INTERAGENCY AUTISM COORDINATING COMMITTEE

2014

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 and 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 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 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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INTRODUCTION

THE 2014 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 underlying biology of autism spectrum disorder (ASD) and potential risk factors, tested approaches for improving early screening and diagnosis, and evaluated caregiver- and parent-mediated intervention strategies. The advances also examine the economic impacts of ASD, issues related to education and employment for adults with ASD, and ASD prevalence. The *2014 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.

ARTICLES SELECTED FOR THE 2014 SUMMARY OF ADVANCES

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QUESTION 1

WHEN SHOULD I BE CONCERNED?

Approaches to enhancing the early detection of autism spectrum disorders: a systematic review of the literature

Daniels AM, Halladay AK, Shih A, Elder LM, Dawson G. *J Am Acad Child Adolesc Psychiatry*. 2014 Feb;53(2):141-52. [*PMID: 24472250*]

Although ASD can be reliably diagnosed in children at about 2 years of age, on average, children in the U.S. are not diagnosed until they are 4 to 5 years old. Early diagnosis allows for early intervention, which improves outcomes, including quality of life. Previous studies have found associations between delayed diagnosis and factors, such as: low socioeconomic status, racial or ethnic minority status, low levels of caregiver awareness, inadequate community resources, and visiting numerous clinicians prior to diagnosis. Later diagnosis is also associated with greater severity of symptoms, presumably due to later intervention. To increase early diagnosis and early intervention, several Federal and national agencies have promoted effective community approaches to early detection (screening to identify children with developmental concerns). In this study, researchers reviewed the scientific literature on ASD screening in order to compare different approaches with respect to populations studied, intervention components, and outcomes. They reviewed 40 screening studies, which they sorted into the following categories: (1) strategies to raise awareness about early detection; (2) routine screening in medical and nonmedical settings; and (3) practices aimed at improving screening, such as provider training.

Of the four studies that described approaches focused on raising awareness about screening in parents, clinicians, and child care professionals, one reported positive results from a 3-year social media campaign. The other three studies assessed the effectiveness of training providers (online or in-person) to recognize ASD or developmental delays (DD). Two of these studies showed positive results, but the most scientifically rigorous study showed no difference in provider knowledge after training. Regarding routine screening, which includes screening using standardized surveys or other types of evaluations, 25 studies described 21 approaches to screening for DD, ASD, or both. Fifteen screening programs were conducted in health care settings; the others were in community settings. Researchers found that the literature reflected a wide variety of screening tools used and a wide variety of outcome measures, including screening rates and the percentage of children who screen positive who are referred for further evaluation. Most,

but not all, screenings that took place in primary care settings happened during the recommended well-child care visits. Some children were screened when they were sick, for example. Only a few studies looked at the change in how many children screened positive and were referred in response to a routine screening intervention. Of those studies, all reported an increase in rates of children screening positive or in rates of referral to intervention, indicating that medical or community-based opportunities for routine screening increase the likelihood that children who need services will be identified. However, more research is needed to connect these increased rates of referral with earlier diagnosis and access to services. The remaining 11 studies focused on 10 ways to enhance screening. A wide range of screening and referral rates was observed in these studies. Screening rates may be improved with a multifaceted approach that includes training clinicians in DD and ASD, ensuring they have validated screening tools, informing them about reimbursement practices, and providing resources for referrals, including partnerships with specialty providers. Going forward, improving the rigor of approaches to early detection and ensuring underserved populations benefit from evidence-based approaches should be high priorities. Establishing state-level benchmarks for early detection may also encourage better tracking.

Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F)

Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. *Pediatrics*. 2014 Jan;133(1):37-45. [*PMID: 24366990*]

The Modified Checklist for Autism in Toddlers (M-CHAT) is one of the world's most widely used, validated screening tools, and it consists of a questionnaire administered to parents about their child's behaviors. Optimally, a screening tool should be reliable and accurately identify children with signs of autism and also minimize the likelihood that some screened children will be incorrectly referred for unnecessary follow-up. In this study, researchers tested the M-CHAT, Revised with Follow-Up (M-CHAT-R/F) to determine if the modifications to the survey improved the ability to detect ASD in 18- and 24-month toddlers. Five revisions were made: (1) three M-CHAT/F questions that did not strongly help identify ASD were dropped; (2) the remaining 20 questions were reorganized to elicit more accurate answers from parents; (3) the top seven items that best differentiated ASD from other disorders were placed among the first 10 questions asked; (4) language was simplified (e.g., "Does your child ever use his/her index finger to point…" was changed to "Does your child point with one finger…"); and (5) examples of behaviors were given to provide additional context. The revised tool (M-CHAT-R/F) remains a two-stage screener. First, providers ask parents to answer 20 yes/no questions, which takes less than 5 minutes. If their child screens positive, parents spend an additional 5 to 10 minutes answering follow-up questions. Providers in metropolitan Atlanta and Connecticut screened 15,612 toddlers (average age 2 years, 2 months). A checkbox on the screener allowed the provider to indicate an independent concern about ASD. Based on parent response, researchers classified the children as low-, medium-, or high-risk for ASD. Parents of children at low risk were not asked to complete the follow-up questionnaire unless the provider had indicated a concern. Parents of children in the medium-risk group were contacted by telephone by the research staff to complete the follow-up. Those whose children were in the high-risk range were not contacted for follow-up, but were directly referred for evaluation. Children that were considered high-risk were those whose total scores were ≥3 in the first stage of the survey and then had a total score of ≥2 after follow-up. Of those children in the high-risk group, 47.5% were at risk of being diagnosed with ASD and 94.6% were at risk of any developmental delay. More than half of the medium-risk children no longer showed risk after the second stage of screening. Children continuing to screen positive and those flagged by providers were offered evaluation. Compared with the original tool, M-CHAT-R/F performed well in detecting toddlers with ASD while reducing unnecessary follow-up among children without ASD. The M-CHAT-R/F may be valued by busy medical offices and parents, as results show there is little to be gained by advancing low-risk or high-risk children to Stage 2 screening. Low-risk children can be screened again at a later date, as recommended. High-risk children, whose Stage 1 scores indicate they will continue to score high on a Stage 2 screening, can advance directly to evaluation. This study demonstrates that the M-CHAT-R/F can detect ASD in children 2 years old—2 years earlier than most cases are currently diagnosed—which optimizes the opportunity for early intervention.

QUESTION 2

HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Synaptic, transcriptional and chromatin genes disrupted in autism

De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Shih-Chen F, Aleksic B, Biscaldi M, Bolton PF, Brownfeld JM, Cai J, Campbell NG, Carracedo A, Chahrour MH, Chiocchetti AG, Coon H, Crawford EL, Curran SR, Dawson G, Duketis E, Fernandez BA, Gallagher L, Geller E, Guter SJ, Hill RS, Ionita-Laza J, Jimenz Gonzalez P, Kilpinen H, Klauck SM, Kolevzon A, Lee I, Lei I, Lei J, Lehtimäki T, Lin CF, Ma'ayan A, Marshall CR, McInnes AL, Neale B, Owen MJ, Ozaki N, Parellada M, Parr JR, Purcell S, Puura K, Rajagopalan D, Rehnström K, Reichenberg A, Sabo A, Sachse M, Sanders SJ, Schafer C, Schulte-Rüther M, Skuse D, Stevens C, Szatmari P, Tammimies K, Valladares O, Voran A, Li-San W, Weiss LA, Willsey AJ, Yu TW, Yuen RK; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium, Cook EH, Freitag CM, Gill M, Hultman CM, Lehner T, Palotie A, Schellenberg GD, Sklar P, State MW, Sutcliffe JS, Walsh CA, Scherer SW, Zwick ME, Barett JC, Cutler DJ, Roeder K, Devlin B, Daly MJ, Buxbaum JD. *Nature.* 2014 Nov;515(7526):209-15. [*PMID: 25363760*]

Hundreds of genes are affected by genetic mutations associated with ASD. In this study, the researchers were interested in identifying and analyzing genes with either inherited or spontaneous (*de novo*) mutations that reduced or eliminated the gene's normal function, known as loss of function (LoF) mutations. The researchers analyzed the genomes of more than 15,400 individuals with and without ASD, making it one of the largest studies of its kind. DNA samples from ASD family "trios" (two parents with a single child with ASD) were examined; an unexpectedly high percentage of the families contained *de novo* LoF mutations, leading the researchers to conclude that the most promising way to identify ASD-associated genes would be to analyze spontaneous and inherited genetic mutations in both individuals with and without ASD. Using this analytical method and controlling strictly for false discoveries, researchers identified 33 genes potentially associated with ASD risk. Fifteen of these genes were already known to be associated with ASD risk, 11 were suspected to play a role in ASD based on previous studies, and seven were seen in this study for the first time. *De novo* mutations in these 33 genes, which are believed to have a large effect on ASD risk, were observed at a higher frequency in females with ASD than males with ASD; this supports the idea that females may be in part "protected" from ASD. LoF variations in this group of genes were unlikely to be inherited from parents without ASD, meaning they were more likely to appear as *de novo* mutations in individuals with ASD.

Adjusting their analysis to control less strictly for false discoveries, the researchers identified 107 genes potentially associated with ASD. They found that more than 5% of the individuals with ASD in this study had a *de novo* LoF mutation in at least one of these genes. The LoF alterations in this second group of genes were more likely to be inherited from the parents than to arise spontaneously in individuals with ASD. Of the 107 genes, the researchers found an overrepresentation of genes involved in biological pathways important for healthy brain development. Furthermore, the researchers used a database to categorize a number of the genes as potentially involved in other disorders; these included 21 candidate genes for intellectual disability, three for epilepsy, 17 for schizophrenia, nine for congenital heart disease, and six for metabolic disorders.

To find other genes that potentially contribute to ASD risk, researchers looked for clusters of gene variations thought to be most harmful to neurodevelopment based on where in the brain they are expressed ("turned on"). This analysis identified 160 genes that may affect risk, including genes related to cell-to-cell communication (synaptic function) and regulation of gene expression (regulation of when and how often genes are "turned on"), which are processes essential to normal brain development. This study furthers our understanding of how genetic factors contribute to the development of ASD, and the identification of specific ASD-associated genes implicates specific biological pathways that can be the focus of further research.

Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection

Fraizer TW, Georgiades S, Bishop SL, Harden, AY. *J Am Acad Child Adolesc Psychiatry*. 2014 Mar;53(3):329-40. e1-3. [*PMID: 24565360*]

Males are at higher risk for ASD than females, so most characteristics that define the disorder are based on studies of males. If females with ASD have characteristics that differ from those seen in males, their symptoms may go unrecognized and females may be underdiagnosed. In the largest and most comprehensive study to date on females with ASD, researchers compared behavioral and cognitive characteristic of boys and girls with ASD, drawing on the Simons Simplex Collection (SSC) of more than 2,000 males and 300 females with ASD, 4 to 18 years of age. The researchers analyzed (1) core autism symptoms, (2) cognitive and motor function, and (3) adaptive behavior (social and practical skills) (4) and associated behavior problems. Regarding core autism symptoms, females showed higher levels of communication impairments, but they have lower levels of repetitive behavior symptoms. In fact, the largest difference between males and females in this study concerned restricted interests (high levels of intensity or focus on topics or objects). Females showed worse adaptive behavior in all areas, as well as greater associated behavior problems, such as irritability and lethargy. On measures of cognition and motor function, females showed lower overall, verbal, and nonverbal cognitive scores, as well as reduced language scores. Boys and girls were comparable on measures of motor function. However, males showed a greater discrepancy between verbal and nonverbal IQ, with the nonverbal IQ scoring higher, whereas females showed a discrepancy in favor of the verbal. Given this discrepancy, researchers also showed that lower IQ in females accounted for other observed differences, specifically, higher social communication impairments and lower adaptive function. IQ did not account for either the lower occurrence of restricted interests or the greater irritability and externalizing behaviors (such as aggression and acting out) in females. The study confirms findings from previous smaller studies that indicated females diagnosed with ASD tend to have generally greater impairments than males, including more social communication, cognitive, language, adaptive function, and behavioral challenges. The study also raises the question of whether high-functioning females with ASD are under-identified because they may have lower levels of symptoms (such as restricted interests) that are commonly seen in males with ASD. Clinicians should be aware that symptom disparities exist between females and males with ASD, and further study is needed to understand sex differences in ASD, including more focused studies of symptom disparities and the association of sex differences with genetic variation.

A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders

Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, Beckmann JS, Rosenfeld JA, Eichler EE. *Am J Hum Genet*. 2014 Mar 6;94(3):415-25. [*PMID: 24581740*]

More males than females have ASD, intellectual disabilities, and other neurodevelopmental disorders, which raises the question of whether females benefit from biological mechanisms that provide "protection" from such disorders. Past studies have shown mixed results, which may be due to sample size and differing methodologies. To address these concerns and to test for a "female protective model," researchers analyzed DNA samples from two groups of people with neurological conditions. The first group consisted of DNA from more than 9,200 males and 6,300 females who had undergone genetic testing because of a suspected developmental disability (DD), intellectual disability (ID), or ASD. The second group consisted of DNA samples from the Swedish Simons Simplex Collection (SSC). (Simplex families are those with only one individual with ASD.) The researchers compared the DNA from these two groups to the DNA of people who were not suspected of having any neurological disorder (all groups were overwhelmingly of European ancestry). The researchers speculated that a protective effect for females would appear as an increased number of harmful genetic mutations in females (compared with males) with neurological disorders. In other words, if females are indeed protected, they would need to possess a larger number of harmful genetic alterations than males do before showing symptoms, and this is precisely what this study found. At the same time and also as expected, females with genetic alterations associated with neurodevelopmental disorders showed more severe symptoms, such as low IQ. Compared with males, females with neurological disorders were shown to have two to three times more genes harmed, as well as more serious alterations to the individual genes affected. This increased burden of genetic mutations remained even when controlling for cognitive ability, measured by IQ, which indicates that other traits besides cognition may also be associated with the increased mutational burden observed in females. Genetic alterations associated with ASD were also more likely to be inherited from the mother than from the father, and alterations inherited from the mother were more harmful than genetic alterations inherited from the father. The researchers found that females carried a larger number of harmful genetic mutations, whether they were parents or offspring, lending credence to the idea that females are biologically protected from some neurological disorders. Stated another way, symptoms of ASD and other disorders will be observable in males with comparatively mild genetic alterations, whereas a female with the same scope or severity of genetic alteration may not show classic symptoms. Further research to elucidate the mechanisms of this neuroprotective effect may be helpful for increasing the understanding of sex differences in autism and future development of approaches to reduce the most disabling symptoms of ASD.

Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis

McElhanon BO, McCracken C, Karpen S, Sharp WG. *Pediatrics.* 2014 May;133(5):872-83. [*PMID: 24777214*]

Gastrointestinal (GI) dysfunction is frequently diagnosed in children with ASD. GI dysfunction is of particular concern in an ASD population due to their increased risk of feeding problems, most notably food selectivity (in which an individual eats only a narrow variety of foods). While this may not be an initial cause of concern, it can lead to multiple co-morbid health conditions (i.e. malnutrition or obesity). Many theories exist about possible connections between GI dysfunction and ASD, including that GI abnormality may be associated with ASD through some pathway that involves abnormality in the immune system; however, the underlying mechanisms and prevalence remain unclear.

To determine the overall difference in GI symptoms between children with and children without ASD, the current study conducted a meta-analysis of medical research into GI diagnoses, signs, and symptoms. The researchers searched multiple scholarly databases for relevant peer-reviewed research that involved collecting and analyzing data on GI symptoms and problems from appropriate subjects (children birth to 18 years with ASD); involved non-ASD comparison groups; and presented data on GI symptoms in credible ways. Fifteen studies meeting these criteria were then analyzed for their findings. Across these studies, the researchers found that children with ASD experienced significantly more general GI concerns, diarrhea, constipation, and abdominal pain than comparison children. The odds of children with ASD having general GI symptoms may have been four times higher than for children without ASD. A limitation of this study is that only four of 15 identified GI symptoms had enough prior published research to be included in this study. The researchers concluded that this indicates a need for more systematic and comprehensive research to identify the causes and long-term impacts of GI symptoms in ASD. Parents and clinicians should be aware of the increased risk of GI dysfunction in children on the autism spectrum, and there is a need for best practices and increased flexibility in the treatment of GI issues in this population.

Convergence of genes and cellular pathways dysregulated in autism spectrum disorders

Pinto D, Delaby E, Merico D, Barbosa M, Merikangas A, Klei L, Thiruvahindrapuram B, Xu X, Ziman R, Wang Z, Vorstman JA, Thompson A, Regan R, Pilorge M, Pellecchia G, Pagnamenta AT, Oliveira B, Marshall CR, Magalhaes TR, Lowe JK, Howe JL, Griswold AJ, Gilbert J, Duketis E, Dombroski BA, De Jonge MV, Cuccaro M, Crawford EL, Correia CT, Conroy J, Conceição IC, Chiocchetti AG, Casey JP, Cai G, Cabrol C, Bolshakova N, Bacchelli E, Anney R, Gallinger S, Cotterchio M, Casey G, Zwaigenbaum L, Wittemeyer K, Wing K, Wallace S, van Engeland H, Tryfon A, Thomson S, Soorya L, Rogé B, Roberts W, Poustka F, Mouga S, Minshew N, McInnes LA, McGrew SG, Lord C, Leboyer M, Le Couteur AS, Kolevzon A, Jiménez González P, Jacob S, Holt R, Guter S, Green J, Green A, Gillberg C, Fernandez BA, Duque F, Delorme R, Dawson G, Chaste P, Café C, Brennan S, Bourgeron T, Bolton PF, Bölte S, Bernier R, Baird G, Bailey AJ, Anagnostou E, Almeida J, Wijsman EM, Vieland VJ, Vicente AM, Schellenberg GD, Pericak-Vance M, Paterson AD, Parr JR, Oliveira G, Nurnberger JI, Monaco AP, Maestrini E, Klauck SM, Hakonarson H, Haines JL, Geschwind DH, Freitag CM, Folstein SE, Ennis S, Coon H, Battaglia A, Szatmari P, Sutcliffe JS, Hallmayer J, Gill M, Cook EH, Buxbaum JD, Devlin B, Gallagher L, Betancur C, Scherer SW. *Am J Hum Genet*. 2014 May 1;94(5):677-94. [*PMID: 24768552*]

Some individuals with ASD carry genetic mutations consisting of duplicated or deleted genes. These copy-number variations (CNVs), as they are known, can be either inherited or *de novo* (spontaneous, and therefore not inherited). In this study, the researchers were particularly interested in rare CNVs (those occurring in less than 1% of cases). DNA samples of 2,446 individuals with ASD and their parents were compared to a "control" group consisting of 2,640 individuals to analyze and measure the impact of CNVs on ASD. Not all genetic mutations are harmful, so regardless of the subject's ASD status, the researchers used information from previous studies to classify each CNV mutation they found as pathologic (disease-related), benign (not harmful), or "uncertain." The researchers found that individuals with ASD had about 1.4 times as many genes affected by rare duplication and deletion CNVs than individuals without ASD. The study also showed that most (64%) of the pathogenic CNVs in people with ASD were *de novo* (spontaneously occurring), while 36% were inherited. The researchers also looked for differences between males and females with ASD. They found that, when compared with the 6:1 ratio of males to females in the ASD group, the subgroup of subjects with ASD that had very harmful CNVs was composed of an increased proportion of females (a male-to-female ratio of 2:1). In addition, the researchers observed that females were nearly twice as likely as males to have CNVs in a specific set of genes associated with low cognitive functioning; this lends support to the hypothesis of a "female protective effect," which postulates that the number of mutations present in these genes must reach a high threshold in girls in order to result in ASD symptoms.

This study also looked at the kinds of genes affected by CNVs in individuals with ASD; this allows scientists to identify the underlying biological pathways that may be altered in ASD. Upon specifically examining genes important for brain function, the researchers found that a larger number of these genes were affected by rare deletion- and duplication-type CNVs in subjects with ASD compared with those in the control group. The researchers also found that rare genetic mutations associated with ASD appear to converge in networks of genes central to key biological processes, such as brain development, function of synapses (the small junctures between

neurons), as well as chromatin and transcription regulation (important for determining whether genes are "turned on" or "turned off"). Overall, the results of this study confirm previous research suggesting there are likely many genes and areas of the genome that may be implicated in autism. Although rare mutations associated with ASD can occur in hundreds of genes, many of these mutations affect particular biological mechanisms, which offer potential targets for future research.

QUESTION 3

WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Most genetic risk for autism resides with common variation

Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, Mahajan M, Manaa D, Pawitan Y, Reichert J, Ripke S, Sandin S, Sklar P, Svantesson O, Reichenberg A, Hultman CM, Devlin B, Roeder K, Buxbaum JD. *Nat Genet.* 2014 Aug;46(8):881-5. [*PMID: 25038753*]

Genetic risk for autism comes from alterations to genes that may be inherited or that may occur spontaneously during fetal development. Many past genetic studies of ASD have focused on the possible roles of rarely occurring inherited mutations and spontaneous genetic mutations. However, common genetic variations—inherited genetic differences in the genetic code that are found in many people with and without autism—are also thought to be an important component of autism risk. This study was designed to estimate the relative contributions of spontaneously occurring mutations, rare inherited mutations, and common genetic variations to the risk of ASD. The researchers analyzed data from Sweden's Population-Based Autism Genetics and Environment Study (PAGES). They looked at nearly 532,000 common genetic variants from 466 individuals with autism and 2,580 individuals who were not known to have autism. They found that common genetic variations accounted for roughly half (49%) of autism heritability in the population. Although each common genetic variant has a relatively small impact on autism risk by itself, taken together, the researchers estimate that common variations present the largest type of heritable risk for autism. In contrast, they found that spontaneous genetic alterations as well as rare inherited alterations each accounted for only about 3% of autism risk. Although spontaneous genetic changes contributed relatively little to autism risk overall, such mutations can exert a disproportionately large influence on an individual's likelihood of exhibiting autism. For example, researchers estimated that of the 14% of autistic individuals with a certain kind of spontaneous mutation contributing to autism risk, the vast majority (approximately 80%) would not have been affected had they not been carrying that particular mutation. The researchers also looked at the relative contribution of non-genetic (environmental) factors on autism risk. Past studies have provided vastly different estimates of the importance of genetic versus other factors, with estimates of the genetic role ranging from 38% to nearly 100%. This study's researchers estimated autism heritability at around 60% (with the majority of risk associated with common genetic variations), and found that other factors account for the remaining 40% of autism risk.

Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay

Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. *Pediatrics*. 2014 May;133(5):e1241-8. [*PMID: 24733881*]

Serotonin is a chemical neurotransmitter that plays an important role in relaying signals from one neuron in the brain to another, and is involved in regulation of mood, appetite, sleep and other important brain functions. It is hypothesized by scientists that serotonin may also play a role in early brain development. Serotonin has been implicated in autism in part because about one third of children with ASD have higher blood levels of this neurotransmitter. The most commonly prescribed medications used to treat depression are drugs that interfere with the normal uptake of serotonin back into nerve cells following release; medications in this class are known as selective serotonin reuptake inhibitors (SSRIs). Using SSRI medication during pregnancy may raise a mother's blood levels of serotonin, which may, in turn, affect serotonin levels in the developing fetus. About one in 25 pregnant women take SSRIs. Previous findings on risk of ASD in children whose mothers take antidepressants during pregnancy are mixed. This population-based case-control study tests for a relationship between mothers' prenatal use of SSRIs and the odds of ASD and developmental disorders (DD) in their children. Cases were drawn from the Childhood Autism Risks from Genetics and Environment (CHARGE) study, which enrolled children with ASD or DD from the general population. Children in the CHARGE study were 2 to 5 years of age at the time of enrollment, born in California to a parent who speaks English or Spanish, and lived with at least one biological parent. The researchers compared these children to a group of children that matched in terms of age, gender, and location, but who had not been diagnosed with ASD or DD. A total of 966 mother-child pairs were studied: 492 ASD, 154 DD, and 320 typical development (TD). Mothers were interviewed by telephone to learn about their SSRI use 3 months before pregnancy and during each trimester, and their medical records were also reviewed. Other information collected included maternal substance use history, use of St John's wort and other supplements that affect serotonin, history of mood or anxiety disorders or other psychiatric conditions, birthplace of the mother, and more.

The researchers found that, taken as a whole, children exposed to SSRIs in the womb were no more likely than unexposed children to have ASD or DD. However, when classified by sex, boys whose mothers used SSRIs were nearly three times more likely to have ASD than were TD children. (There were too few exposed girls to analyze.) The strongest relationship was seen in boys with ASD exposed to SSRIs in the first trimester. SSRI use also was correlated with DD, with the strongest relationship seen in boys exposed in the second and third trimesters. In previous studies of SSRI use and ASD or DD, it has been difficult to determine whether SSRI use or the underlying depression, anxiety, or other mood disorder may be increasing the risk of certain developmental outcomes. To help address this question, the researchers in this study restricted their analysis of SSRI use to those mothers who reported a history of anxiety or mood disorder at any time prior to birth. A pattern of results similar to those in previous studies (correlating SSRI use with ASD/DD) was found, suggesting that the observed association of

ASD and DD with maternal SSRI use in this study was not confounded by maternal mental health. The strength of this study in comparison to others on the same topic is that the study captured actual use of medication and not just whether medication was dispensed, but the interview-based approach has the limitation of recall bias (that participants may not have accurately recalled/reported their earlier activities). The researchers note that due to the overall low prevalence of SSRI use during pregnancy and other factors that may have a stronger influence on the development of ASD, SSRI use among pregnant women will likely not drive increasing rates of ASD. They also caution that untreated depression during pregnancy carries known risks for both mother and child and conclude that the benefits and risks of using SSRIs to treat depression during pregnancy must be carefully considered.

The contribution of de novo coding mutations to autism spectrum disorder

Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, Stessman HA, Witherspoon KT, Vives L, Patterson KE, Smith JD, Paeper B, Nickerson DA, Dea J, Dong S, Gonzalez LE, Mandell JD, Mane SM, Murtha M, Sullivan CA, Walker MF, Waqar Z, Wei L, Willsey AJ, Yamrom B, Lee YH, Grabowska E, Dalkic E, Wang Z, Marks S, Andrews P, Leotta A, Kendall J, Hakker I, Rosenbaum J, Ma B, Rodgers L, Troge J, Narzisi G, Yoon S, Schatz MC, Ye K, McCombie WR, Shendure J, Eichler EE, State MW, Wigler M. *Nature*. 2014 Nov 13;515(7526):216-21. [*PMID: 25363768*]

Because ASD tends to run in families, much research has focused on inherited genetic mutations that increase the risk of autism. However, less is known about how or to what extent spontaneously occurring mutations (known as *de novo* mutations) increase ASD risk, compared to the contributions of inherited mutations. To begin to address this question, the researchers in this study analyzed the DNA of more than 2,500 children with ASD, 1,900 of their siblings without autism, and their parents. Based on their analysis, the researchers estimate that *de novo* mutations accounted for about 30% of the ASD diagnoses in low-risk families (having only one child with ASD). At the same time, *de novo* mutations were found to account for about 45% of ASD in females. Some *de novo* genetic mutations—specifically, Likely Gene Disrupting (LGD) mutations—are relatively rare yet were found to be more harmful; the researchers estimate that, when these kinds of mutations do occur, a large percentage of them (roughly 43%) contribute to ASD. Siblings with and without ASD had similar rates of *de novo* mutations, but the children with ASD had significantly higher rates of LGD mutations compared with their unaffected siblings.

The researchers then looked more closely at the LGD mutations across their study population of children with ASD and identified 391 different LGD mutations affecting a total of 353 genes. Of these, 27 genes were affected by more than one *de novo* mutation (known as a recurrent mutation). The LGD mutations in ASD tended to affect genes thought to be important in early neurological development, including genes involved in the modification of chromatin (part of a cell that packages DNA and determines whether genes are "turned on" or "turned off"), genes important for brain plasticity, and genes active in stages of embryonic development.

Among individuals with ASD attributable to *de novo* mutations, the researchers observed key differences between two groups: (1) high-IQ males (those with a nonverbal IQ >90); and (2) females of all IQ levels and low-IQ males. For instance, both females and low-IQ males shared a number of the same genes targeted by LGD mutations, while the genes found to be affected in the high-IQ males did not overlap. In addition, the affected genes in females and low-IQ males also overlapped significantly with genes targeted by mutations associated with schizophrenia and intellectual disability; genes of high-IQ males did not, suggesting there may be different molecular pathways involved in the high-IQ group. Recurrent mutations may be associated with the more severe symptoms seen in females and low-IQ males. For example, in this study, males with recurrent LGD mutations had on average a 20-point lower IQ than unaffected individuals. By examining these rare yet particularly harmful mutations and gaining a better understanding of the genes affected in ASD, the researchers are hopeful that their observations will lead to a deeper knowledge of the underlying biology of autism and perhaps enable the future development of treatments with widespread promise for those with ASD.

The familial risk of autism

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. *JAMA*. 2014 May 7;311(17):1770-7. [*PMID: 24794370*]

ASD is considered the most heritable of all developmental disorders, which has led to much research on the genetic factors that contribute to the development of autism. Although these studies have produced evidence about alterations to genes associated with ASD, they have not been able to measure the individual risk of ASD. This study addresses that knowledge gap. In Sweden, all children are assessed for development disorders at age 4, and diagnostic information is reported to the National Patient Register. The Register contains virtually complete national coverage of psychiatric disorders from 1973. This study aimed to calculate the individual risk of an autism diagnosis by analyzing data on all births in Sweden from 1982 through 2006. The study looked at data from more than two million families, including approximately 20,000 children with ASD. To date, it is the largest long-term study of the risk of ASD in families. Specifically, the study aimed to estimate relative recurrence risk (RRR), which is the risk that a sibling of a child who has autism will also have an autism diagnosis compared with a sibling of a child who does not have autism. The study measured RRR for fraternal and identical twins, full siblings, half siblings, and cousins of full siblings of children with ASD. The researchers also accounted for the psychiatric history of parents prior to the child's birth, the ages of parents at birth of the child, the birth year, and the child's sex. Results showed that RRR increased with closer familial relationships. Compared with a full sibling of a child without ASD, a full sibling of a child diagnosed with ASD was more than 10 times more likely to also have a diagnosis. Similarly, a maternal half sibling was more than three times more likely, a paternal half sibling was nearly three times more likely, and a cousin was twice as likely to have ASD. There was no significant difference in risk between boys or girls with a sibling with ASD based on the sex of that sibling (a boy with a sister with ASD is at similar risk for ASD as a girl with a brother with ASD and vice versa). For individuals without a sibling with ASD, the chance of having an ASD diagnosis by age 20 was 1% (one out of 100). In comparison, a cousin of an individual with ASD has a 3% chance of being diagnosed with ASD before age 20, a paternal half sibling: 7%, a maternal half-sibling: 9%, full siblings and fraternal twins: 13%, and identical twins: 59%. The study also assessed the importance of environmental and genetic factors and estimated that genetics accounted for 50% of the risk for ASD.

Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies

Taylor LE, Swerdfeger AL, Eslick GD. *Vaccine.* 2014 Jun 17;32(29):3623-9. [*PMID: 24814559*]

Though several research studies conducted in recent years have suggested that there is not a link between vaccines and autism, this issue continues to be a concern for some members of the autism community and the general public. This study was conducted to review existing research in finer detail to try to determine whether the body of scientific literature to date supports a link between vaccines and autism. The study used a meta-analysis approach, which is a method of pooling research data across studies and evaluating outcomes, to examine the relationship between two variables, which in this case are ASD and vaccines. Multiple biomedical research databases were searched for studies that looked at any of the proposed causes associated with vaccination (measles, mumps, and rubella [MMR]; mercury; or thimerosal), and included development of conditions on the autistic spectrum as an outcome. The researchers identified 10 studies as meeting the inclusion criteria: five case-control studies (a type of observational study that compares two groups of study subjects) involving just over 1.2 million children, and five cohort studies (a type of observational study that follows the same group of subjects over a long period of time) involving close to 10,000 children. None of the 10 studies reported a positive link between ASD and MMR, mercury, or thimerosal. When researchers pooled the data from the five cohort studies, they found that exposure to vaccine or vaccine components had no effect on the risk of developing autism, either when all data were pooled or when separated by type of exposure. The researchers found the same result with the five case-control studies; MMR, thimerosal, and mercury exposure did not increase the risk of developing ASD either overall or individually. This meta-analysis found overall that across multiple studies using rigorous methodology, which when pooled included over 1.2 million children, there was no evidence for a link between vaccines or vaccine components and the development of any ASD outcome.

QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Caregiver-mediated intervention for low-resourced preschoolers with autism: an RCT

Kasari C, Lawton K, Shih W, Barker TV, Landa R, Lord C, Orlich F, King B, Wetherby A, Senturk D. *Pediatrics.* 2014 Jul;134(1):e72-9. [*PMID: 24958585*]

Families at the lower end of the socioeconomic scale with children with ASD are not often recruited to participate in ASD research, including research on early interventions for children with ASD. Over the past 10 years, ASD Early Intervention (EI) researchers have come to understand a great deal more about how such interventions can have real and positive effects on children with ASD, including by improving key behaviors, language, and social communication skills. However, proof of how well EIs could work for low resource families and their children has been lacking. To address this gap, the study authors recruited and screened a large number (112) of underserved families and their preschool-aged children with ASD to participate in a comparative study of two 3-month long, low-intensity EIs involving caregivers rather than professionals as the interventionists. The goal of the study was to determine if such short-term interventions handled primarily by the caregivers would improve key behaviors in the children. To begin, each participating family was randomly assigned to either the Caregiver Mediated Module (CMM) group, which facilitated the participation of children and caregivers in two 1-hour sessions per week at home together, or the Caregiver Education Module (CEM) group, which involved small group-based caregiver training for 2 hours each week in a neighborhood location without the child present. The two groups shared similar educational materials focused on teaching communication, the basics of behavior management, and developing routines. At the end of the study, study authors found that the children with caregivers in both groups improved in joint engagement (with their caregivers) and initiating joint attention (a child pointing to share something, for example). However, improvement in both behaviors was significantly greater among the children whose caregivers had worked with them in the home (CMM). At the 3-month follow-up assessment, the researchers found that the children who had received either intervention had maintained their improved skills in initiating joint attention compared to when they entered the program. For the CMM group the authors assessed changes in the children's play behavior. While there was improvement in symbolic play (e.g., child has a doll feed a dog), there was no change in functional play skills (e.g., stacking blocks). The study was one of the first of its type to enroll a large racially and ethnically diverse

sample of low resource families. As such, it is valuable for having supplied some of the first data on the success of interventions involving these families and for having indicated that caregiver-mediated interventions can help mitigate some of the most challenging symptoms of ASD in these children.

Parent-implemented social intervention for toddlers with autism: an RCT

Wetherby AM, Guthrie W, Woods J, Schatschneider C, Holland RD, Morgan L, Lord C. *Pediatrics*. 2014 Dec;134(6):1084-93. [*PMID: 25367544*]

Effective early intervention (EI) for children with ASD could improve outcomes, particularly if the intervention begins "early," meaning not too long after a stable diagnosis of ASD (possible at 18–24 months). Some studies testing interventions with preschoolers have shown significant improvements in joint engagement (two-way communication with care-givers), IQ score, and language skills. Other studies testing interventions with children near 24 months but younger than preschool age have also shown promise, primarily by improving parents' early intervention skills, which are key to fostering long-term improvements in their children. With these past studies in mind, the current study authors decided to create an Early Social Interaction (ESI) Project to facilitate the involvement of parents, reduce the need for more intensive interventions later in life, and enable interventions to be more easily accepted and implemented at the community level. The purpose of this study was to test the comparative effects on toddlers with ASD of two 9-month parent-implemented interventions. The study consisted of 82 toddlers with a diagnosis of ASD and the children and their parents were randomly assigned to one of two groups. The first was called individual-ESI and the second was called group-ESI. The individual-ESI had parents meet with professional interventionists individually for three sessions per week (two at home and one at the clinic) for 6 months, then engage in two sessions per week (one at home and one in a community setting) for 3 months. Sessions included practicing supports and strategies, problem solving, and planning. The group-ESI included four or five families that met for one session per week. These sessions were usually held in playgroups at a clinic where parents could talk with the professional interventionists and other parents and practice using strategies to support their children's social communication skills.

The study findings at the end of the 9-month period indicated that toddlers in the individual-ESI showed significant improvement in social communication at a rate much faster than the group-ESI. Children in the individual-ESI showed improvement in the areas of social affect (social demeanor and/or behavior, how one comes across to others) and expressive language (skills in expressing one's wants and needs); however, the group-ESI saw no change in these areas. Also, the individual-ESI showed parent self-efficacy had positive gains in early social skills, including social communication, verbal skills, and daily living activities, whereas parents in the group-ESI saw worsening or no change in these skills. The study's findings support individual-ESI over group-ESI for effectiveness in terms of child social skills and behaviors, and by using a parent-implemented model it can hopefully reduce the use of professionals and be more successful on a community level.

QUESTION 5

WHERE CAN I TURN FOR SERVICES?

Costs of autism spectrum disorders in the United Kingdom and the United States
Buescher AV, Cidav Z, Knapp M, Mandell DS. *JAMA Pediatr*. 2014 Aug; 168(8): 721-8. [*PMID: 24911948*]

Most previous estimates on ASD's economic costs to society were narrow (focusing largely on health care) and based on data that have since been updated and refined. This study expanded cost estimates to areas other than health care, estimated lifetime costs, and provided comprehensive costs associated with ASD in the United States and the United Kingdom. To estimate comprehensive lifetime costs in two countries, researchers conducted a literature review of peer-reviewed studies and consulted other sources of data to compile updated information on ASD prevalence (how many people have ASD), how many people with ASD also have intellectual disability, average lifespan, and place of residence. They also gathered data on the types of medical and nonmedical ASD services people with ASD use, as well as indirect economic factors, such as productivity loss for individuals with ASD and their caregivers. The researchers used the data to calculate the average annual medical, nonmedical, and indirect economic and lifetime costs borne by individuals with autism, their families, and society. To have the most accurate costs estimates, researchers estimated them separately for individuals with and without intellectual disability (ID), which can greatly increase costs. The researchers estimated the number of people with ASD in the United States and United Kingdom as approximately 3,541,000 and 604,800, respectively. Lifetime costs of supporting an individual with ASD and an intellectual disability were estimated at $2.4 million in the United States and £1.5 million (US $2.2 million) in the United Kingdom. The lifetime costs of supporting an individual with ASD who does not have an intellectual disability was $1.4 million in the United States and £0.92 million (US $1.4 million) in the United Kingdom. The researchers estimated that 40–60% of children with ASD also have ID, and concluded that the total annual cost of supporting children with ASD is about $4.5–5 billion (£3.1–3.4 billion) in the United Kingdom and $61–66 billion in the United States. The researchers found that the largest contributors to total costs in both countries for children were direct nonmedical costs, such as special education (including early intervention services), and indirect nonmedical costs, such as parental productivity loss. For adults with ASD, again assuming that 40–60% have ID, the researchers estimated total annual costs (minus benefit payments) of $175–196 billion in

the United States and $43–46 billion (£29–31 billion) in the United Kingdom. The largest contributors to total costs for adults with ASD in both countries were accommodation (residential care or supportive living accommodation), followed by direct medical costs, and individual productivity loss. The study found that medical costs for adults are much higher than for children in both countries. These estimates of lifetime societal costs associated with ASD are much higher than found in previous studies, although the per person costs were less than those estimated in the most recent prior study that used a similar approach (Ganz, 2006). These findings are relevant for numerous policy considerations, such as those regarding lifelong supports for ASD (including residential concerns), as well as policies supporting caregivers, particularly addressing disrupted employment.

Economic burden of childhood autism spectrum disorders

Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. *Pediatrics*. 2014 Mar;133(3):e520-9. [*PMID: 24515505*]

The prevalence of ASD among children in the United States has grown quickly over a short period of time. Despite the increased proportion of children diagnosed with ASD and the specialized health and education services they require, there has not been a comprehensive cost analysis that accounts for the range of services used. Past studies have assessed primarily health care-related costs, although there are indications that costs unrelated to health care may also be significant contributors to the total economic burden of ASD. To get a broader and more complete economic picture of the costs of ASD during childhood, researchers in this study sought to estimate utilization and costs associated not only with health care, but also with education, ASD-related therapy, family-coordinated services, and caregiver time. The study included families with children age 3 to 17 years old with ASD. Families in control groups had no reported ASD. Estimates of costs related to health care were obtained using data from the CDC's National Health Interview Survey and the AHRQ's Medical Expenditure Panel Survey, including 109 subjects in the ASD group and more than 18,000 in the control group. Estimates of non-health care related costs were obtained using a large, national panel survey including more than 137 respondents in the ASD group, and 121 respondents as controls. The researchers found that children with ASD used more health care, education services, ASD-related therapy, and family coordinated services compared with controls. Regarding usage of the health care system, the children with ASD made significantly more visits to physician and non-physician offices compared to children in the control group; children with ASD also showed a higher level of prescription medication usage. When other services were assessed, the researchers found that, compared with the control group, the children with ASD were more likely to attend public school (versus attending private school) or be home schooled, to participate in special education programs, and to use tutoring services. ASD-related therapy, such as applied behavior analysis or sensory integration therapy, was reportedly used by 31% of the ASD group. The two groups did not differ significantly in caregiver time.

The researchers calculated that caring for a child with ASD can cost more than $17,000 per year more than caring for a child without ASD, but only 18% of these costs were associated with increased use of health care. Specifically, ASD was associated with $3,020 higher health care costs and $14,061 higher aggregated non-health care costs. However, after controlling for epilepsy and intellectual disability, health care costs did not significantly differ between the two groups. The majority of costs not associated with health care were related to education ($8,610 annually). The researchers found that higher costs of schooling in families with ASD were associated with their much higher use of special education services, including in public schools. Not surprisingly, costs increased as ASD severity levels increased. In contrast with previous studies, this study did not find that parents of children with ASD spent more time caregiving or had more out-of-pocket expenses compared with control groups, except in cases

of severe autism. In sum, researchers estimated that the total societal cost of ASD during childhood in the United States is $11.5 billion annually, with a large proportion of this cost attributable to the special education services offered by public schools. Recognizing the crucial role of public schools in the provision of ASD services can help ensure that policies and funding meet children's needs.

QUESTION 6

WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

A longitudinal examination of 10-year change in vocational and educational activities for adults with autism spectrum disorders

Taylor JL, Mailick MR. *Dev Psychol.* 2014 Mar;50(3):699-708. [*PMID: 24001150*]

Relative to youth with other disabilities, when many young adults with ASD leave high school, they often receive fewer services and are less engaged in education and employment. However, it is not known whether these youth are experiencing a temporary or long-term setback. To address this gap, this study examined the vocational and educational activities of a sample of adults with ASD over a 10-year period. The researchers also looked at personal characteristics (such as intellectual disability, maladaptive behaviors, and daily living skills) and contextual resources (such as family income and parental social networks) that might impact levels of independence in employment and educational activities after high school. The current study drew on a subsample of 161 adults (ages 18–52) already enrolled in a larger longitudinal study of families with adolescent and adult children with ASD. The larger study collected data on families at six points over a 10-year period 1998–2010. Nearly three quarters of the adults with ASD in the current study were male, and about 80% had some level of ID. Most subjects (who were all 18 years or older) were living with a parent or other relative when the current study began. The researchers sought to determine whether the vocational and educational activities of these adults had become more independent, stayed the same, or had become less independent over a 10-year period. This study showed that independence in educational and employment activities had significant declines. Less than 25% of adults showed any improvement in vocational activities, and less than 5% had any improvements that were considered substantial. The results suggested that poor outcomes after high school are not a temporary setback, but stay the same and even worsen for some throughout adulthood. Women experienced particularly severe vocational declines, with a 15 times greater decline than the average male subject over the 10-year study period. While researchers determined that women's worsening employment status over time was not associated with greater impairment, there are other factors that may have played a role such as gender stereotyping and parental expectations. The researchers predicted that contextual supports such as family income or receipt of various support services outside the family would improve the level of job independence of subjects over time; however, the effect of such support was only marginal.

Consistent with the researchers' hypothesis, adults with ASD who had greater independence in their daily living activities were more independent in their vocational and educational activities. Though, researchers could not isolate if independence in daily living leads to more independence in vocational and educational activities, or if the effect is vice versa. These findings indicate a need for additional research on the challenges faced by adults with ASD after leaving high school, and especially on the worsening gender disparities in employment faced by adult females with ASD.

QUESTION 7

WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010
Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). *MMWR Surveill Summ.* 2014 Mar 28;63(2):1-21. [*PMID: 24670961*]

The Autism and Developmental Disabilities Monitoring Network (ADDM Network) estimates ASD prevalence in the United States (U.S.). It does this by systematically gathering and analyzing data, including ASD diagnoses, among children 8 years of age whose parents or guardians live in ADDM Network sites in the U.S. Such monitoring (surveillance) first involves collecting, organizing, and analyzing data from many sources, including health clinics, specialized programs for children with developmental disabilities, and records of children receiving special education services in public schools. Trained clinicians then determine and verify a child's ASD status (case status) based on the data and criteria provided by the American Psychiatric Association in its Diagnosis and Statistical Manuals of Mental Disorders (DSM). The current study is a report by the ADDM Network's principal investigators primarily presenting their ASD prevalence estimates for 2010 based on data on 5,338 children 8 years of age with verified ASD diagnoses and case status living in 11 ADDM Network sites that year. The main finding was an estimated overall prevalence rate of 14.7 per 1,000 or 1 in 68 children 8 years of age. Further, the estimated rate varied from site to site, from a low of 5.7 per 1,000 for the ADDM site in Alabama to a high of 21.9 per 1,000 for the ADDM site in New Jersey. Four of the 11 ADDM sites with limited or no access to children's education records reported the lowest rates, possibly due to the lack of key data such as special education reports and intellectual ability ratings.

Other findings indicated that more boys (one in 42) than girls (one in 189) in the communities were identified with ASD. In addition, non-Hispanic white children were somewhat more likely to be identified with ASD than non-Hispanic black children, but much more likely to be identified with ASD than Hispanic children. The researchers were also interested in what data they were able to collect from seven sites on the levels of intellectual ability in ASD, finding that at these sites, 31% of the 8-year-old children with ASD had IQ scores in the range of intellectual disability (ID), 23% were in the borderline range, and 46% were in the average or above average range (IQ greater

than 85). Further, they found that ASD prevalence was lower for ASD co-occurring with ID (4.7 per 1,000) than for ASD not co-occurring with ID (10.2 per 1,000). The researchers also calculated that about half the children studied were over 4 years old before they had their earliest known ASD diagnosis. In discussing their findings, the authors noted their estimates of ASD prevalence do not represent the entire country; their reports are "far more accurate" when they have access to school records; and they intend to further investigate the socioeconomic factors that may be influencing relatively late diagnoses and treatments, such as interventions more effectively applied early in a child's life. The researchers also noted an observation they are not yet able to explain but certainly intend to explore further—they observed a shift in who is being identified with ASD. In most years until recently, the highest percentage of the ASD cases were found among children with low levels of intellectual ability, but now that trend is changing to the point where in 2010, 46% of the ASD cases were among children with average or above average intellectual ability. Last, the ADDM Network researchers made a series of recommendations, including but not limited to improving recognition and documentation of ASD symptoms in children "with an emphasis on those whose early symptoms may often be missed," including girls as well as boys, children without ID, and children in all racial/ethnic groups, as well as lowering the age when children are first evaluated for ASD and subsequently enrolled in community support services.

The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism

Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, Anderson JS, Assaf M, Bookheimer SY, Dapretto M, Deen B, Delmonte S, Dinstein I, Ertl-Wagner B, Fair DA, Gallagher L, Kennedy DP, Keown CL, Keysers C, Lainhart JE, Lord C, Luna B, Menon V, Minshew NJ, Monk CS, Mueller S, Müller RA, Nebel MB, Nigg JT, O'Hearn K, Pelphrey KA, Peltier SJ, Rudie JD, Sunaert S, Thioux M, Tyszka JM, Uddin LQ, Verhoeven JS, Wenderoth N, Wiggins JL, Mostofsky SH, Milham MP. *Mol Psychiatry*. 2014 Jun;19(6):659-67. [*PMID: 23774715*]

ASD is a complex, lifelong condition with symptoms that vary substantially among individuals. Large ASD studies that yield important advancements are currently facilitated by allowing researchers worldwide open access to genetic data. However, no similar open sharing has occurred for brain imaging data, which is also important to understanding and treating ASD. In response, a multicenter research team created the Autism Brain Imaging Data Exchange (ABIDE) to compile and openly share brain imaging data for scientific research. Among other uses, brain imaging can help researchers understand how parts of the brain are interconnected and how this connectivity may be altered in mental disorders. Currently, ABIDE contains more than 1,100 brain scans of individuals 7–64 years of age; roughly half have ASD and half are unaffected controls. The imaging data were collected from individuals who were not performing any mental tasks (resting-state functional magnetic resonance imaging, or R-fMRI). In addition to the imaging data, the scientists have compiled basic information, including age, sex, IQ, and diagnosis, for each subject. To demonstrate the utility of ABIDE, the researchers examined the basic biological connections within the brains of subjects with ASD compared with those of a control group. They selected the data from scans of 360 male subjects with ASD; the control group included 403 males of the same age without ASD. Compared with the functioning of brains in the control group, the researchers found some individuals with ASD exhibited decreased nerve connectivity and others showed increased connectivity, although decreased connectivity was the predominant characteristic observed; these mixed observations are consistent with previous studies. The reduced connectivity was particularly noticeable in two areas of the brain associated with social processing, cognition, and affect (outward display of emotions, such as facial expression). The researchers' analysis also revealed altered connectivity in brain circuits important for learning and sensory-motor function; this finding warrants future research. In addition, this study showed disrupted connectivity between the two hemispheres of the brain in people with ASD and hints that this altered connectivity may be more extensive than indicated in previous studies. Some of the differences in brain functionality observed in individuals with ASD appeared to remain the same across age groups, implying that brain maturity has no impact on some aspects of functional connectivity; however, in the future, more imaging of children under age 6 is needed to confirm this observation. In general, ongoing efforts to image the brains of children and adolescents with ASD will help researchers gain a better understanding of the developing brain. The ABIDE R-fMRI resource provides an unprecedented opportunity for scientists to replicate key analyses and make new discoveries. The researchers expect that by collecting and consolidating multiple international data sets, ABIDE can help increase the pace of scientific advances.

Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates

Maenner MJ, Rice CE, Arneson CL, Cunniff C, Shieve A, Carpenter LA, Braun KVN, Kirby, RS, Bakian AV, Durkin MS. *JAMA Psychiatry*. 2014 Mar;71(3):292-300. [*PMID: 24452504*]

Determining how many children have ASD in any given time period depends on the criteria used to diagnose them. The primary reference guide for such diagnoses is the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association (APA). In 2013, APA released a new version of the DSM (DSM-5), which revised diagnostic criteria for ASD. Unlike in the previous versions, the DSM-5 classifies ASD as a single disorder, without any subtypes such as autistic disorder and Asperger disorder; it recognizes only two domains of impairment—social communication and restricted repetitive patterns of behavior, interests, or activities; and specifies only seven distinct diagnostic criteria compared to the 12 diagnostic criteria previously needed. Some experts have suggested that the new criteria may reduce the number of children diagnosed with ASD. Also, the revised diagnostic criteria pose challenges for monitoring prevalence of ASD over time and differentiating changes in prevalence due to risk factors from changes associated with diagnostic criteria. The current study aimed to evaluate the potential effects of the new criteria on ASD prevalence by using DSM-5 criteria on ASD prevalence estimation data previously measured under the earlier DSM version. The study looked at prevalence estimates of ASD among 8-year-old children living in 11 Autism and Developmental Disabilities Monitoring (ADDM) Network sites within the United States in 2006 and three additional ADDM Network sites in 2008. After reviewing the data that served as the basis for these estimates, experts determined that 6,577 of the children had a verifiable ASD diagnosis (ASD case status) based on the previous version of the DSM. The researchers then sought to determine how many of these diagnosed children would also likely be diagnosed using DSM-5 criteria. The researchers determined that 81.2% (5,339) met criteria for ASD diagnosis based on the DSM-5. Of those children who did not, most fell short of an ASD diagnosis by only one criterion. The researchers then adjusted ASD prevalence estimates from the ADDM Network for 2006 and 2008 so that the estimates included only children who met the DSM-5 diagnostic criteria. The results were that prevalence estimates fell in both years, from nine to 7.4 per 1,000 for 2006 and from 11.3 to 10 per 1,000 for 2008. DSM-5 had a smaller effect on prevalence in 2008 than it did in 2006, which may suggest that the DSM-5 will not change the trend of increasing ASD prevalence over time. However, the authors caution other researchers to take care when interpreting trends in ASD prevalence that include data based on differing diagnostic criteria.

ARTICLES SELECTED FOR THE 2014 SUMMARY OF ADVANCES

QUESTION 1: WHEN SHOULD I BE CONCERNED?

Daniels AM, Halladay AK, Shih A, Elder LM, Dawson G. Approaches to enhancing the early detection of autism spectrum disorders: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry*. 2014 Feb;53(2):141-52. [*PMID: 24472250*]

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QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

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