses each patient had received between the ages of 0 and 15 years) into categories in order to characterize the key patterns of ASD comorbidities that appeared in the records. This clustering analysis revealed three ASD subgroups, representing approximately 11% of the total study population, that exhibited different specific comorbidity patterns: one group was characterized by seizure disorders (120 people), one was characterized by psychiatric disorders such as depression and anxiety disorders (197 people), and one was characterized by more complex multisystem disorders (212 people), including auditory and GI disorders and infections. The remainder (4,316 people, or 89%) could not be grouped into meaningful clusters. Interestingly, across the 15-year period studied, the developmental trajectories—including developmental delays and age of diagnosis—of the different subgroups varied from one another. For example, those in the psychiatric disorder subgroup were more likely to be diagnosed with ASD earlier than those in the other subgroups, and the seizure subgroup was characterized by a spike in ASD diagnosis at age 10. The prevalence of psychiatric disorders was not correlated with seizure activity, but a significant correlation was found between GI disorders and seizures. These correlational results were validated using a second, smaller sample of 496 individuals from a hospital located in another geographic region. Delineated by different patterns of comorbidities, these ASD subgroups might reflect distinct biological underpinnings due to different genetic and environmental contributions. However, prospective longitudinal studies and additional clinical and molecular characterizations will be needed to validate and refine these findings. Such efforts will be helpful to further differentiate the developmental trajectories associated with each subgroup, providing valuable information about potential windows for intervention to reduce the disabling effects of these comorbidities.

Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders

Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. *Cell.* 2013 Dec 19;155(7):1451-63. [*PMID: 24315484*]

Gastrointestinal (GI) problems frequently co-occur with ASD, and research has suggested that the presence of GI symptoms is correlated with more severe ASD symptoms. The composition of the bacteria found in the gastrointestinal tract, collectively referred to as gut microbiota, is vital to proper GI functioning, and several studies have suggested that people with ASD may have differences in their gut microbiota, though the nature of those possible differences has not yet been characterized. Some data from animal and human studies suggest that the gut microbiota could potentially affect social behaviors, emotion, and brain development, all of which are also impacted in ASD. In this study, researchers investigated how changes in the gut microbiota might affect behaviors in the offspring of maternal immune activation (MIA) mice, a mouse model whose offspring exhibit ASD-like behavioral characteristics, including problems with sensory processing, communication, and social behaviors. Examination of the GI tract of MIA mice showed a nearly three-fold increase of the permeability of the intestinal barrier, or the tendency of molecules in the gut to cross the intestinal wall and exit into the general circulation. These mice also had a different composition of species within their gut microbiota compared to control mice and higher expression of cytokines (proteins associated with immune response and inflammation). Next, the MIA mice were given an oral probiotic supplement containing the bacterial species *Bacteroides fragilis*, which is found in the human gut and has previously been shown to effectively treat experimental colon inflammation in an animal model. Remarkably, the MIA mice treated with an oral probiotic containing *B.fragilis* restored intestinal barriers, repopulated gut microbial species that more closely resembled controls, and normalized cytokine levels.

Treatment with *B.fragilis* also corrected behavioral symptoms of MIA mice; their abnormalities in sensory processing, communication, repetitive behaviors, and anxiety were reversed. Only social interactions remained altered in MIA mice after *B.fragilis* treatment; both treated and untreated MIA mice chose to spend significantly less time in proximity to other mice. Finally, the researchers examined the levels of certain metabolites—or molecules that result from the process of metabolism in the gut—that have been shown to cross the weakened intestinal barrier into the bloodstream in MIA mice (a process that is reversed in these mice by probiotic treatment with *B.fragilis*). They found that not only can an induced increase in some of these metabolites cause anxiety-like behaviors in normal mice, but both normal metabolite levels and normal behaviors can be restored by *B.fragilis* treatment. In summary, this study establishes the presence of GI symptoms in a mouse strain that exhibits ASD-like symptoms, suggesting the possibility that in humans, the roles of the gut, the microbiome, and the brain may be similarly intertwined in causing ASD symptoms. The study demonstrates the ability of *B.fragilis* to correct both GI and behavioral symptoms in these mice, suggesting that if similar relationships are found in human ASD, it may be possible to develop innovative new treatments for ASD that target the composition of the gut microbiota.

Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism

Willsey AJ, Sanders SJ, Li M, Dong S, Tebbenkamp AT, Muhle RA, Reilly SK, Lin L, Fertuzinhos S, Miller JA, Murtha MT, Bichsel C, Niu W, Cotney J, Ercan-Sencicek AG, Gockley J, Gupta AR, Han W, He X, Hoffman EJ, Klei L, Lei J, Liu W, Liu L, Lu C, Xu X, Zhu Y, Mane SM, Lein ES, Wei L, Noonan JP, Roeder K, Devlin B, Sestan N, State MW. *Cell*. 2013 Nov 21;155(5):997-1007. [*PMID: 24267886*]

As techniques for studying the human genome have advanced, an increasing number of genes are being associated with ASD; it is important to find the connections between these ASD-linked genes in order to understand how they may contribute to ASD. A new resource called the BrainSpan1 atlas provides researchers with three dimensional maps showing when and where genes turn on and off in the human brain, from embryonic stages through older adulthood. This study used the BrainSpan atlas to identify commonalities in when and where ASD-associated genes are expressed. It focused on nine genes with *de novo* (or spontaneous) loss of function (LoF) mutations that have each been identified in multiple families with ASD, providing a high level of confidence that these genes are associated with ASD; these are notated as "high-confidence" ASD genes or "hcASD genes." Comparison of the expression patterns of these genes throughout the structures of the brain as it develops revealed that the greatest overlap of hcASD genes occurred in deep layers of the cortex during the period of fetal development ranging from 10-24 weeks post-conception (the midfetal period, during the first and second trimesters of pregnancy). Next, this time and location of overlap in hcASD gene expression were examined for expression of *de novo* LoF mutations that have been associated with ASD in one family, referred to as "probable ASD" (pASD) genes. This analysis showed enrichment of pASD genes in two specific brain regions, the prefrontal and primary motor-somatosensory cortex, during the midfetal period. The researchers also looked at hcASD gene products (RNA and protein) in brain tissue taken during this midfetal developmental time point, and found high expression in deep cortical layer neurons that send information over long distances, called cortical projection neurons. The finding that midfetal brain development is important in ASD corroborates previous studies that have shown pregnancy to be a key time window in the development of ASD. The findings also have important treatment implications by linking genetic information to the specific functional processes they control. By using the shared characteristics of different gene mutations implicated in ASD, this study creates a picture of the developmental processes that are changed in these cases. This image provides a sharper focus for the development of targeted treatments, and even holds potential for the development of personalized interventions based on genotype.

QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism

Parikshak NN, Luo R, Zhang A, Won H, Lowe JK, Chandran V, Horvath S, Geschwind DH. *Cell*. 2013 Nov 21;155(5):1008-21. [*PMID: 24267887*]

New research is grouping together ASD-linked genes based on similarities in the timing and location of their expression. As more information is collected and analyzed about the genetic differences found in people with ASD, an increasing number of genes have been identified that could potentially play a role in the development of the condition. The next step is to understand how these genes may be altering brain development in ways that result in ASD. Genes turn on and off in different brain areas at different times during development, and this information has now been collected in the BrainSpan atlas, a powerful new database that shows the expression of genes in three dimensions across the entire human brain as it develops from infancy into adulthood. Many genes can also be grouped broadly by their function, such as a role in building connections between neurons (synapses) or in nervous system development.

In this study, the researchers used the BrainSpan atlas to group all genes that are expressed in the brain based on their timing of expression during brain development, location of expression, and function; they called the 12 resulting groups of related genes "modules." Next, they examined these modules for genes that have previously been associated with ASD or intellectual disability (ID). The results showed that ID-associated genes were not overrepresented in any of the 12 modules, while ASD-associated genes were mostly found (enriched) in modules 13, 16, and 17, which are groups of genes that are responsible for establishing synapse function during prenatal and early postnatal development. The highest enrichment of ASD genes was found in module 16, whose expression increases during fetal development, starting in the 10th week after conception. A separate analysis of rare *de novo* gene mutations linked to ASD revealed enrichment in modules 2 and 3, modules whose expression peaks between the 10th and 22nd week after conception (the midfetal period, during the first and second trimesters of pregnancy) and whose genes are involved in neuronal differentiation and migration. The study also looked at factors related to the ways in which ASD-related genes are expressed. Gene expression turns on and off with the help of proteins known as transcription factors and translational regulators—and more than one gene can be controlled by the same factor or regulator. The researchers found 17 transcription factors whose targets link the different modules enriched for ASD-related genes. One translational regulator strongly associated with the ASD modules was FMRP, which is the protein mutated in Fragile-X syndrome, which can also cause ASD. Finally, the researchers looked for whether these ASD and ID gene sets were more likely to be found in particular cortical layers. Interestingly, the localization of expression of ASD and ID genes differed, with ASD genes being more highly expressed in a different cortical layer than the one that was enriched for ID genes, a finding that suggests that ASD and ID are biologically distinct. This study and the Willsey *et al.* study (also included in the Top 20 Summary of Advances) both used the BrainSpan atlas, although the criteria they used for including genes in the studies were different. However, both studies converged on the importance of prenatal brain development and the role of cortical neurons in ASD. Both also contribute to a better understanding of how genes are linked to ASD symptoms, which may lead to improved treatments.

QUESTION 3

WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey

Bauman MD, Iosif AM, Ashwood P, Braunschweig D, Lee A, Schumann CM, Van de Water J, Amaral DG. *Transl Psychiatry*. 2013 Jul 9;3:e278. [*PMID: 23838889*]

New research suggests that prenatal exposure of a pregnant monkey to antibodies taken from human mothers of children with ASD results in monkey offspring that exhibit atypical behavior and brain development. This lends support to the argument that fetal exposure to certain maternal antibodies may play a role in the development of ASD. Antibodies—also known as immunoglobulins (Ig)—are proteins found in our blood that provide us with immune protection by marking potentially harmful substances and microbes, such as bacteria and viruses, for destruction and elimination. During gestation, maternal IgG antibodies cross the placenta and protect the fetus, conferring the mother's immunities to the developing child. However, in addition to the protective antibodies generated by all pregnant women during gestation, some maternal immune systems may go awry and generate autoantibodies that cross the placenta and attack developing fetal tissue, rather than protect it. IgG antibodies that target particular fetal brain proteins have been found in 12% of mothers of children with ASD, but not in mothers of typically developing children. In the current study, non-human primates were used to investigate the effect of these autism-linked IgG autoantibodies from humans on brain and behavioral development in monkeys. During the first and second trimesters, eight pregnant rhesus monkeys were exposed to IgG taken from human mothers of children with ASD, and the monkey offspring were studied for 2 years. The behavior of these young monkeys developed to be markedly different from that seen in the offspring of monkeys that were either untreated, or who received antibodies from mothers of typically developing children. The monkeys exposed in-utero to ASD-linked autoantibodies showed species-inappropriate behavior, approaching both familiar and unfamiliar monkeys of the same age more frequently than was observed in monkeys who had not been exposed to these antibodies. In addition, the young monkeys exposed to the ASD-linked autoantibodies were reacted to differently by other monkeys, including their own mothers, suggesting that they may have sensed subtle changes in social behaviors displayed by the treated monkeys. In parallel with these behavioral changes, magnetic resonance imaging (MRI) brain scans taken at several time points across the treated offspring's development revealed that the males (but not females) had enlarged brain volume, largely as a result of an increase in white matter (nerve bundles).

These differences were most pronounced in the frontal lobes, a brain area that is key to social cognition. Both the behavioral and brain differences observed in the treated monkey offspring mirror some of the differences that have been observed in children with ASD, suggesting the possibility that exposure to maternal autoantibodies in humans may in some way be contributing toward the development of ASD in children. While the similarities between humans and monkeys in terms of brain structure and social complexity lend credibility to this hypothesis, these findings need to be replicated and further explored in future studies. Additional research may help identify the mechanisms by which maternal autoantibodies may affect brain development and behavior so that scientists can better understand how this may contribute to ASD and identify molecular targets for interventions.

Autism risk across generations: a population-based study of advancing grandpaternal and paternal age

Frans EM, Sandin S, Reichenberg A, Långström N, Lichtenstein P, McGrath JJ, Hultman CM. *JAMA Psychiatry*. 2013 May;70(5):516-21. [*PMID: 23553111*]

Several recent studies have shown an increased risk for ASD in the children of older fathers. Sperm cells from older men have more "*de novo*" or spontaneous mutations, which are mutations that have newly arisen in the sperm cells (i.e., they were not inherited from a parent), but they can be passed down to the next generation. These mutations can result from errors in copying DNA during the cell division process that generates sperm or from exposure to environmental factors that damage DNA. One possible explanation for the role of *de novo* mutations in increasing risk for ASD in children of older parents is that while a small number of such mutations in reproductive cells may have little or no effect, the accumulation of many such mutations over time can result in cellular and molecular functions that are altered strongly enough to give rise to ASD symptoms in the next generation. Since the mutations in a sperm cell are passed to the offspring, not only do the children of an older father have an increased risk of developing ASD, but those children also can pass the same mutations on to their future children. It is therefore possible that the age of a child's grandfather could impact his or her risk of developing ASD. This study used the extensive and meticulous record-keeping of the Swedish population registry to analyze information from 5,933 people with and 30,904 people without ASD. First, the study confirmed previous findings that the children of older fathers have an increased risk of ASD and found that, in this population sample, 6% of risk for ASD was attributable to paternal age over 40. The researchers also found that men who had fathered a daughter when they were 50 years or older were 1.79 times more likely to have a grandchild with autism, and men who had fathered a son when they were 50 years or older were 1.67 times more likely to have a grandchild with autism, compared with men who had fathered children when they were 20 to 24 years old. The researchers calculated that 3% of autism risk in their sample was attributable to grandpaternal age on both the paternal and maternal sides, with the highest risk found in grandfathers who had their own children after age 50. Overall, this study provided the first evidence that a grandfather's age is associated with risk of childhood autism, independent of paternal or maternal age, with the genetic effects persisting across generations. The study also corroborated previous findings that advanced paternal age is a risk factor for ASD. Future work to identify more specific genetic changes that cause an increase in ASD risk for the grandchildren of older grandfathers may provide further insight into how ASD develops.

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

Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children

Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T, Schjølberg S, Davey Smith G, Øyen AS, Susser E, Stoltenberg C. *JAMA*. 2013 Feb 13;309(6): 570-7. [*PMID: 23403681*]

Recent research indicates that the use of prenatal folic acid supplements around the time of conception is associated with a lower risk of ASD. It has been known for some time that that prenatal folic acid supplements reduce the risk of neural tube defects in children; by comparison, little has been known about whether such supplements might protect against other neurodevelopmental disorders such as ASD. For ethical reasons, it has not been possible to use a randomized control trial to study the association between the use of prenatal maternal folic acid supplements and the subsequent risk of ASD in the offspring. However, observational studies of mothers who do and do not use supplements can be used to address this question. In this study, 85,176 children from the population-based, prospective Norwegian Mother and Child Cohort Study (MoBa), born between 2002 and 2008, were assessed. Mothers were recruited for MoBa at ultrasound examinations around week 18 of pregnancy. Cases of ASD (autistic disorder, Asperger syndrome, pervasive developmental disorder–not otherwise specified [PDD-NOS]) in offspring were subsequently identified via several mechanisms: parental report at various time-points, professional and parental referrals, and data on clinical diagnoses as recorded by the Norwegian Patient Registry. In children whose mothers took folic acid from 4 weeks before to 8 weeks after the start of pregnancy, 0.10% had autistic disorder—the most severe form of ASD—compared with 0.21% in those whose mothers did not take folic acid. No association was found between folic acid supplementation and Asperger syndrome or PDD-NOS. However, the small number of children with these diagnoses in the current sample meant that the power was limited. Although these correlational findings suggest an association between prenatal folic acid supplementation and a decreased risk of autistic disorder, it is important to note that they do not establish causality. Moving forward, it will be important to replicate these findings and to conduct research to understand the mechanism by which folic acid may be acting as a protective factor against development of ASD.

QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Preschool based JASPER intervention in minimally verbal children with autism: pilot RCT

Goods KS, Ishijima E, Chang Y-C, Kasari C. *J Autism Dev. Disord.* 2013 May;43(5):1050–1056. [*PMID: 22965298*]

Children with ASD who attain verbal skills by 5 years of age have been found to demonstrate the best social outcomes. Early intervention studies have found that improvement in such skills as joint attention can positively impact the development of verbal communication in these children. Traditionally, these studies have only evaluated children meeting specific developmental age or intellectual ability/IQ criteria, thus overlooking children with the greatest developmental impairments, including those who have made minimal progress in acquiring spoken language skills (those who are "minimally verbal"). As a result, little knowledge exists concerning the impact that early interventions may have on improving communication in minimally verbal children with ASD. To address this gap, researchers in the current study specifically focused on minimally verbal children with ASD who had not been responsive to intensive behavioral therapy, and conducted a randomized controlled trial of 24 sessions over 12 weeks to evaluate whether a novel play-based intervention employing communicative gestures, known as Joint Attention Symbolic Play Engagement and Regulation (JASPER), would improve social communication outcomes. Fifteen preschool aged children (3 to 5 years old) with a clinical diagnosis of ASD and spoken language skills of fewer than 10 spontaneous, functional, and communicative words initially took part in this study, with 11 children completing the study. Baseline assessments were conducted prior to the start of the study and included diagnostic confirmation of ASD using the Autism Diagnostic Observation Scale (ADOS), the Mullen Scales of Early Learning (MSEL) to assess mental age and development (e. g. , visual reception, fine motor, receptive language, and expressive language skills), and the Reynell Developmental Language Scales (RDLS) to assess verbal comprehension. All children in this study participated in 30 hour-per-week behaviorally based interventions as well as speech and occupational therapy. Seven of the children were randomly assigned to a treatment group where they were pulled twice a week from their standard weekly interventions for 30-minute sessions of JASPER (considered a "low dose" therapy), while the control group children only received their standard 30 hour-per-week speech and occupational therapies. After 12 weeks, researchers observed that children who had received JASPER demonstrated less repetitive patterns while playing, initiated more social gestures in the classroom setting, and

indicated greater attention engagement with others, compared to those who had not received JASPER. No change was observed in generalized joint attention measures, though that was another targeted behavior. The researchers hypothesized that perhaps they saw changes in play and engagement related behaviors because spontaneous communication changes naturally come later in the developmental progression, or perhaps because more time would be needed for that change to develop. Investigators thus concluded that brief interventions show much potential in targeting joint attention and play skills and can result in the improvement of core deficits in minimally verbal children with ASD.

Oxytocin enhances brain function in children with autism

Gordon I, Vander Wyk BC, Bennett RH, Cordeaux C, Lucas MV, Eilbott JA, Zagoory-Sharon O, Leckman JF, Feldman R, Pelphrey KA. *Proc Natl Acad Sci*. 2013 Dec;110(52):20953–20958. [*PMID: 24297883*]

Difficulty with social interaction is one of the hallmarks of ASD. A number of ASD treatments have targeted social impairment; however, there is no established drug treatment to address this aspect of the disorder. Researchers have recently begun to examine oxytocin, a naturally occurring hormone secreted by the brain's pituitary gland, as a drug candidate to ameliorate the social impairments found in ASD. Previous work in children and adults with ASD suggests that oxytocin treatment can increase social cognition, decrease repetitive behaviors, and enhance willingness to interact socially. Although a number of these behavioral improvements have been documented, overall results of oxytocin treatment have been mixed. While studies of changes in the brain activity of adults in response to oxytocin have shed some light on the behavioral effects observed in adults, there has been a gap in knowledge regarding the effects of oxytocin on the brain activity of children. Filling this knowledge gap has become even more important, as a number of clinical trials have recently launched to investigate the effects of oxytocin administration in children with ASD.

Investigators in the current study used a double blind, crossover trial design (having each person participate once with placebo and once with the experimental treatment, but without knowing which was which) to study the impact of oxytocin on brain activity in children and adolescents with ASD using brain imaging. After treatment with an oxytocin nasal spray, activity in the brains of 17 children and adolescents (8 to 16.5 years old) was observed using functional magnetic resonance imaging (fMRI) as they performed a task that involved making social judgments (labeling a mental state based on viewing a picture of a person's eyes) or non-social judgments (labeling the category when shown a picture of a motor vehicle). The researchers found that oxytocin treatment, but not placebo treatment, had distinct effects on brain activity. Oxytocin administration increased brain activity during social judgments in specific brain regions that are important for social attention, reward, perception, and reasoning about others' mental states—all of which are under-active in ASD. A subset of these social brain areas showed more activity as the amount of oxytocin measured in the body increased. Interestingly, oxytocin treatment also resulted in decreased brain activity in social brain areas during non-social tasks. The researchers hypothesized that by enhancing responses in social situations and suppressing responses in non-social situations, oxytocin focuses this brain circuitry on processing social information. Though oxytocin caused a visible change in brain activity, the study results did not demonstrate an impact on the children's autism behavioral symptoms. The authors suggested that perhaps behavioral improvements in response to oxytocin treatment can only be observed when tested in a richer, more realistic social context that includes opportunities for social learning. The results of this study, showing how oxytocin administration alters brain activity in areas important for social cognition in children with ASD, suggest that oxytocin holds promise as a treatment for these individuals, and also refines its potential role. If oxytocin primes the brain for responding to social input, it may be most beneficial if delivered immediately before evidence-based behavioral interventions, to maximize their benefit.

QUESTION 5

WHERE CAN I TURN FOR SERVICES?

Comparative efficacy of LEAP, TEACCH and non-model-specific special education programs for preschoolers with autism spectrum disorders

Boyd BA, Hume K, McBee MT, Alessandri M, Gutierrez A, Johnson L, Sperry L, Odom SL. *J Autism Dev Disord.* 2014 Feb;44(2):366-380. [*PMID: 23812661*]

For children with ASD, early intervention can greatly enhance social, behavioral, and cognitive skills, leading to more favorable developmental trajectories and improved outcomes. Like most young children, those with ASD spend a significant amount of time in school settings; therefore, it is critically important to ensure that school-based treatment programs are efficacious. Researchers in this study sought to examine the effects of two different comprehensive treatment models (CTMs) that are widely used in schools: the Learning Experiences and Alternative Program for Preschoolers and their Parents (LEAP) and the Training and Education of Autistic and Related Communication-Handicapped Children (TEACCH) program. These are two long standing CTMs that are used frequently, yet have very different approaches. LEAP uses applied behavior analysis (ABA) approaches as well as some principles of early childhood education, with the goal of reducing characteristics of ASD that interfere with learning. The LEAP intervention is employed in inclusive settings, with children with ASD receiving instruction in the same classrooms as typically developing students who learn to help their autistic peers socially and academically. TEACCH, on the other hand, makes changes and accommodations to the student's environment to promote the child's engagement and learning. Thus, in most classrooms where TEACCH is used, children with ASD are educated using an adult-led approach in a group separate from their typically developing peers. For this study, investigators assessed 185 preschool students with ASD in 22 LEAP, 25 TEACCH, and 27 non-model specific (NMS) classrooms across four states: North Carolina, Colorado, Florida, and Minnesota. All classrooms had to meet an ''average'' rating (score of 3 out of 5) on four subscales of a validated classroom quality measure—the PDA Program Assessment. NMS classrooms were considered the control group, did not use TEACCH or LEAP methods, and were a mixture of inclusive and self-contained classrooms. The teachers were offered "refresher" instruction to maintain fidelity of how the LEAP and TEACCH interventions were implemented, and researchers controlled for fidelity of the interventions to ensure they were being delivered appropriately. Students were assessed on a number of measures that included cognitive, behavioral, psychological, and social skills at the beginning and end of

the school year. All data were obtained at least 6 months apart, across three data sources (parent report, teacher report and student performance).

Investigators assembled the test measures into seven composite variables that were grouped based on the features and outcomes being rated and statistical correlation between student's scores on each individual measure. These variables included: autism characteristics and severity, communication, sensory and repetitive behaviors (parent and teacher report), reciprocal social interaction (parent and teacher report), and fine motor skills. At the end of one school year, researchers found that students in each type of classroom performed better at the end of the year in the areas of autism characteristics and severity, communication, and fine motor skills. Of note, there were no significant differences found in students' scores between intervention models. However, with regard to cognitive ability, children in TEACCH classrooms with lower ability showed more improvement in measurements for autism characteristics and severity. This may be due to the environmental and behavioral supports found in TEACCH classrooms that are more advantageous to children with greater cognitive impairment, or perhaps children with more severe symptoms have more room for improvement. Researchers found that, while the LEAP and TEACCH approaches are different (i.e., LEAP is peer-mediated in inclusive settings and TEACCH is adult-led in specialized settings), many teachers used a number of similar classroom practices. Therefore, these common best practices, as well as common features between the various instructional approaches, may be what influence the child's improvement the most. While reports of the importance of high-quality classrooms have been anecdotally reported in the literature in the past, this study provides evidence to support that claim. Overall, these data imply that high quality classrooms lead to benefits for ASD children; however, the degree of ASD severity may play a role in the type of classroom that best fits the individual child.

Comparing cognitive outcomes among children with autism spectrum disorders receiving community-based early intervention in one of three placements
Nahmias AS, Kase C, Mandell DS. *Autism Int J Res Pract.* 2014 Apr;18(3):311-320. [*PMID: 23188885*]

The Individuals with Disabilities Educational Act (IDEA) requires that, to the maximum extent possible and appropriate, children with disabilities should receive a free public education in the "least restrictive environment" (i.e., in a "regular classroom" with non-disabled peers). Several studies on treatment models for preschool aged children with ASD have observed that inclusion of children with ASD in classroom settings alongside their typically developing peers have resulted in cognitive gains for children with ASD. However, such studies are few and often not generalizable to broader populations as they were not implemented by community providers, lacked comparison groups, or contained insufficient sample sizes. In addition, researchers continue to debate the feasibility of employing ASD intervention strategies in inclusive classroom settings, with some researchers arguing that inclusive classrooms may expose children with ASD to social rejection from typically developing peers. Researchers in this study thus sought to comparatively examine the impact of community-based early intervention. They reviewed the preschool educational records of 98 preschool aged children with ASD placed in one of three settings: inclusive classrooms (with typically developing peers), mixed disability classrooms, and autism-only classrooms. Children in inclusive groups received intervention services (typically 3 hours a day, 3 days a week) from early childhood or special education teachers in classrooms for typically developing children. Children in mixed disability classrooms in center-based preschools received early intervention (typically 2-3 hours a day, 3 days a week) from early childhood or special education teachers in classrooms with children with developmental or other disabilities. Children in autism-only groups received early intervention in center-based autism support preschools (typically 5 hours a day, 5 days a week) via one or a combination of the following interventions: Applied Behavioral Analysis (ABA); Training and Education of Autistic and Related Communication Handicapped Children (TEACCH); Developmental, Individual Difference, Relationship-based (DIR)/Floortime model; visual supports; sensory integration; and creative art therapies. Most programs in all groups included instruction based on a curriculum aligned with early learning standards (e.g. Creative Curriculum, HighScope). Children in all groups also received speech, occupational, and physical therapies in addition to their weekly early intervention services.

Investigators noted that gender, type of household and previous history of intervention did not differ significantly among the three placement groups. Researchers controlled all analyses for participants' age, ethnicity, and baseline communication ability (collected at the start of preschool early intervention), which did differ significantly between placement groups. Researchers also controlled all analyses for all other baseline measures of children's abilities, even though they did not differ significantly among the groups. Baseline measures of children's abilities were determined by a multidisciplinary evaluation team using the Developmental Assessment of Young Children (DAYC), which measures cognition, communication, social-emotional development, physical development, and adaptive behavior in children from birth through age 5 years, 11 months. Children's progress over an average

period of 2 years was assessed by trained master's level research staff using a cognitive abilities test called the Differential Abilities Scales (DAS), designed for use in children between the ages of 2 and 17 across a broad range of developmental levels. Investigators determined that children undergoing early intervention in inclusive settings resulted in significantly higher DAS-based cognitive scores compared to children with ASD in mixed disability placements and autism-only placements, though the difference in the latter case was not statistically significant. Cognitive scores between children in mixed classrooms and autism-only placements did not significantly differ. Strikingly, relative improvement following early intervention in inclusive settings versus that seen in mixed disability settings was greatest in children with more severe social impairments (lower social-emotional baseline scores), decreased adaptive behaviors (lower adaptive behavior baseline scores), and with at least some expressive or receptive communication. The researchers hypothesize that children with ASD in inclusive classroom settings may benefit from observing and imitating social engagement, social behaviors, and cognitive skills shown by their typically developing peers. While this research highlighted intriguing outcomes related to the incorporation of early intervention in inclusive community settings, prospective studies examining cognitive development over time and randomized intervention trials are needed to further elucidate the effects of peer interactions so that future learning environments may be designed to best serve children with ASD.

QUESTION 6

WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

Optimal outcome in individuals with a history of autism

Fein D, Barton M, Eigsti I-M, Kelley E, Naigles L, Schultz RT, Stevens M, Helt M, Orinstein A, Rosenthal M, Troyb E, Tyson K. *J Child Psychol Psychiatry*. 2013 Feb;54(2):195-205. [*PMID: 23320807*]

ASD is generally considered to be a lifelong condition. However, recent research demonstrates that some people who have been accurately diagnosed with the disorder as children will subsequently go on to lose their symptoms and hence their ASD diagnosis as they grow up, eventually functioning socially on par with their typically developing peers. There have been previous reports of this nature, but concerns about whether the individuals had been diagnosed correctly initially, and whether they had indeed fully recovered, have remained. This case-control study documented 34 children between the ages of 7 and 21, who experienced what this research group termed an 'optimal outcome' (OO). Researchers compared the children's previous and current functioning to that of 34 age-, sex-, and nonverbal IQ-matched typically developing children, and 44 children with 'high-functioning' ASD. After independently verifying that the ASD diagnosis of all children was correct, standard cognitive and observational tests and parent questionnaires were conducted. The OO children performed similarly to typically developing children on measures of socialization, communication, face recognition, and language. This suggests that their ASD symptoms really had improved to the point that their ASD diagnosis had been appropriately dropped. To better understand how this group differs from others with ASD, the researchers used patient histories, including previous test scores and clinical descriptions, to examine the early childhoods of the OO children, comparing their behavior to that of children with 'high-functioning' ASD. Upon examination, researchers found that earlier on in life, OO children generally had milder social deficits and slightly higher IQs compared to those with 'high-functioning' ASD, but had equally severe difficulties with communication and repetitive behaviors. Although it is possible that deficits in more subtle aspects of social interaction or cognition still remain in these individuals, the results do substantiate reports of individuals who were correctly diagnosed with ASD as young children, but who no longer meet the criteria for ASD. With this result confirmed, the researchers are now investigating brain function in OO children and determining whether they have subtle residual social deficits. They are also reviewing records on the types of interventions the children received, in order to learn to what extent interventions may have played a role in the transition from ASD to optimal outcome.

The cost-effectiveness of supported employment for adults with autism in the United Kingdom

Mavranezouli I, Megnin-Viggars O, Cheema N, Howlin P, Baron-Cohen S, Pilling S. *Autism Int J Res Pract.* 2013 Oct. [Epub ahead of print] [*PMID: 24126866*]

Unemployment is high among adults with ASD—only 15% are employed in full-time paid jobs, and such jobs are typically poorly paid. Therefore, adults with disabilities, such as those with ASD, often enroll in supported employment programs, which provide assistance in finding and retaining jobs. These employment programs introduce job seekers to competitive programs offering individualized placements as well as continued support throughout employment. While these supported employment programs have been found to result in greater individual satisfaction, greater financial gains, and more independent living, such programs are also costly—particularly for the publicly funded National Health Service (NHS) in the United Kingdom (UK). Investigators in this study therefore sought to evaluate the cost-effectiveness of supported employment programs for a sample of 50 adults with ASD in the UK. Supported employment for adults in this study (30 participants) was administered by support workers whose duties include the assessment of clients' level of functioning, job finding, work preparation, and ensuring that clients can cope with the social and occupational requirements of the job. Individuals in the comparison group (20 participants) all had access to employment advice from Disability Employment Advisors (DEAs, who aided individuals with disabilities seek work, acquire new skills, and conducted employment assessments to identify suitable jobs), but did not have full-time guidance from a supported employment worker. Participants in the supported employment group all received a formal diagnosis of autism or Asperger syndrome and had an IQ of at least 70. The control group included individuals with ASD who were matched in intellectual and linguistic abilities. All participants in the study were actively seeking work in the UK, had no additional psychiatric or physical problems that adversely affected employability and none lived in areas of high unemployment.

Researchers examined the impact of supported employment programs on two outcomes: total number of weeks in employment and quality-adjusted life year (QALY; a measure of burden on an individual's life in terms of quality and quantity). Researchers determined that supported employment produces improved outcomes compared to that of standard care services (standard care costs for the control group were estimated via the cost of day services). These benefits were observed to cost an additional £18 ($30) per week of employment or £5,600 ($9,330) per quality-adjusted life year. These figures are well below thresholds that define maximum spending per QALY, as set by the UK's National Institute for Health and Care Excellence (NICE) clinical guidelines. In addition, results indicated that supported employment programs were more cost-effective relative to standard care services. Though supported employment programs are initially more expensive than standard services, researchers declare that these costs decrease over time as individuals gain independence. Moreover, investigators of this study suggest that the cost of supported employment programs is outweighed by the significant benefits in employment and quality of life for adults with ASD—outcomes that can also lead to the overall reduction in economic burden to a nation's health and social services spending.

QUESTION 7

WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Minneapolis Somali autism spectrum disorder prevalence project: community report 2013

Hewitt A, Gulaid A, Hamre K, Esler A, Punyko J, Reichle J, Reiff M. *University of Minnesota, Institute on Community Integration, Research and Training Center on Community Living.* 2013 Dec. Available at: *http://rtc.umn.edu/autism/doc/Autism_report.pdf*

The Minneapolis Somali Autism Spectrum Disorder Prevalence Project was developed to determine if more Somali children aged 7 to 9 had ASD than non-Somali children in Minneapolis in 2010.[1] The project was launched in response to community concerns that prompted an earlier analysis conducted by the Minnesota Department of Health that showed that a greater proportion of Somali children with ASD were participating in preschool special education programs in area public schools, compared with children of other races/ethnic backgrounds.[2] The concerns raised by the community were shared by the Interagency Autism Coordinating Committee (IACC) and they responded by fostering a collaboration between government and private funders to support a population-based surveillance project in Minneapolis.[3,4] The main aim of the surveillance project was to determine if there was a higher prevalence of ASD among Somali children in Minneapolis than among non-Somali children, regardless of special education placement. Researchers used the same methodology employed by the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network to estimate population prevalence. School and medical service records were reviewed by clinicians to identify children with ASD, based on information contained in the records that conformed to the definition of ASD outlined in the *Diagnostic and Statistical Manual of Mental Disorders (DSM, Fourth Revision)*. Results showed that approximately 1 in 32 Somali children ages 7 to 9 were identified as having ASD in Minneapolis in 2010. Somali and White children (1 in 36) were about equally likely to be identified as having ASD and more likely to be diagnosed than non-Somali Black (1 in

[1] Minneapolis Somali Autism Spectrum Disorder Prevalence Project website: *http://rtc.umn.edu/autism/*

[2] Autism Spectrum Disorders Among Preschool Children Participating in Minneapolis Public Schools Early Childhood Special Education Programs. Available at: *http://www.leg.state.mn.us/docs/2009/other/090520.pdf*

[3] NIMH Teams Up to Study ASD Rates in Somali-American Children. Available at: *http://www.nimh.nih.gov/news/science-news/2011/nimh-teams-up-to-study-asd-rates-in-somali-american-children.shtml*

[4] Autism Speaks Collaborates on Prevalence Investigation of Autism in the Somali Population in Minneapolis. Available at: *http://www.autismspeaks.org/about-us/press-releases/autism-speaks-collaborates-prevalence-investigation-autism-somali-population*

62) and Hispanic (1 in 80) children in Minneapolis. An unexpected and important finding of this study was that, compared to other racial and ethnic groups, Somali children with ASD were more likely to also have an intellectual disability (IQ of less than 70) than other groups. Approximately one third of all the children with ASD identified in this study (including all ethnic groups) had an associated intellectual disability. However, 100% of the 20 Somali children with IQ included in their records had an intellectual disability, while the proportion was closer to 20% for White, non-Somali Black and Hispanic children. This finding was limited by the small number of children with ASD in the study, but suggested that Somali children may, as a group, have more severe forms of ASD than other groups. Further studies will be needed to understand this difference and the possible contribution of genetic or environmental risk factors. The study also found that children in Minneapolis are, in general, not being diagnosed as early as they could be; irrespective of racial and cultural background, the average age of receiving an ASD diagnosis is 5 years. Since ASD can now be reliably diagnosed by age 2, this finding highlights an opportunity for improvement in service provision in Minneapolis, suggesting that more efforts are needed to increase awareness, outreach, and access to diagnostic services, especially in underserved and culturally diverse areas, using culturally-sensitive approaches. As the largest study of Somali children with autism to date in the U.S., this study provides a solid foundation for future research to explore why and how autism affects Somali and non-Somali children differently and can also be used by a number of different groups (e.g., parents, providers, community groups, and advocates) to increase awareness and early intervention for children, especially in diverse communities.

Evaluating changes in the prevalence of the autism spectrum disorders (ASDs)

Rice CE, Rosanoff M, Dawson G, Durkin MS, PhD, Croen LA, PhD, Singer A, Yeargin-Allsopp M. *Public Health Reviews*. 2013 March;34(6);2.

This article describes the outcomes of a 2011 workshop that was convened by the CDC and Autism Speaks to explore data and trends related to the rising prevalence of ASD in the U.S. and worldwide. Prevalence refers to the number or proportion of people with a particular condition, such as ASD, in a population at a given time. The identified prevalence of ASD has increased significantly in a short time period based on data from multiple studies including the U.S. Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network. At the time when this article was written, the CDC's ADDM Network estimated the prevalence of ASD in the United States to be 1 in 88 children, which is greater than 1% of the population and far greater than the prevailing estimate of 1 in 2,000 that persisted through the 1980s. It should be noted that early estimates only considered autistic disorder, whereas more recent estimates used a broader definition of autism, including related "autism spectrum" diagnoses such as Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS) and Asperger's disorder.

Workshop participants discussed the strong interest of the ASD community in understanding the reasons underlying the increased prevalence of ASD. They hypothesized that greater awareness of ASD and better identification—especially in populations with good access to healthcare—are likely responsible for some portion of the increase in ASD prevalence. Changes in genetic and environmental risk factors were also considered as a potential reason that could also account for some of the increase, but participants noted that in order to be identified as such, risk factors must be shown to be strongly associated with ASD, modifiable, and to have an effect size in the population that aligns with the increase in prevalence. The issue of health disparities was also discussed. The authors noted that ASD is more prevalent in higher socioeconomic status (SES) families, unlike many other disorders that tend to be more prevalent in lower SES families. They hypothesized that this may be related to differences in access to services, and that as services gaps are closed in underserved communities, diagnosis in the low SES population may rise. This prediction appears to have been borne out in more recent prevalence studies, with ASD prevalence rising in minority populations as outreach and services have improved; in spite of improvements, however, major disparities remain. The authors discussed the pros and cons of various prevalence measurement methodologies, including records-based estimates and screening-based estimates. They also described lessons learned from diseases where the range of symptoms and presentations (heterogeneity), and changes in risk factors or in diagnostic approaches have presented challenges for accurate determination of prevalence, including schizophrenia, Parkinson's disease, asthma, and cancer. Overall, the workshop participants summarized that changes in ASD prevalence are likely caused by a very complex combination of identification and risk factors. In order to best study these factors, collaboration both within the ASD field and with other, similar fields of study will be needed, along with maintenance and expansion of careful population data collection, and informed data analysis. Though many questions surrounding the increased prevalence of ASD remain, workshop participants concluded that even the documentation of this increase has been an important step forward, as it focuses attention on the needs of those with ASD, contributes to the development and availability of services and supports, and highlights the need for continued research.

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QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Goods KS, Ishijima E, Chang Y-C, Kasari C. Preschool based JASPER intervention in minimally verbal children with autism: pilot RCT. *J Autism Dev Disord*. 2013 May;43(5):1050–1056. [*PMID: 22965298*]

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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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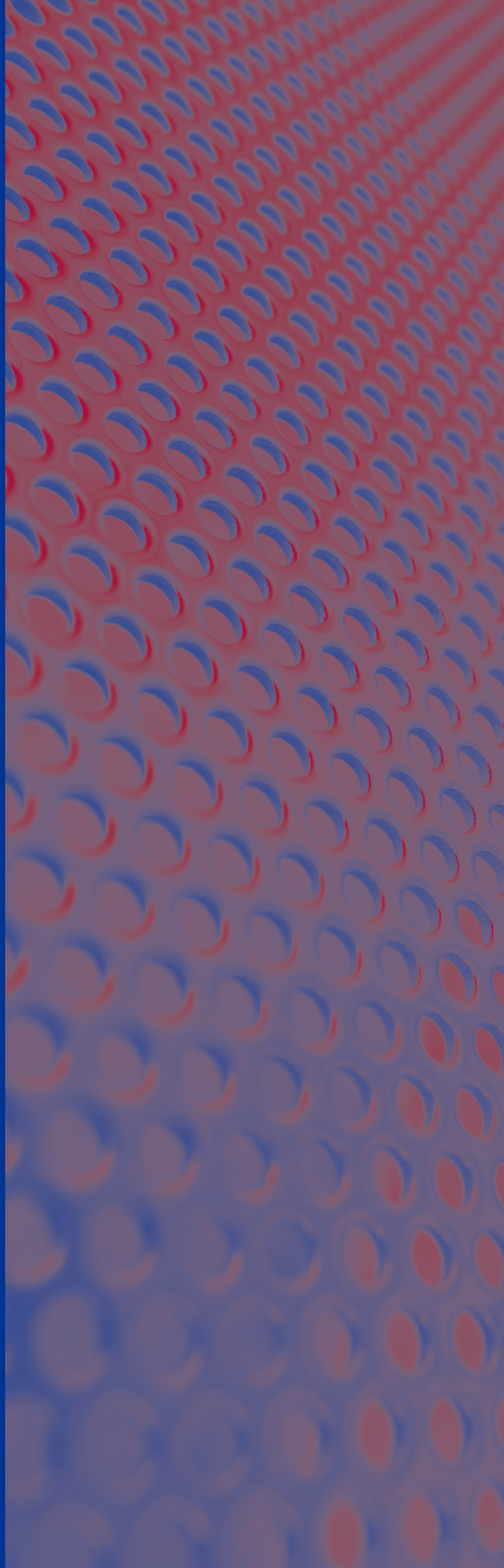

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