2017 Summary of Advances Nominations: January – December 2017*

*Those shaded gray are newly nominated since the October meeting and have not been discussed.

Question 1 (Screening and Diagnosis)	
Laura Kavanagh	Chatham CH, Taylor KI, Charman T, Liogier D'ardhuy X, Eule E, Fedele A, Hardan AY, Loth E, Murtagh L, Del Valle Rubido M, San Jose Caceres A, Sevigny J, Sikich L, Snyder L, Tillmann JE, Ventola PE, Walton-Bowen KL, Wang PP, Willgoss T, Bolognani F. **Adaptive behavior in autism: minimal clinically important differences on the Vineland-II**. Autism Res. 2017 Sep 21. [Epub ahead of print] [PMID: 28941213]
	Justification for Nomination: Difficulties with adaptive behaviors in Autism Spectrum Disorder (ASD) emerge early, but with development many individuals will fall increasingly behind their typically-developing peers. These cumulative differences in adaptive behavior are impactful: they are associated with the ultimate level of educational attainment, with the likelihood of living independently from parents and caregivers, with the number of medical support services that will be needed later in life, and with the number of medical needs that society will fail to address. Consequently, adaptive behavior is clearly a key target for interventions in ASD, yet we lack an understanding of how much adaptive behavior must change for an improvement to be truly meaningful. To address this gap, we estimated the "minimal clinically important difference" (MCID) on the most common assessment of adaptive behavior, the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II; Sparrow et al, 2005) Survey Interview form. We pooled data from several consortia/registries (EU-AIMS LEAP study, ABIDE-I, ABIDE-II, INFOR, Simons Simplex Collection and Autism Treatment Network [ATN]) and clinical investigations and trials (Stanford, Yale, Roche) resulting in a dataset of over 9,000 individuals with ASD, and over 10,000 individual assessments of the Vineland-II. We employed every widely-accepted statistical technique for estimating these MCIDs. *Scientific Insights: In addition to this practical advance, the work has also led to more fundamental advances in our understanding of ASD's clinical presentation and assessment. First, using the techniques and large data collected through this effort, we were able to fully characterize the dependence of adaptive behavior on intelligence and age, as well as to derive equations that correct the Vineland-II standardized scores for the influences of these demographic traits. Second, we were able to detect fundamental associations not previously reported – for example, the fact that individuals with ASD show much less variance in adaptive behavior than in other phenotypic traits (for example, IQ), contrasting with the heterogeneity widely reported to characterize ASD as a whole. Finally, we were able to assemble a large group of collaborators with access to*

	unparalleled clinical data from ASD, informing several novel interventions that are currently under investigation. *Significant Impact: We believe that this work represents the most comprehensive statistical estimate of the MCID ever undertaken in this condition, for any measure. As a result of our work, it is now possible to more fully evaluate the efficacy of new interventions for ASD in terms of their effects on critical and impactful adaptive behaviors.*
Joshua Gordon	Donohue MR, Childs AW, Richards M, Robins DL. **Race influences parent report of concerns about symptoms of autism spectrum disorder**. Autism. 2017 Nov 1:1362361317722030. [PMID: 29100475]
	Mental health disparities are a critical concern in autism research because of evidence that children and youth from racial and ethnic minority groups, systemically have less access to appropriate services for ASD screening, diagnosis, and treatment. This study investigated a possible contributor to health disparities by examining differences between Black and White parental reports of concerns about children's ASD symptomology. Researchers analyzed data from parents (N=147) of toddlers (18-40 months of age) who completed a free-response questionnaire about their child's development, following an initial positive screen for ASD, but prior to a formal ASD diagnosis. Relative to White parents, Black parents reported significantly fewer concerns about autism in general; and about their child's social, restricted, and repetitive behavior specifically. However, there was no evidence of racial group differences in parents' non-autism concerns, nor in reports of disruptive behaviors. The value of these findings point to potential areas of children's development, particularly in terms of social, restricted, and repetitive behaviors, that researchers and clinicians can target to educate and inform minority parents as potential early signs of autism.
Joshua Gordon	Emerson RW, Adams C, Nishino T, Hazlett HC, Wolff JJ, Zwaigenbaum L, Constantino JN, Shen MD, Swanson MR, Elison JT, Kandala S, Estes AM, Botteron KN, Collins L, Dager SR, Evans AC, Gerig G, Gu H, McKinstry RC, Paterson S, Schultz RT, Styner M; IBIS Network, Schlaggar BL, Pruett JR Jr, Piven J. **Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age**. Sci Transl Med. 2017 Jun 7;9(393). pii: eaag2882. [PMID: 28592562]
	Funded by NIMH and NICHD; highlighted in NIMH and NIH press releases, as well as Dr. Collins' blog: • *https://www.nimh.nih.gov/news/science-news/2017/neuroimaging-technique-may-help-predict-autism-among-high-risk-infants.shtml* • *https://www.nih.gov/news-events/news-releases/neuroimaging-technique-may-help-predict-autism-among-high-risk-infants* • *https://directorsblog.nih.gov/2017/06/13/autism-spectrum-disorder-progress-toward-earlier-diagnosis/*

Joshua Gordon *Walter Koroshetz* *Jennifer Johnson* *Geraldine Dawson*	Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, Elison JT, Swanson MR, Zhu H, Botteron KN, Collins DL, Constantino JN, Dager SR, Estes AM, Evans AC, Fonov VS, Gerig G, Kostopoulos P, McKinstry RC, Pandey J, Paterson S, Pruett JR, Schultz RT, Shaw DW, Zwaigenbaum L, Piven J; IBIS Network; Clinical Sites; Data Coordinating Center; Image Processing Core; Statistical Analysis. **Early brain development in infants at high risk for autism spectrum disorder**. Nature. 2017 Feb 15;542(7641):348-351. [PMID: 28202961]
	Using magnetic resonance imaging (MRI) in infants with older siblings with autism, researchers from around the country were able to correctly predict 80 percent of those infants who would later meet criteria for autism at two years of age.
	In this prospective neuroimaging study of 106 infants at high familial risk of ASD and 42 low-risk infants, we show that hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months. Brain volume overgrowth was linked to the emergence and severity of autistic social deficits. A deep-learning algorithm that primarily uses surface area information from magnetic resonance imaging of the brain of 6-12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%). These findings demonstrate that early brain changes occur during the period in which autistic behaviours are first emerging.
	This study explored the timing and characteristics of the relationship between brain enlargement and ASD symptoms. Infants at high (n=106) or low (n=42) familial risk for ASD underwent neuroimaging examination at 6, 12, and 24 months. Analyses revealed that early increased expansion of cortical surface area preceded subsequent volume overgrowth in 15 high risk infants diagnosed with autism at 24 months. The enlarged brain volume was associated with onset and severity of autism-related social deficits. Moreover, an algorithm based on MRI surface area measurements could predict ASD diagnosis at 24 months among the high-risk sample (81% PPV and 88% sensitivity). These findings point to a role in early post-natal overexpansion of cortical surface area in the development of ASD and provide proof of principle for the utility of a prodromal brain biomarker for ASD.
Geraldine Dawson	Hull L, Mandy W, Petrides KV. **Behavioural and cognitive sex/gender differences in autism spectrum condition and typically developing males and females**. Autism. 2017 Aug;21(6):706-727. [PMID: 28749232]
	This systematic review suggests that individuals with autism spectrum conditions display typical sex/gender differences in core autism spectrum condition traits, suggesting that diagnostic criteria based on these symptoms should take into account typical sex/gender differences.

Joshua Gordon	Lewis JD, Evans AC, Pruett JR Jr, Botteron KN, McKinstry RC, Zwaigenbaum L, Estes AM, Collins DL, Kostopoulos P, Gerig G, Dager SR, Paterson S, Schultz RT, Styner MA, Hazlett HC, Piven J; Infant Brain Imaging Study Network. **The emergence of network inefficiencies in infants with autism spectrum disorder**. Biol Psychiatry. 2017 Aug 1;82(3):176-185. [PMID: 28460842]
	This study uses data from 260 infants at 6 and 12 months of age, including 116 infants with longitudinal data. Diffusion data was used to obtain measures of the length and strength of connections between brain regions to compute network efficiency. Group differences were assessed in efficiency within linear mixed-effects models determined by the Akaike information criterion. Inefficiencies in high-risk infants later classified with ASD were detected from 6 months onward in regions involved in low-level sensory processing. In addition, within the high-risk infants, these inefficiencies predicted 24-month symptom severity. These results suggest that infants with ASD, even before 6 months of age, have deficits in connectivity related to low-level processing, which contribute to a developmental cascade affecting brain organization and eventually higher-level cognitive processes and social behavior.
Geraldine Dawson	Mandy W, Wang A, Lee I, Skuse D. **Evaluating social (pragmatic) communication disorder**. J Child Psychol Psychiatry. 2017 Oct;58(10):1166-1175. [PMID: 28741680]
	This study pf 1,081 individuals did not find evidence that SPCD is qualitatively distinct from ASD. Rather, it appears to lie on the borderlands of the autism spectrum, describing those with autistic traits that fall just below the threshold for an ASD diagnosis. SPCD may have clinical utility for identifying people with autistic traits that are insufficiently severe for ASD diagnosis, but who nevertheless require support.
Laura Kavanagh	Mazurek MO, Lu F, Symecko H, Butter E, Bing NM, Hundley RJ, Poulsen M, Kanne SM, Macklin EA, Handen BL. **A prospective study of the concordance of DSM-IV and DSM-5 diagnostic criteria for autism spectrum disorder**. J Autism Dev Disord. 2017 Sep;47(9):2783-2794. [PMID: 28620892]
	Brief justification for nomination: This was the first large-scale study to prospectively examine the concordance of DSM-IV and final DSM-5 criteria in a well-characterized clinical sample of children referred for autism diagnostic evaluation. The study addressed significant methodological weaknesses of prior studies by using a prospective rather than retrospective design, and by using final rather than draft DSM-5 criteria. The study directly tested concordance and discordance using a consistent diagnostic battery and including those not meeting criteria based on either DSM-IV or DSM-5. In addition, the order in which DSM checklists were completed was randomly assigned, thereby controlling for potential order effects. The methodological rigor of the study and its findings yield important information about the clinical implications of the transition from DSM-IV to DSM-5.

	Scientific insights: DSM-5 criteria demonstrated excellent overall specificity and good sensitivity relative to DSM-IV criteria. Sensitivity and specificity were strongest for children meeting DSM-IV criteria for Autistic Disorder. In contrast, a substantial percentage of children who met DSM-IV criteria for Asperger's disorder and PDD NOS did not meet DSM-5 criteria for ASD (20% and 75%, respectively). Higher IQ, older age, female sex, and less pronounced ASD symptoms were associated with greater discordance. *Significant impact: Most children (89%) who met DSM-IV criteria for an ASD continued to meet DSM-5 criteria, indicating that the overall diagnostic determination in most cases will not be affected by these DSM changes. However, substantial discordance was found among the subgroups of children who would have met criteria for Asperger's disorder and PDD NOS. In fact, twenty percent of those meeting criteria for Asperger's Disorder and 75% of those meeting criteria for PDD NOS did not meet criteria for ASD on DSM-5. In general, subtle or ambiguous symptoms are less likely to meet DSM-5 criteria for ASD. The study also provided new information about child-specific characteristics that affect concordance and discordance. Children meeting DSM-IV criteria for an ASD who had higher cognitive functioning, were older at the time of assessment, or had less pronounced social and behavioral symptoms were less likely to be diagnosed with ASD according to DSM-5. The results also indicated greater diagnostic discordance among girls than boys, suggesting that girls may be disproportionately affected by the transition from DSM-IV to DSM-5.*
Laura Kavanagh	McIntyre NS, Solari EJ, Grimm RP, E Lerro L, E Gonzales J, Mundy PC. **A comprehensive examination of reading heterogeneity in students with high functioning autism: distinct reading profiles and their relation to autism symptom severity**. J Autism Dev Disord. 2017 Apr;47(4):1086-1101. [PMID: 28160222]
	Brief (3-5 sentences) justification for nomination: The data reported in this paper indicate that a majority of school aged verbally fluent children with ASD have difficulty with reading comprehension. The paper also provides data indicating that reading comprehension learning disability is part of the developmental social communication phenotype of verbally fluent children with ASD. Finally, the paper provides an unusual and informative level of detail about the heterogeneity of expression of reading comprehension learning disability within school aged students with ASD. *Scientific insights: The paper provides evidence to support that hypothesis that a developmental conceptualization of the phenotype of ASD would be helpful and that for verbally fluent children risk for reading comprehension disability should be included in the nosology.* *Significant impact: Recognizing that reading comprehension disability is an important feature of ASD in verbally fluent children will inform how schools*

	may leverage reading and literacy curriculums to better addresses the specific cognitive and social developmental needs of verbally fluent elementary and high school students with ASD.
Laura Kavanagh *Jennifer Johnson*	Moody EJ, Reyes N, Ledbetter C, Wiggins L, DiGuiseppi C, Alexander A, Jackson S, Lee LC, Levy SE, Rosenberg SA. **Screening for autism with the SRS and SCQ: variations across demographic, developmental and behavioral factors in preschool children**. J Autism Dev Disord. 2017 Nov;47(11):3550-3561. [PMID: 28856480]
	Brief justification for nomination: Screening for autism is a critical first step to receive a diagnosis and ultimately access services. While there are several available screeners that generally perform well, there is growing awareness that most screeners do not perform equally well across all demographic groups. This study found that two commonly used instruments have extremely high false positive rates when the child has any other developmental concern, or come from racial/ethnic minorities or low socioeconomic background. This provides further evidence that the well-known health disparities related to various demographic groups could emerge even at this critical first step in the diagnostic process. *Scientific insights: A large multi-site sample was collected through a case-control design through the Study to Explore Early Development. For children with any concern from the Child Behavior Checklist or Mullen Scales for Early Learning, Specificity dropped to unacceptable levels, in many cases as low as 20%. Similarly, there were decreases in Specificity as maternal education and family income decreased, or from African American and Hispanic families.* *Significant impact: This study suggests that existing screeners perform inadequately for children with other non-autism developmental challenges, or from disadvantaged groups. Given the well-known health disparities in these groups, this finding is concerning as a high false positive screening rate may not lead to increased subsequent diagnosis in these groups. Further work is needed to refine screeners to be more effective, to increase the use of screeners in these groups and to determine how to facilitate progression from screening to subsequent diagnosis and treatment. Further, this highlights the challenge of accurately distinguishing autism from other non-autism challenges.*
	The Social Communication Questionnaire (SCQ) and the Social Responsiveness Scales (SRS) are commonly used screeners for autism spectrum disorder (ASD). Data from the Study to Explore Early Development were used to examine variations in the performance of these instruments by child characteristics and family demographics. For both instruments, specificity decreased as maternal education and family income decreased. Specificity was decreased with lower developmental functioning and higher behavior problems. This suggests that the false positive rates of the SRS and the SCQ are associated with child characteristics and family demographic

	factors. There is a need for ASD screeners that perform well across socioeconomic and child characteristics. Clinicians should be mindful of differential performance of these instruments in various groups of children.
Jennifer Johnson	Sabapathy T, Madduri N, Deavenport-Saman A, Zamora I, Schrager SM, Vanderbilt DL. **Parent-reported strengths in children with autism spectrum disorders at the time of an interdisciplinary diagnostic evaluation**. J Dev Behav Pediatr. 2017 Apr;38(3):181-186. [PMID: 28368969]
	Parents of children with autism spectrum disorders (ASD) often focus on concerns in discussions with health care providers. A study was thus conducted to identify parent-reported strengths in a sample of children with ASD. Parent report of child's strengths were qualitatively analyzed, coded, and clustered into themes. Parents reported more strengths in the Cognitive Functioning and Personality Characteristics meta-themes. Pediatricians have a unique opportunity to discuss parental positive perceptions of children with ASD and to learn about their strengths.
David Amaral	Shen MD, Kim SH, McKinstry RC, Gu H, Hazlett HC, Nordahl CW, Emerson RW, Shaw D, Elison JT, Swanson MR, Fonov VS, Gerig G, Dager SR, Botteron KN, Paterson S, Schultz RT, Evans AC, Estes AM, Zwaigenbaum L, Styner MA, Amaral DG, Piven J; Infant Brain Imaging Study Network; Infant Brain Imaging Study Network, The Infant Brain Imaging Study (IBIS) Network is a National Institutes of Health–funded Autism Center of Excellence project and consists of a consortium of eight universities in the United States and Canada, Piven J, Hazlett HC, Chappell C, Dager S, Estes A, Shaw D, Botteron K, McKinstry R, Constantino J, Pruett J, Schultz R, Zwaigenbaum L, Elison J, Evans AC, Collins DL, Pike GB, Fonov V, Kostopoulos P, Das S, Gerig G, Styner M, Gu H. **Increased Extra-axial Cerebrospinal Fluid in High-Risk Infants Who Later Develop Autism.** Biol Psychiatry. 2017 Aug 1;82(3):186-193. [PMID: 28392081]
	This is a replication and extension of work initially published in 2013. It demonstrates that children at risk for ASD because they have a sibling with the disorder, have increased cerebrospinal fluid between the brain and skull which can be detected as early as 6 months of life. This abnormal brain profile may be a helpful biomarker of risk for ASD.
Joshua Gordon	Wolff JJ, Swanson MR, Elison JT, Gerig G, Pruett JR Jr, Styner MA, Vachet C, Botteron KN, Dager SR, Estes AM, Hazlett HC, Schultz RT, Shen MD, Zwaigenbaum L, Piven J; IBIS Network. **Neural circuitry at age 6 months associated with later repetitive behavior and sensory responsiveness in autism.** Mol Autism. 2017 Mar 4;8:8. [PMID: 28316772]
	Longitudinal diffusion tensor imaging data were collected from 217 infants at high familial risk for ASD. Forty-four of these infants were diagnosed with ASD at age 2. Targeted cortical, cerebellar, and striatal white matter pathways were defined and measured at ages 6, 12, and 24 months. Dependent variables included the Repetitive Behavior Scale-Revised and the Sensory Experiences Questionnaire. Findings suggest that restricted and

	repetitive behaviors contributing to a diagnosis of ASD at age 2 years are associated with structural properties of callosal and cerebellar white matter pathways measured during infancy and toddlerhood. They further identified that repetitive behaviors and unusual sensory response patterns co-occur and share common brain-behavior relationships. *These brain-behavior relationships were remarkably specific, suggesting a possible neurobiological mechanism wherein atypical neural development in infancy precedes the emergence of core autistic features within the domain of restricted and repetitive behaviors. Identifying pre-symptomatic markers of later behavior in ASD also affords the possibility of developing enhanced approaches to screening and preventative interventions.*
Question 2 (Underlying Biology)	
Joshua Gordon	Bruno JL, Romano D, Mazaika P, Lightbody AA, Hazlett HC, Piven J, Reiss AL. **Longitudinal identification of clinically distinct neurophenotypes in young children with fragile X syndrome**. Proc Natl Acad Sci U S A. 2017 Oct 3;114(40):10767-10772. [PMID: 28923933]
	In this study, investigators identified two distinct subgroups of children with fragile X syndrome. Based on longitudinal MRI data (N=42), the researchers utilized a multivariate classification algorithm known as topological data analysis to identify two subgroups of children who were differentiated on the basis of significant neuroanatomical alterations. These two groups also differed on comparison measures of cognition, adaptive functioning, and autism severity scores across a distinct period in early development. These findings hold the potential to predict later outcomes and guide design of targeted therapies for individuals with FXS.
Joshua Gordon *Geraldine Dawson*	Constantino JN, Kennon-McGill S, Weichselbaum C, Marrus N, Haider A, Glowinski AL, Gillespie S, Klaiman C, Klin A, Jones W. **Infant viewing of social scenes is under genetic control and is atypical in autism**. Nature. 2017 Jul 20;547(7663):340-344. [PMID: 28700580]
	In the attached paper, the authors report that variation in viewing of social scenes, including levels of preferential attention and the timing, direction and targeting of individual eye movements, is strongly influenced by genetic factors, with effects directly traceable to the active seeking of social information. In a series of eye-tracking experiments conducted with 338 toddlers, including 166 epidemiologically ascertained twins (enrolled by representative sampling from the general population), 88 non-twins with autism and 84 singleton controls, we find high monozygotic twin–twin concordance (0.91) and relatively low dizygotic concordance (0.35). Moreover, the characteristics that are the most highly heritable, preferential attention to eye and mouth regions of the face, are also those that are differentially decreased in children with autism ($\chi 2 = 64.03$, $P < 0.0001$). These results implicate social visual engagement as a neurodevelopmental endophenotype not only for autism, but also for population-wide variation in social-information seeking.

David Amaral	Duvekot J, van der Ende J, Verhulst FC, Greaves-Lord K. **Examining bidirectional effects between the autism spectrum disorder (ASD) core symptom domains and anxiety in children with ASD**. J Child Psychol Psychiatry. 2017 Oct 27. [Epub ahead of print] [PMID: 29076153]
	This paper reports data from a longitudinal study that demonstrates that anxiety symptoms contribute to higher levels of social communication impairment but not vice versa. It also shows a disconnect between anxiety symptoms and repetitive behaviors.
Walter Koroshetz	Ecker C, Andrews DS, Gudbrandsen CM, Marquand AF, Ginestet CE, Daly EM, Murphy CM, Lai MC, Lombardo MV, Ruigrok AN, Bullmore ET, Suckling J, Williams SC, Baron-Cohen S, Craig MC, Murphy DG; Medical Research Council Autism Imaging Multicentre Study (MRC AIMS) Consortium. **Association between the probability of autism spectrum disorder and normative sex-related phenotypic diversity in brain structure**. JAMA Psychiatry. 2017 Apr 1;74(4):329-338. [PMID: 28196230]
	This study explored sex differences in ASD that may be related to normative differences in brain structure phenotype. The authors conducted MRI scans on high-functioning ASD adults (n=98) and matched neurotypical control adults (n=98) 18-42 years of age, and developed predictive models of biological sex based on cortical thickness. Analyses of the neuroanatomical diversity and patterns revealed that more male-typical patterns of brain anatomy among biological females led to three-fold increase in risk for ASD as compared to biological females with a more female characteristic brain phenotype. In addition, the patterns of regional neuroanatomical variability and their correlations with low or high ASD risk were sex specific, and were observed in regions that have been linked to core ASD behavioral deficits. This paper sheds light on potential neurobiological mechanisms that may underpin sex differences in ASD and points to the need for consideration of brain structure phenotype when assessing ASD risk.
Geraldine Dawson	Eggebrecht AT, Elison JT, Feczko E, Todorov A, Wolff JJ, Kandala S, Adams CM, Snyder AZ, Lewis JD, Estes AM, Zwaigenbaum L, Botteron KN, McKinstry RC, Constantino JN, Evans A, Hazlett HC, Dager S, Paterson SJ, Schultz RT, Styner MA, Gerig G, Das S, Kostopoulos P; IBIS Network, Schlaggar BL, Petersen SE, Piven J, Pruett JR Jr. **Joint attention and brain functional connectivity in infants and toddlers**. Cereb Cortex. 2017 Mar 1;27(3):1709-1720. [PMID: 28062515]
	The authors show that the functional organization of the brain is intimately related to the emergence of joint attention using functional connectivity magnetic resonance imaging and dimensional behavioral assessments in a large semilongitudinal cohort of infants and toddlers. The strongest brain-behavior associations cluster within connections between a small subset of functional brain networks; namely between the visual network and dorsal attention network and between the visual network and posterior cingulate aspects of the default mode network. These observations mark the earliest

	known description of how functional brain systems underlie an early symptom of ASD, namely, joint attention.
Joshua Gordon	Gupta AR, Westphal A, Yang DYJ, Sullivan CAW, Eilbott J, Zaidi S, Voos A, Vander Wyk BC, Ventola P, Waqar Z, Fernandez TV, Ercan-Sencicek AG, Walker MF, Choi M, Schneider A, Hedderly T, Baird G, Friedman H, Cordeaux C, Ristow A, Shic F, Volkmar FR, Pelphrey KA. **Neurogenetic analysis of childhood disintegrative disorder.** Mol Autism. 2017 Apr 4;8:19. [PMID: 28392909]
	This study suggests that Childhood Disintegrative Disorder (CDD), a rare form of ASD characterized by late-onset, severe regression, is biologically distinct from other forms of autism. CDD candidate genes were found to be more highly expressed in non-neocortical regions than neocortical regions. This expression profile was similar to that of an independent cohort of ASD probands with regression. The non-neocortical regions overlapped with those identified by fMRI as abnormally hyperactive in response to viewing faces, such as the thalamus, cerebellum, caudate, and hippocampus. Eye-tracking analysis showed that, among individuals with ASD, subjects with CDD focused on eyes the most when shown pictures of faces. These results suggest differences between CDD and other forms of ASD on the neurobiological as well as clinical level.
Walter Koroshetz	Khundrakpam BS, Lewis JD, Kostopoulos P, Carbonell F, Evans AC. **Cortical thickness abnormalities in autism spectrum disorders through late childhood, adolescence, and adulthood: a large-scale MRI study**. Cereb Cortex. 2017 Mar 1;27(3):1721-1731. [PMID: 28334080]
	Heterogeneity in ASD, and small sample sizes in previous studies, have led to inconclusive evidence on a potential role of cortical thickness abnormalities in autism. This current study used a subset of data from the Autism Brain Imaging Data Exchange (ABIDE) data set to determine age-specific differences in cortical thickness in ASD and its relation to symptom severity. The study included 560 male subjects (266 ASD and 294 controls; age = 6-35 years) and computed cortical thickness measurements using the CIVET process followed by stringent multi-reviewer quality control procedures. Data were analyzed for age-related abnormalities and explored for association with symptom severity based on ADOS scores. The data showed significantly increased cortical thickness between ages 6 and 14; the effect was more pronounced in the left hemisphere. There was also a significant positive correlation between residual cortical thickness and severity scores for social affect and communication symptoms. This study used a robust data set to explore an unanswered question regarding brain structure abnormalities in autism. Longitudinal studies across the life span are needed to further explore the relationship between brain structure and development in ASD.
Joshua Gordon	Palmer N, Beam A, Agniel D, Eran A, Manrai A, Spettell C, Steinberg G, Mandl K, Fox K, Nelson SF, Kohane I. **Association of sex with recurrence of**

	autism spectrum disorder among siblings. JAMA Pediatr. 2017 Sep 25. [PMID: 28973142]
	Among the 3,166,542 children (1,547,266 females and 1,619,174 males; mean [SD] age, 11.2 [4.7] years) in the study, the prevalence of ASD was 1.96% (95% CI, 1.94%-1.98%) among males and 0.50% (95% CI, 0.49%-0.51%) among females. When a male was associated with risk in the family, ASD was diagnosed in 4.2% (95% CI, 3.8%-4.7%) of female siblings and 12.9% (95% CI, 12.2%-13.6%) of male siblings. When a female was associated with risk in the family, ASD was diagnosed in 7.6% (95% CI, 6.5%-8.9%) of female siblings and 16.7% (95% CI, 15.2%-18.4%) of male siblings. These findings are in agreement with the higher rates of ASD observed among males than among females in the general population. The study provides more specific guidance for the screening and counseling of families and may help inform future investigations into the environmental and genetic factors that confer risk of ASD.
Walter Koroshetz	Sethna F, Feng W, Ding Q, Robison AJ, Feng Y, Wang H. **Enhanced expression of ADCY1 underlies aberrant neuronal signalling and behaviour in a syndromic autism model**. Nat Commun. 2017 Feb 20;8:14359. [PMID: 28218269]
	Approximately 50% of males with Fragile X Syndrome (FXS) are diagnosed with autism. Loss of functional FMRP, which causes FXS, leads to abnormal intracellular signaling and altered synthesis of synaptic proteins. This study identified and manipulated a pathway by which these changes occur that involves type 1 adenylyl cyclase (ADCY1) mRNA and protein synthesis pathways. In Fmr1 mutant mice, genetic reduction of ADCY1 protein normalized the aberrant signaling cascades that are mediated by ERK1/2 and PI3K, and attenuated autism-related repetitive and social behaviors and audiogenic seizures. Peripheral administration of an experimental compound that suppresses ADCY1 activity also reduced the behavioral deficiencies in the Fmr1 mutant mice. Gq-coupled muscarinic acetylcholine receptors are also upregulated in Fmr1 mutant mice and implicated in the ERK1/2 and PI3K signaling cascades, and thus may represent a novel target for pharmacological intervention in ASD.
Laura Kavanagh	Silverman LB, Eigsti IM, Bennetto L. **I tawt i taw a puddy tat: Gestures in canary row narrations by high-functioning youth with autism spectrum disorder**. Autism Res. 2017 Aug;10(8):1353-1363. [PMID: 28371492]
	Brief (3-5 sentences) justification for nomination: *A diagnostic criterion for ASD is impairment in nonverbal communication such as gesture production. However, most studies on gesture production have focused on preverbal toddlers and preschoolers with ASD. Participants in the study by Silverman and colleagues were verbally fluent teenagers. The study yielded a surprising and clinically important result: Youth with ASD were found to produce the same types of gestures that other youth produce, yet their gestures were less frequent and more difficult for others to understand.*

	Scientific insights: *The decreased clarity of gestures in youth with ASD is likely to exacerbate their difficulties with social communication.* *Significant impact:* *This study clarifies what aspects of gesture production are and are not impaired in verbally fluent individuals with ASD: They appear to use the same repertoire of gestures that others use, but their gestures are often less clear and potentially confusing their communication partners. This impairment could be an important target for intervention.*
David Amaral	Solomon M, Iosif AM, Reinhardt VP, Libero LE, Nordahl CW, Ozonoff S, Rogers SJ, Amaral DG. **What will my child's future hold? phenotypes of intellectual development in 2-8-year-olds with autism spectrum disorder**. Autism Res. 2017 Oct 27. [Epub ahead of print] [PMID: 29076255]
	This paper reports the cognitive development of a large cohort of children involved in a longitudinal analysis of ASD.There is both good news and not so good news here. At least 35% of children with ASD show very substantial IQ gains between 3 and 5 years of age. This should provide parents with some hope that there is the potential for substantial improvement in their children over time. The not so good news is that there is a group of children (around 20%) that are very impaired at initial diagnosis and show little or no improvement over the next few years. The paper emphasizes that there are different trajectories of development for children diagnoses with ASD at an early age.
Joshua Gordon	Weir RK, Bauman MD, Jacobs B, Schumann CM. **Protracted dendritic growth in the typically developing human amygdala and increased spine density in young ASD brains**. J Comp Neurol. 2018 Feb 1;526(2):262-274. [Epub 2017 Oct 26] [PMID: 28929566]
	This study examined the mechanisms that may underlie why the amygdala undergoes early and rapid volumetric growth in autism spectrum disorder (ASD) compared to typically developing individuals (TD). Focusing specifically on dendritic growth and spine density, the investigators examined post-mortem amygdala tissue from 32 human brains (7-46 years of age) to test for evidence that, (a) dendritic arborization in the amygdala followed protracted growth in TD and early overgrowth in ASD and (b), whether spine density in the amygdala in ASD cases differs from TD from youth to adulthood. The findings showed that while dendritic growth into adulthood occurred among both ASD and TD, spine density was greater among younger ASD cases (<18 years of age) and that spine density declined among adults with ASD, relative to TD cases. The significance of these findings highlight the unique growth trajectory of the amygdala in ASD overall, and more specifically that spine density may contribute to aberrant development and function of the amygdala in children and adolescents with ASD.

Question 3 (Risk Factors)	
Linda Birnbaum	Andrews SV, Ellis SE, Bakulski KM, Sheppard B, Croen LA, Hertz-Picciotto I, Newschaffer CJ, Feinberg AP, Arking DE, Ladd-Acosta C, Fallin MD. **Cross-tissue integration of genetic and epigenetic data offers insight into autism spectrum disorder**. Nat Commun. 2017 Oct 24;8(1):1011. [PMID: 29066808]
	Advance: *This study reports two important technical advances for autism research: 1) It answers a key question regarding the use of blood to study epigenomic changes in inaccessible tissues such as brain; and 2) it analyzes the interplay between the genetic code and chemical tags (epigenetic marks) on the DNA that control whether genes switch on or off, revealing insights into the biology of ASD.* ***Summary:*** *Along with genetic variation, epigenetic regulation (e.g., via chemical modifications on DNA that direct how specific cell types "read" genetic code) has been implicated in causation of ASD; however, how this variation contributes to the functional biology of ASD is not well understood. This study integrates genotypic and epigenetic data (i.e., DNA methylation states) from cord blood, peripheral blood, and lung and fetal brain, finding that more genetic code variations in autism-related genes are associated to DNA methylation states than expected. Gene ontology enrichment for these methylated gene targets of ASD-associated gene variants found that most are involved in biological pathways related to immune system functions. These findings help reconcile some previous genetic and gene expression studies that have implicated different pathways (i.e., chromatin regulation and immune dysregulation, respectively). The described methods of combining genetic and epigenetic information can be used to help elucidate and expand regions and target genes of interest as well as inform future functional studies.*
Linda Birnbaum	Arora M, Reichenberg A, Willfors C, Austin C, Gennings C, Berggren S, Lichtenstein P, Anckarsäter H, Tammimies K, Bölte S. **Fetal and postnatal metal dysregulation in autism.** Nat Commun. 2017 Jun 1;8:15493. [PMID: 28569757]
	Advance: Studies of environmental risk factors for autism are hampered by the difficulty in assessing exposures and their timing during etiologically relevant periods of early development, which occur years before diagnosis. The authors address this challenge and demonstrate the utility of tooth matrix exposure biomarkers for identifying different temporal patterns of uptake of essential and toxic metals in ASD cases and controls. *Summary: This study used teeth collected from twins that either were concordant or discordant for ASD diagnosis, and examined levels of both essential and toxic metals in precise layers of dentine from shed deciduous teeth (baby teeth) during prenatal and early postnatal periods. Levels of lead were elevated in ASD cases, particularly in the early postnatal period*

	(5-20 weeks post-birth). Levels of the essential metals manganese and zinc also differed in ASD cases vs. controls. Manganese levels were lower in ASD cases during two time frames, one prenatally (10 weeks prior to birth) and the other during an early postnatal phase (5-20 weeks after birth). Zinc levels, meanwhile, were only lower during a latter prenatal to early postnatal phase (10 weeks prior to birth until 5 weeks after). Furthermore, metal levels at three months after birth were predictive of severity of ASD later in life. This study is an important advance for identifying biomarkers of exposure to environmental risk factors during critical windows of development and supports the idea that ASD may be associated with altered regulation of essential and toxic metals.
Geraldine Dawson	Bishop SL, Farmer C, Bal V, Robinson EB, Willsey AJ, Werling DM, Havdahl KA, Sanders SJ, Thurm A. **Identification of developmental and behavioral markers associated with genetic abnormalities in autism spectrum disorder**. Am J Psychiatry. 2017 Jun 1;174(6):576-585. [PMID: 28253736]
	Children with de novo mutations (n=112) showed greater likelihood of motor delays during early development (i.e., later age of walking), but less impairment in certain measures of ASD core symptoms (parent-rated social-communication impairment and clinician-rated diagnostic certainty) in later childhood. Children with ASD with de novo mutations may exhibit a "muted" symptom profile with respect to social-communication and language deficits, relative to those with ASD with no identified genetic abnormalities. Such findings suggest that examining early milestone differences and standardized testing results may be helpful in etiologic efforts, and potentially in clinical differentiation of various subtypes of ASD, but only if developmental/demographic variables are properly accounted for first.
Laura Kavanagh	Brucato M, Ladd-Acosta C, Li M, Caruso D, Hong X, Kaczaniuk J, Stuart EA, Fallin MD, Wang X. **Prenatal exposure to fever is associated with autism spectrum disorder in the boston birth cohort**. Autism Res. 2017 Nov;10(11):1878-1890. [PMID: 28799289]
	Brief (3-5 sentences) justification for nomination: Autism spectrum disorder (ASD) is phenotypically and etiologically heterogeneous, with evidence for genetic and environmental contributions to disease risk. Research has focused on the prenatal period as a time where environmental exposures are likely to influence risk for ASD. Epidemiological studies have shown significant associations between prenatal exposure to maternal immune activation (MIA), caused by infections and fever, and ASD. However, due to differences in study design and exposure measurements no consistent patterns have emerged revealing specific times or type of MIA exposure that are most important to ASD risk. This study estimated the association between prenatal exposure to fever and maternal infections and ASD in a prospective birth cohort of an understudied minority population in a city in the United States.

	Scientific insights: In a nested sample of 116 ASD cases and 988 typically developing controls, prenatal exposure to fever was associated with increased ASD risk (aOR 2.02 [1.04-3.92]) after adjustment for educational attainment, marital status, race, child sex, maternal age, birth year, gestational age, and maternal smoking. This effect may be specific to fever during the third trimester (aOR 2.70 [1.00-7.29]). No association was found between prenatal exposure to genitourinary infections or flu and the risk of ASD in the crude or adjusted analyses. *Significant impact: This study found that children were at increased risk for ASD when their mothers had a fever during pregnancy. These findings provide a focus for future research efforts and ASD prevention strategies across diverse populations.*
Joshua Gordon	Geisheker MR, Heymann G, Wang T, Coe BP, Turner TN, Stessman HAF, Hoekzema K, Kvarnung M, Shaw M, Friend K, Liebelt J, Barnett C, Thompson EM, Haan E, Guo H, Anderlid BM, Nordgren A, Lindstrand A, Vandeweyer G, Alberti A, Avola E, Vinci M, Giusto S, Pramparo T, Pierce K, Nalabolu S, Michaelson JJ, Sedlacek Z, Santen GWE, Peeters H, Hakonarson H, Courchesne E, Romano C, Kooy RF, Bernier RA, Nordenskjöld M, Gecz J, Xia K, Zweifel LS, Eichler EE. **Hotspots of missense mutation identify neurodevelopmental disorder genes and functional domains**. Nat Neurosci. 2017 Aug;20(8):1043-1051. [PMID: 28628100]
	The current study sought out to deepen our understanding of genetic risk for Neurodevelopmental disorders (NDD). The research focused on identifying novel, previously less studied-missense mutations associated with NDD. Using a genome wide approach, utilizing publicly available large sample sequencing data, the research team has identified 200 genes with significant clustering of novel patient specific, protein coding missense mutations. Further analysis of the identified hotspot genes showed enrichment for synaptic signaling, and chromatin mediated regulation of transcription pathways both previously implicated in ASD and other psychiatric disorders. The current findings are a significant step forward in the complex process of identification and refinement of potential functional genetic targets that can lead to better understanding of disease etiology, course, outcome and possible personalized targeted treatment development.
Linda Birnbaum	Golding J, Ellis G, Gregory S, Birmingham K, Iles-Caven Y, Rai D, Pembrey M. **Grand-maternal smoking in pregnancy and grandchild's autistic traits and diagnosed autism.** Sci Rep. 2017 Apr 27;7:46179. [PMID: 28448061]
	Advance: This study demonstrates that environmental exposures can have effects across multiple generations. As we seek to understand autism risk and etiology, it is important to consider how we will study and measure these exposures across generations. *Summary: This study used data from the Avon Longitudinal Study of Parents and Children, a long-running population-based British study of how*

	environment and genotype affect health outcomes. Parents of children enrolled in this study were asked about their parents' smoking habits--whether they ever smoked and if mothers smoked during pregnancy. The relationship between grandparental smoking and social and communication traits predictive of autism were studied. Granddaughters of maternal grandmothers who smoked had increased odds of adverse scores in social communication and repetitive behaviors. Smoking by maternal grandmothers was also associated with autism diagnosis, particularly in grandsons (this might be in part related to the sex bias in diagnosis; there were only 212 diagnosed cases and 4 males for every female diagnosed).
Linda Birnbaum	Kim D, Volk H, Girirajan S, Pendergrass S, Hall MA, Verma SS, Schmidt RJ, Hansen RL, Ghosh D, Ludena-Rodriguez Y, Kim K, Ritchie MD, Hertz-Picciotto I, Selleck SB. **The joint effect of air pollution exposure and copy number variation on risk for autism.** Autism Res. 2017 Sep;10(9):1470-1480. [PMID: 28448694]
	Advance: While there is general agreement that both genes and environment contribute to risk of ASD, understanding their joint effects has been difficult, as it requires collection of detailed genetic and environmental data for the same group of individuals and appropriate gxe analytic approaches. The present study brought together these essential ingredients to demonstrate, for the first time, an interaction of global copy number variation (cnv) and ozone exposure in determining autism risk. The findings underscore the importance of considering how such interactions contribute to the risk architecture of ASD as well as the mechanisms by which genomics and environmental exposures may amplify the risks associated with the other. *Summary: Using a sample of 158 ASD cases and 147 typically developing controls from the NIEHS-funded Childhood Risk from Genes and Environment (CHARGE) study, this publication examines the interaction between global CNV burden and air pollution--specifically ozone. The authors report that children with high CNV burden (duplications) and high ozone exposure were at significantly greater risk for autism than those with low CNV burden and low ozone exposure, and that the risk would not have been found if these factors were studied independently. This interaction of ozone and global CNV burden was specific to autism, as there was no interaction observed with other components of air pollution (i.e., particulate matter). It is speculated that the high levels of CNVs and ozone, an oxidizing agent, may converge on oxidative and cellular stress pathways to potentiate ASD risk.*
Geraldine Dawson	Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, Longman RS, Honda K, Littman DR, Choi GB, Huh JR. **Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring**. Nature. 2017 Sep 13. [PMID: 28902840]
	Data from this study of mice suggest that defined gut commensal bacteria with a propensity to induce TH17 cells may increase the risk of

	neurodevelopmental disorders in the offspring of pregnant mothers undergoing immune system activation owing to infections or autoinflammatory syndromes.
Joshua Gordon	Kosmicki JA, Samocha KE, Howrigan DP, Sanders SJ, Slowikowski K, Lek M, Karczewski KJ, Cutler DJ, Devlin B, Roeder K, Buxbaum JD, Neale BM, MacArthur DG, Wall DP, Robinson EB, Daly MJ. **Refining the role of de novo protein-truncating variants in neurodevelopmental disorders by using population reference samples.** Nat Genet. 2017 Apr;49(4):504-510. [PMID: 28191890]
	Recent research has uncovered an important role for de novo variation in neurodevelopmental disorders. Using aggregated data from 9,246 families with autism spectrum disorder, intellectual disability, or developmental delay, the authors found that ~1/3 of de novo variants are independently present as standing variation in the Exome Aggregation Consortium's cohort of 60,706 adults, and these de novo variants do not contribute to neurodevelopmental risk. They further used a loss-of-function (LoF)-intolerance metric, pLI, to identify a subset of LoF-intolerant genes containing the observed signal of associated de novo protein-truncating variants (PTVs) in neurodevelopmental disorders. LoF-intolerant genes also carry a modest excess of inherited PTVs, although the strongest de novo–affected genes contribute little to this excess, thus suggesting that the excess of inherited risk resides in lower-penetrant genes. These findings illustrate the importance of population-based reference cohorts for the interpretation of candidate pathogenic variants, even for analyses of complex diseases and de novo variation.
Joshua Gordon	Lim ET, Uddin M, De Rubeis S, Chan Y, Kamumbu AS, Zhang X, D'Gama AM, Kim SN, Hill RS, Goldberg AP, Poultney C, Minshew NJ, Kushima I, Aleksic B, Ozaki N, Parellada M, Arango C, Penzol MJ, Carracedo A, Kolevzon A, Hultman CM, Weiss LA, Fromer M, Chiocchetti AG, Freitag CM; Autism Sequencing Consortium Church GM, Scherer SW, Buxbaum JD, Walsh CA. **Rates, distribution and implications of postzygotic mosaic mutations in autism spectrum disorder**. Nat Neurosci. 2017 Jul 17. [PMID: 28714951]
	About 8 percent of de novo, or non-inherited, mutations in people with autism appear in only some of the body's cells, according to an analysis of sequences from nearly 20,000 people. These mutations arise after conception; the later they occur, the fewer cells they affect. Previous studies missed the vast majority of these so-called 'mosaic mutations.' The analyses also showed that the mutations in the subjects with ASD occur disproportionately in genes expressed in the amygdala, which plays an important role in emotional and social functioning.
David Amaral	Pardo CA, Farmer CA, Thurm A, Shebl FM, Ilieva J, Kalra S, Swedo S. **Serum and cerebrospinal fluid immune mediators in children with autistic disorder: a longitudinal study.** Mol Autism. 2017 Jan 5;8:1. [PMID: 28070266]

	This article addresses the issue of whether an ongoing inflammatory process contributes to the symptoms of ASD. The conclusion is that there is no evidence of an inflammatory process. There are also interesting data that cytokine and chemokine levels are very different in peripheral blood and CSF.
Laura Kavanagh	Raghavan R, Riley AW, Volk H, Caruso D, Hironaka L, Sices L, Hong X, Wang G, Ji Y, Brucato M, Wahl A, Stivers T, Pearson C, Zuckerman B, Stuart EA, Landa R, Fallin MD, Wang X. **Maternal multivitamin intake, plasma folate and vitamin B12 levels and autism spectrum disorder risk in offspring**. Paediatr Perinat Epidemiol. 2017 Oct 6. [Epub ahead of print] [PMID: 28984369]
	Brief justification for nomination: Folic acid supplementation to prevent neural tube defects has been a major public health initiative in the US and many countries in the world. However, limited data exist on maternal suboptimal folate status and autism in urban, low income, high-risk U.S. population. This study is one of the first few to look at the relationship between maternal B vitamin status as assessed by both self-report multivitamin supplementation and by plasma folate, B12, and homocysteine biomarkers during pregnancy and risk of autism in the Boston Birth Cohort, a predominantly urban low income minority population. This study found that about one third of mothers did not have optimal plasma folate levels, either too low or too high, and both were associated with increased risk of autism. *Scientific insights: Our study revealed a "U shaped" relationship between maternal multivitamin intake during pregnancy and risk of autism in their children. We confirmed previous notion that maternal folate insufficiency was a risk factor of autism. More importantly, for the first time, our study showed that extremely high levels of mother's plasma folate and vitamin B12 at birth are associated with increased risk of ASD in offspring. Our findings underscore that both clinicians and public health professionals need to ensure optimal maternal folate nutrition, that is, not too low, and not too high.* *Significant Impact: This paper was presented in 2016 IMFAR and received great media attention, including press releases by IMFAR and Johns Hopkins Bloomberg School of Public Health. Within a month of publication, this paper is cited by a review paper titled "Is High Folic Acid Intake a Risk Factor for Autism?—A Review", which was published in a high impact journal, Brain Science (IF=20), 2017.*
Alison Singer	Tabet A, Rolland T, Ducloy M, Lévy J, Buratti J, Mathier A, Haye D, Perrin L, Dupont C, Passemard S, Capri Y, Verloes A, Drunat, S, Keren B, Mignot C, Marey I, Jacquette A, Whalen S, Pipras E, Benzacken B, Chantot-Bastaraud S, Afenjar A, Héron D, Le Caignec C, Beneteau C, Pichon O, Isidor B, David A, El Khattabi L, Kemeny S, Gouas L, Vago P, Mosca-Boidron A, Faivre L, Missirian C, Philip N, Sanlaville D, Edery P, Satre V, Coutton C, Devillard F,

	Dieterich K, Vuillaume M, Rooryck C, Lacombe D, Pinson L, Gatinois V, Puechberty J, Chiesa J, Lespinasse J, Dubourg C, Quelin C, Fradin M, Journel H, Toutain A, Martin D, Benmansour A, Leblond CS, Toro R, Amsellem F, Delome R, Bourgeron T. **A framework to identify contributing genes in patients with Phelan-McDermid syndrome**. npj Genomic Med. 2017;2:32. [available at: https://www.nature.com/articles/s41525-017-0035-2.pdf]
	No justification provided.
Joshua Gordon	Turner TN, Coe BP, Dickel DE, Hoekzema K, Nelson BJ, Zody MC, Kronenberg ZN, Hormozdiari F, Raja A, Pennacchio LA, Darnell RB, Eichler EE. **Genomic patterns of de novo mutation in simplex autism**. Cell. 2017 Sep 27. pii: S0092-8674(17)31006-1. [PMID: 28965761]
	To further understanding of the genetic etiology of autism, genome sequence data from 516 idiopathic autism families (2,064 individuals) was generated and analyzed. This resource includes >59 million single-nucleotide variants (SNVs) and 9,212 private copy number variants (CNVs), of which 133,992 and 88 are de novo mutations (DNMs), respectively. Comparing probands and unaffected siblings, we observe several DNM trends. Probands carry more gene-disruptive CNVs and SNVs, resulting in severe missense mutations and mapping to predicted fetal brain promoters and embryonic stem cell enhancers. These differences become more pronounced for autism genes (p = 1.8 × 10-3, OR = 2.2). Patients are more likely to carry multiple coding and noncoding DNMs in different genes, which are enriched for expression in striatal neurons (p = 3 × 10-3), suggesting a path forward for genetically characterizing more complex cases of autism.
Geraldine Dawson	Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S. **Autism risk following antidepressant medication during pregnancy**. Psychol Med. 2017 Dec;47(16):2787-2796. [PMID: 28528584]
	Previous studies have examined if maternal antidepressant medication during pregnancy increase the risk of autism spectrum disorder (ASD) in the offspring, but the results have been conflicting. In a population-based cohort of 179 007 children born in 2006 and 2007 and followed through 2014 when aged 7 and 8, we estimated relative risks (RRs) of ASD and 95% confidence intervals (CIs) from Cox regression in children exposed to any antidepressant medication during pregnancy, and nine specific antidepressant drugs. Medication with antidepressants during pregnancy does not appear to be causally associated with an increased risk of ASD in the offspring. Instead, the results suggest that the association is explained by factors related to the underlying susceptibility to psychiatric disorders. Based on these findings, the risk of ASD in the offspring should not be a consideration to withhold treatment with commonly used antidepressant drugs from pregnant women.
Geraldine Dawson	Wang M, Li K, Zhao D, Li L. **The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders**

	in children: a meta-analysis. Mol Autism. 2017 Oct 2;8:51. [PMID: 29026508]
	The authors conducted a comprehensive meta-analysis to reassess the relationship between folic acid and the risk of ASD. A total of 12 articles with 16 studies comprising 4514 ASD cases were included in this report. It was found that supplementation with folic acid during pregnancy could reduce the risk of ASD [RR = 0.771, 95% CI = 0.641–0.928, I2 = 59.7%, P heterogeneity = 0.001] as compared to those women without folic acid supplementation. The associations were significant among Asian, European, and American populations. This comprehensive meta-analysis suggested that maternal use of folic acid supplements during pregnancy could significantly reduce the risk of ASD in children regardless of ethnicity, as compared to those women who did not supplement with folic acid.
Geraldine Dawson	Webb SJ, Garrison MM, Bernier R, McClintic AM, King BH, Mourad PD. **Severity of ASD symptoms and their correlation with the presence of copy number variations and exposure to first trimester ultrasound**. Autism Res. 2017 Mar;10(3):472-484. [PMID: 27582229]
	The authors found that male children with ASD, copy number variations (CNVs), and exposure to first trimester ultrasound had significantly decreased non-verbal IQ and increased repetitive behaviors relative to male children with ASD, with CNVs, and no ultrasound. These data suggest that heterogeneity in ASD symptoms may result, at least in part, from exposure to diagnostic ultrasound during early prenatal development of children with specific genetic vulnerabilities.
Geraldine Dawson *Alison Singer*	Weiner DJ, Wigdor EM, Ripke S, Walters RK, Kosmicki JA, Grove J, Samocha KE, Goldstein JI, Okbay A, Bybjerg-Grauholm J, Werge T, Hougaard DM, Taylor J; iPSYCH-Broad Autism Group; Psychiatric Genomics Consortium Autism Group, Skuse D, Devlin B, Anney R, Sanders SJ, Bishop S, Mortensen PB, Børglum AD, Smith GD, Daly MJ, Robinson EB. **Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders**. Nat Genet. 2017 Jul;49(7):978-985. [PMID: 28504703]
	Using a novel approach called the polygenic transmission disequilibrium test and data from 6,454 families with a child with ASD, this study shows that polygenic risk for ASD, schizophrenia, and greater educational attainment is over-transmitted to children with ASD. These findings hold independent of proband IQ. It is found that polygenic variation contributes additively to risk in ASD cases who carry a strongly acting de novo variant. Lastly, the study shows that elements of polygenic risk are independent and differ in their relationship with phenotype. These results confirm that the genetic influences on ASD are additive and suggest that they create risk through at least partially distinct etiologic pathways.
	First, common polygenic risk -- the tiny little effects of common genetic variation spread throughout the genome -- appear relevant, and almost

	equally so, to all groups examined. Regardless of whether the cases had intellectual disability or not, were male or female, or carried a large impact de novo mutation, common polygenic risk was a significant contributor. Second, evidence was presented showing that genetic risk for ASD comes in many different flavors. The very large impact de novo variants that create risk for ASD, for example, are strongly associated with intellectual disability, epilepsy, and motor delays. The common variant risk factors are comparatively neurologically gentle. They don't show those associations. In fact, common polygenic risk for ASD is associated with higher IQ in general population samples.
Geraldine Dawson	Yuen RKC, Merico D, Bookman M, L Howe J, Thiruvahindrapuram B, Patel RV, Whitney J, Deflaux N, Bingham J, Wang Z, Pellecchia G, Buchanan JA, Walker S, Marshall CR, Uddin M, Zarrei M, Deneault E, D'Abate L, Chan AJ, Koyanagi S, Paton T, Pereira SL, Hoang N, Engchuan W, Higginbotham EJ, Ho K, Lamoureux S, Li W, MacDonald JR, Nalpathamkalam T, Sung WW, Tsoi FJ, Wei J, Xu L, Tasse AM, Kirby E, Van Etten W, Twigger S, Roberts W, Drmic I, Jilderda S, Modi BM, Kellam B, Szego M, Cytrynbaum C, Weksberg R, Zwaigenbaum L, Woodbury-Smith M, Brian J, Senman L, Iaboni A, Doyle-Thomas K, Thompson A, Chrysler C, Leef J, Savion-Lemieux T, Smith IM, Liu X, Nicolson R, Seifer V, Fedele A, Cook EH, Dager S, Estes A, Gallagher L, Malow BA, Parr JR, Spence SJ, Vorstman J, Frey BJ, Robinson JT, Strug LJ, Fernandez BA, Elsabbagh M, Carter MT, Hallmayer J, Knoppers BM, Anagnostou E, Szatmari P, Ring RH, Glazer D, Pletcher MT, Scherer SW. **Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder**. Nat Neurosci. 2017 Apr;20(4):602-611. [PMID: 28263302]
	This is a report of sequencing of 5,205 samples from families with ASD, accompanied by clinical information, creating a database accessible on a cloud platform and through a controlled-access internet portal. The research team identified 18 new candidate ASD-risk genes.
Question 4 (Treatments and Interventions)	
Alison Singer	Brian JA, Smith IM, Zwaigenbaum L, Bryson SE. **Cross-site randomized control trial of the Social ABCs caregiver-mediated intervention for toddlers with autism spectrum disorder**. Autism Res. 2017 Oct;10(10):1700-1711. [PMID: 28574669]
	Another randomized clinical trial – multisite no less – shows the effectiveness of targeting very early behaviors for the treatment of autism.
Larry Wexler	Corbett BA, Blain SD, Ioannou S, Balser M. **Changes in anxiety following a randomized control trial of a theatre-based intervention for youth with autism spectrum disorder.** Autism. 2017 Apr;21(3):333-343. [PMID: 27154909]
	Corbett and colleagues examined the impact of peer-mediated, theatre-based intervention on reducing anxiety and stress. Thirty youth with autism spectrum disorder (ASD) (ages 8-14) participated in the study. Seventeen

	youth were randomized into the experimental (EXP) group. Sixteen participants were randomized into the waitlist (WLC) control group. The EXP group received interventions during a 10-week period. The WLC group received interventions during a 10-week summer session after the EXP group had completed their trial. Results indicated a reduction in trait-anxiety and an overall increase in social competence for the EXP group. Recommendations include continued studies in this area with the incorporation of physiological and self-report metrics of stress or anxiety and the use of other anxiety reduction techniques. Students with ASD often exhibit greater anxiety in comparison to typically developing peers. This study provides an innovative approach to identify strategies that support children with ASD in reducing anxiety.
Laura Kavanagh	Drmic IE, Aljunied M, Reaven J. **Feasibility, acceptability and preliminary treatment outcomes in a school-based CBT intervention program for adolescents with ASD and anxiety in Singapore**. J Autism Dev Disord. 2017 Dec;47(12):3909-3929. [PMID: 28101845]
	Brief justification for nomination: Anxiety symptoms are highly co-occurring in youth with ASD and lead to significant challenges and interference in functioning across multiple contexts. Treatment trials examining the efficacy of modified CBT to manage the anxious symptoms of youth with ASD have yielded very promising results as significant reductions in anxiety have occurred following participation in intervention. However, only a small segment of the population is able to access these much needed interventions; therefore, schools represent the "location of choice" for provision of evidence-based treatments for students with ASD. This paper describes one of the first studies to systematically modify and implement an evidence based program to treat anxiety in youth with ASD for school settings. Of critical import, is the detail with which the adaptations (particularly cultural adaptations) are outlined in this manuscript. Significant reductions in anxiety symptoms occurred for the students with ASD in Singapore schools. These findings have significant implications for adapting evidence based treatments for underserved populations. *Scientific Insight: It is critical to close the research to practice gap and provide evidence based programs for youth with ASD and anxiety in contexts other than specialized clinics, since many youth with ASD and anxiety cannot access these clinic programs. Schools represent one of the best locations to deliver these services because barriers to access are significantly reduced. The results of this study indicated that not only can the group CBT program be modified for school settings thereby increasing access to much needed evidence based treatment, but the results also indicated that the program can be modified for use in a markedly different cultural context.* *Scientific Impact: Careful implementation of evidence based interventions, including cultural adaptations are essential to make in order to address the*

	vast disparities that exist in our country for families (e.g., underrepresented racial/ethnic minorities). Results from his study represent an initial step in closing the research to practice gap for youth with ASD and anxiety.
Laura Kavanagh *Jennifer Johnson*	Handen BL, Anagnostou E, Aman MG, Sanders KB, Chan J, Hollway JA, Brian J, Arnold LE, Capano L, Williams C, Hellings JA, Butter E, Mankad D, Tumuluru R, Kettel J, Newsom CR, Peleg N, Odrobina D, McAuliffe-Bellin S, Marler S, Wong T, Wagner A, Hadjiyannakis S, Macklin EA, Veenstra-VanderWeele J. **A randomized, placebo-controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with autism spectrum disorder: open-label extension**. J Am Acad Child Adolesc Psychiatry. 2017 Oct;56(10):849-856.e6. [PMID: 28942807]
	Brief (3-5 sentences) justification for nomination: This paper describes the open-label extension following a randomized trial of metformin for the treatment of weight gain in children with ASD who were prescribed atypical antipsychotics. The paper was recently published in JAACAP, an issue that included an editorial on antipsychotic-inducted weight gain and metformin that specifically referenced the Handen et al. paper. Hence, the Handen et al. findings not only will have an important impact on those treating the ASD population, but within child psychiatry in general. *Scientific insights: Those participants who had initially been on placebo during the double-blind metformin trial, evidenced significantly lower BMI z-scores after 16 weeks of open-label treatment (responding similarly to those participants who had been prescribed metformin during the initial trial). Conversely, participants who had initially been taking metformin during the double-blind trial maintained prior decreases in BMI z-scores but did not have additional weight loss. Adverse events were generally restricted largely to gastrointestinal distress, including nausea and diarrhea* *Significant impact: Metformin can be effective for decreasing weight gain associated with atypical antipsychotic use and maintaining prior improvement in children and adolescents with ASD. Practitioners could also consider starting metformin concurrent with antipsychotic treatment, especially for those children with risk factors for obesity (however, studies examining the actual merits of such an approach have not yet been conducted).*
	This article is accompanied by Clinical Guidance at the end, as well as an editorial in the same issue of the journal: ***Antipsychotic-Induced Weight Gain and Metformin**.* *Walkup JT, Cottingham E.* *J Am Acad Child Adolesc Psychiatry. 2017 Oct;56(10):808-810. doi: 10.1016/j.jaac.2017.08.009. No abstract available.* *PMID: 28942801*

	The article describes an open-label extension of a randomized clinical trial of metformin for antipsychotic induced weight gain that was previously published in 2016: ***Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder: A Randomized Clinical Trial.*** *Anagnostou E, Aman MG, Handen BL, Sanders KB, Shui A, Hollway JA, Brian J, Arnold LE, Capano L, Hellings JA, Butter E, Mankad D, Tumuluru R, Kettel J, Newsom CR, Hadjiyannakis S, Peleg N, Odrobina D, McAuliffe-Bellin S, Zakroysky P, Marler S, Wagner A, Wong T, Macklin EA, Veenstra-VanderWeele J.* *JAMA Psychiatry. 2016 Sep 1;73(9):928-37. doi: 10.1001/jamapsychiatry.2016.1232.* *PMID: 27556593* *I am recommending the article for inclusion in the 2017 IACC Summary of Advances because this open-label extension demonstrates the safety and effectiveness of metformin in treating antipsychotic medication induced weight gain in youth with autism. The two FDA approved medications for treatment of irritability in autism (Risperidone and Aripiprazole) have seen marked increases in prescribed use for this population, with up to 23% of youth with autism receiving these drugs. This places a large number of youth at risk of their metabolic side effects of increased weight gain and increased risk of developing type II diabetes mellitus. This open label extension provides evidence to support strong consideration of use of metformin as adjunctive medication in treating patients with autism spectrum disorders who are receiving atypical antipsychotics. The impact of this clinical recommendation has the potential to make a significant impact on the quality of life in the ASD community.*
Geraldine Dawson	Jones EJ, Dawson G, Kelly J, Estes A, Jane Webb S. **Parent-delivered early intervention in infants at risk for ASD: effects on electrophysiological and habituation measures of social attention**. Autism Res. 2017 May;10(5):961-972. [PMID: 28244271]
	This study is the first to show that an early parent-mediated intervention delivered to high risk infants before onset of ASD has the potential to impact the brain systems underpinning social attention in infants at familial risk for ASD. Compared to infants who only received assessment and monitoring, infants who received the intervention showed improvements in neurocognitive metrics of social attention, as reflected in a greater reduction in habituation times to face versus object stimuli between 6 and 12 months, maintained at 18 months; a greater increase in frontal EEG theta power between 6 and 12 months; and a more comparable P400 response to faces and objects at 12 and 18 months.
Laura Kavanagh	Keefer A, Kreiser NL, Singh V, Blakeley-Smith A, Duncan A, Johnson C, Klinger L, Meyer A, Reaven J, Vasa RA. **Intolerance of uncertainty predicts**

	anxiety outcomes following CBT in youth with ASD. J Autism Dev Disord. 2017 Dec;47(12):3949-3958. [PMID: 27405445]
	Brief justification for nomination: This study examines the construct of intolerance of uncertainty (IU) in a group of youth with autism spectrum disorders (ASD) ages 8–14 years who underwent a modified cognitive–behavioral therapy program (Facing Your Fears; Reaven et al. 2012) aimed at reducing anxiety. Given preliminary evidence linking IU to both anxiety and ASD, the current study extends research on IU by examining whether pre-treatment IU is associated with treatment outcomes following MCBT for anxiety in youth with ASD. The study is also important given that it is one of the first studies that has investigated factors associated with treatment response to Facing Your Fears. *Scientific insights: This is one of the first studies to stratify outcomes of modified cognitive behavioural therapy according to pre-intervention intolerance of uncertainty levels. Results indicate that higher levels of pre-intervention intolerance of uncertainty are associated with higher levels of anxiety and worry post-intervention.* *Significant impact: Results from this study suggest that IU may not respond to current modified CBT strategies and appears to be related to poorer outcomes following intervention. Current CBT protocols may need to be modified to target IU and to enhance response to anxiety intervention for ASD youth.*
Joshua Gordon	Lake JK, Denton D, Lunsky Y, Shui AM, Veenstra-VanderWeele J, Anagnostou E. **Medical conditions and demographic, service and clinical factors associated with atypical antipsychotic medication use among children with an autism spectrum disorder**. J Autism Dev Disord. 2017 May;47(5):1391-1402. [PMID: 28210827]
	This study aimed to describe rates of antipsychotic medication use and the association between their use and demographics, clinical variables, and the use of behavioral/education services among children with ASD. For children with ASD ages 2–11 (n = 4749) and those 12–17 (n = 401), 5.4 and 17.7% were prescribed at least one atypical antipsychotic medication (aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone) respectively. In young children, older age, use of multiple psychotropic medications, prior ASD diagnosis, non-white Hispanic race/ethnicity, and oppositional defiant problems were associated with antipsychotic use. Among older children, only older age was associated with antipsychotic use. In at least one age group, antipsychotic medication use was also related to behaviour, family and occupational therapy, public insurance, site region, externalizing problems, body mass index, and sleep and gastrointestinal problems. Young children with ASD prescribed atypical antipsychotic medication were more likely to experience feeling tired, but had fewer problems with sleep onset delay and falling asleep in the car. Older children were more likely to experience gastrointestinal problems. Across

	both age groups, children were also more often overweight or obese compared to children who were not prescribed this medication.
Laura Kavanagh	Mruzek DW, McAleavey S, Loring WA, Butter E, Smith T, McDonnell E, Levato L, Aponte C, Travis RP, Aiello RE, Taylor CM, Wilkins JW, Corbett-Dick P, Finkelstein DM, York AM, Zanibbi K. **A pilot investigation of an iOS-based app for toilet training children with autism spectrum disorder**. Autism. 2017 Dec 1:1362361317741741. [Epub ahead of print] [PMID: 29212345]
	Brief (3-5 sentences) justification for nomination: This study is the first randomized controlled trial (RCT) of an innovative iOS-based app for toilet training children with autism spectrum disorder (ASD; N=33) conducted in the home setting by parents. Key elements include: (1) development of a user-friendly training app (I.e., "Moisture Pager" or MP) that uses Bluetooth connectivity to alert caregivers at the onset of a learner's urine accident, as well as a number of other potentially helpful features to aid training; (2) Development of a module-based, manualized intervention for caregivers for implementation of the MP intervention; (3) Development and successful piloting of measures of user-friendly data collection procedures for measuring the acquisition of toileting skills of the participating children in the MP intervention and comparison intervention (i.e., a standard behavioral intervention); and (3) development of measures of fidelity of parent training, fidelity of parent implementation of the MP intervention, and parent satisfaction with their assigned intervention. *Scientific insights: Results support the feasibility of parent-mediated toilet training studies (e.g., 84% retention, 92% fidelity of parent-implemented intervention). Though outcome data revealed no significant group differences for rate of urine accident, toilet usage, or parent satisfaction between groups at close of intervention or 3-month follow-up, the MP group trended toward greater rate of skill acquisition with significantly less day-to-day intervention.* *Significant impact: This study provides data to suggest that with brief initial training and some follow-up, parents of children with ASD can implement systematic toilet training programs successfully, including interventions that employ MP technology. Furthermore, this study demonstrates that reliable and valid studies of RCT of toilet training can be conducted, as implemented by parents in the home setting. Finally, results indicate that further development of the iOS-based alarm and related technology and future comparative studies with a greater number of participants are warranted.*
Geraldine Dawson	Parker KJ, Oztan O, Libove RA, Sumiyoshi RD, Jackson LP, Karhson DS, Summers JE, Hinman KE, Motonaga KS, Phillips JM, Carson DS, Garner JP, Hardan AY. **Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism**. Proc Natl Acad Sci U S A. 2017 Jul 25;114(30):8119-8124. [PMID: 28696286]

	Using a double-blind, randomized, placebo-controlled, parallel design, the authors tested the efficacy and tolerability of 4-wk intranasal OXT treatment (24 International Units, twice daily) in 32 children with ASD, aged 6-12 y. When pretreatment neuropeptide measures were included in the statistical model, OXT compared with placebo treatment significantly enhanced social abilities in children with ASD [as measured by the trial's primary outcome measure, the Social Responsiveness Scale (SRS)].
Geraldine Dawson	Sathe N, Andrews JC, McPheeters ML, Warren ZE. **Nutritional and dietary interventions for autism spectrum disorder: a systematic review**. Pediatrics. 2017 Jun;139(6). pii: e20170346. [PMID: 28562286]
	A systematic review of nutritional and dietary interventions for autism. It was concluded that there is little evidence to support the use of nutritional supplements or dietary therapies for children with ASD. Note that there is an accompany editorial, which I am not nominating as an advance but might be of interest to the committee: https://www.ncbi.nlm.nih.gov/pubmed/28562291
Larry Wexler	Shire SY, Chang YC, Shih W, Bracaglia S, Kodjoe M, Kasari C. **Hybrid implementation model of community-partnered early intervention for toddlers with autism: a randomized trial.** J Child Psychol Psychiatry. 2017 May;58(5):612-622. [PMID: 27966784]
	Using an effectiveness-implementation hybrid design in tandem with the Joint Attention, Symbolic Play, Engagement, and Regulation model (JASPER), Shire and colleagues tested 113 children enrolled in local public early intervention classrooms in low SES settings. Shire and colleagues addressed the practicability of supervised teacher assistant (TA)-implemented JASPER within an early intervention program and the influence of intervention on children's core developmental challenges concerning JASPER related skills. Results indicated fidelity of implementation by paraprofessionals and notable increases in engagement between children and paraprofessionals. Students receiving JASPER interventions demonstrated gains in joint engagement, joint attention, and play skills. Recommendations include formal evaluation of supervisor's TA coaching, adding additional measures to more fully understand clinical significance of staff questionnaire scores, and extension of intervention analysis. This study is consequential because paraprofessionals are often assigned to work with children with ASD. This study shows how to support paraprofessionals in implementing an intervention with fidelity.
Larry Wexler	Strain PS. **Four-year follow-up of children in the LEAP Randomized Trial: some planned and accidental findings.** Top Early Childhood Sp Educ. 2017 Jun 23;1-6. [http://journals.sagepub.com/doi/pdf/10.1177/0271121417711531]
	Strain described a 4-year follow-up study from the Learning Experiences and Alternative Program for Preschoolers and their Parents (LEAP) randomized trial. In the previous randomized study trial, moderate to large effect size

	differences were evident for students receiving the complete LEAP inclusion model. Due to such promising outcomes, Strain and colleagues received funding for the 4-year follow-up study. In this study, Strain outlined four a-priori questions: What is the stability of classroom placement across 4 years (K-3)? What is driving initial kindergarten placement decisions? How did classroom quality vary across settings? What do children in the LEAP Randomized Control Trial (RCT) look like 4 years away from intervention? Initial decisions about placement seemed to be made according to preestablished district perceptions of students with autism, not based on individual student need. Statistically significant differences were observed, with students in inclusive settings performing better than those in segregated settings. Recommendations include program replication and further longitudinal studies. This article is noteworthy because it shows that a decision about a child's placement (which appeared to be based more on district policy then a child's individualized need) can significantly impact their developmental trajectory and their academic success.
Geraldine Dawson	Weitlauf AS, Sathe N, McPheeters ML, Warren ZE. **Interventions targeting sensory challenges in autism spectrum disorder: a systematic review**. Pediatrics. 2017 Jun;139(6). pii: e20170347. [PMID: 28562287]
	A systematic review of interventions targeting sensory challenges in autism. It was concluded that some interventions may yield modest short-term (<6 months) improvements in sensory- and ASD symptom severity-related outcomes; the evidence base is small, and the durability of the effects is unclear. Although some therapies may hold promise, substantial needs exist for continuing improvements in methodologic rigor.
David Mandell	Weitlauf AS, Sathe N, McPheeters ML, Warren ZE. **Interventions targeting sensory challenges in children with autism spectrum disorder – an update [internet]**. AHRQ Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 May. Report No.: 17-EHC004-EF. [PMID: 29064644]
	Findings from this rigorous systematic review suggest the disappointing results of interventions to improve sensory outcomes in individuals with autism and the need for further intervention development in this area.
Question 5 (Services)	
David Mandell *Joshua Gordon*	Barry CL, Epstein AJ, Marcus SC, Kennedy-Hendricks A, Candon MK, Xie M, Mandell DS. **Effects of state insurance mandates on health care use and spending for autism spectrum disorder**. Health Affairs (Millwood). 2017 Oct 1; 36(10), 1754-1761. [PMID: 28971920]
	This study comprises the most rigorous study to date of the effects of states' autism insurance mandates on service use and spending among children with autism. The study finds that mandates result in substantial increases in spending on autism-specific services, although the effect is not apparent until two years after the mandates are passed. A notable finding is that the effect is concentrated among younger children and dissipates among

	adolescents, suggesting the need for additional strategies to improve service access and use among older children with autism.
	The following study supported by NIMH funding addressed an important policy-relevant question of the extent to which state-issued insurance mandates to cover services for children and families with autism, have had a measurable impact on family use of additional medical service to treat ASD. The study utilized a very extensive database of medical claims data from 2008-12 from 3 nationwide medical insurers which resulted in a final sample of 106,977 individuals and 3.7 million person-months. *The results will have significant impact for the autism community because the findings show that autism insurance mandates were associated with large increases in both the likelihood of using health care services and average spending on these services for children with autism. The effects of insurance mandates were significant, showing that children with ASD covered by mandates were 3.4 percentage points more likely to use ASD-specific services in a month; and that mandates raised spending on ASD-specific services by an estimated annual average of $924 ($77 per month multiplied by 12 months).*
Larry Wexler	Caron V, Bérubé A, Paquet A. **Implementation evaluation of early intensive behavioral intervention programs for children with autism spectrum disorders: A systematic review of studies in the last decade.** Eval Program Plann. 2017 Jun;62:1-8. [PMID: 28189054]
	Caron and colleagues reviewed studies, within a ten-year period, related to Early Intensive Behavior Interventions (EIBI). These interventions were provided to children with autism spectrum disorders (ASD). Researchers catalogued program implementation components evidenced in the studies. Twenty-eight studies met the selection criteria. Implementation components included dosage, adherence, differentiation, quality, and participation. Variables related to dosage and adherence were well described throughout selected studies, while the majority of studies did not report on participation, differentiation, or quality. Recommendations include examining the fidelity of EIBI interventions, a more comprehensive definition of EIBI programs, and enhanced evaluations of implementation in practice. This study is significant because it provides an expansive overview of EIBI interventions through the examination of current research.
Larry Wexler	Chou Y, Wehmeyer ML, Palmer SB, Lee J. **Comparisons of self-determination among students with autism, intellectual disability, and learning disabilities: a multivariate analysis.** Foc on Autism and Other Dev Disabil. 2017 Jun 1;32(2):124-132. [http://journals.sagepub.com/doi/pdf/10.1177/1088357615625059]
	Chou and colleagues considered the differences in self-determination between students with autism spectrum disorders (ASD), students with intellectual disability (ID), and students with learning disabilities (LD). Researchers selected 222 participants, with equal numbers in disability categories. Using a multivariate analysis of covariance (MANCOVA), Chou

	and colleagues examined four dependent variables: autonomy, self-regulation, psychological empowerment, and self-realization. Students with ASD scored lower in the categories of autonomy and psychological empowerment than students with ID or LD. However, students with ASD did not demonstrate significant variance from students with ID or LD in self-regulation. Implications for educators include, but are not limited to, selection of domain interventions based upon profile distinctions and increasing educational opportunities for students with ASD to develop self-determination skills and participate in inclusive settings. This study should be considered because students with disabilities typically do not demonstrate self-determination practices to the degree of their general education peers. Therefore, engaging in studies that examine such behaviors may lead to increased strategies for self-determination practices among students with disabilities.
Geraldine Dawson *David Mandell*	Cidav Z, Munson J, Estes A, Dawson G, Rogers S, Mandell D. **Cost offset associated with Early Start Denver Model for children with autism**. J Am Acad Child Adolesc Psychiatry. 2017 Sep;56(9):777-783. [PMID: 28838582]
	This study determined the effect of early intensive behavioral treatment of young children with autism on health care service use and costs. In the postintervention period, compared with children who had earlier received treatment as usual in community settings, children in the early intervention group used less ABA/EIBI, occupational/physical therapy, and speech therapy services, resulting in significant cost savings in the amount of about $19,000 per year per child. Costs associated with ESDM treatment were fully offset within a few years after the intervention because of reductions in other service use and associated costs.
	First study to empirically demonstrate the cost savings associated with high quality early intervention.
Laura Kavanagh	Hepburn SL. **Strengthening informal supports to promote behavioral health of youth with intellectual and/or developmental disabilities in rural communities**. International Rev of Res in Dev Disabil. 2017;53:203-234. [available at: http://www.sciencedirect.com/science/article/pii/S2211609517300039]
	Brief justification for nomination: This review examines current research and future directions for leveraging existing positive youth development programs in an effort to reach underserved youth in rural communities with Autism Spectrum Disorders and other developmental disabilities. The focus is on building collaborations with existing programs, such as 4-H and Boys and Girls Clubs, in order to improve the quality of life and community engagement of youth with ASD. The strategy described is consistent with IACC priorities 5 ("What kinds of services and supports are needed to maximize quality of life for people on the autism spectrum?") and 7 ("How do we continue to build, expand and enhance the infrastructure system to meet the needs of the ASD community?")

	Scientific insights: The Cooperative Extension System (CES) is an under-utilized resource for supporting persons with ASD and their families. Networks already exist in every county in the United States. Specialists in ASD intervention could reach underserved rural families by collaborating with extension agents and the social services programs with whom they already collaborate. Expanding access to existing community-based experiences requires an intentional commitment to nurture informal supports, yet very few practitioners actually focus on this aspect of service delivery. *Significant impact: Leveraging existing systems is an important, low cost approach for expanding the reach of evidence-based practices in intervention. In addition to improving access to formal supports, professionals can promote meaningful inclusion in community activities by providing technical assistance, training and coaching through the positive youth development programs that already exist in local communities. Research is needed on efficient strategies for bringing autism specialists into active collaborations with youth services professionals, which has the potential to scale-up efforts to promote community engagement for persons with ASD.*
David Mandell	Jamison JM, Fourie E, Siper PM, Trelles MP, George-Jones J, Buxbaum Grice A, Krata J, Holl E, Shaoul J, Hernandez B, Mitchell L, McKay MM, Buxbaum JD, Kolevzon A. **Examining the efficacy of a family peer advocate model for black and hispanic caregivers of children with autism spectrum disorder**. J Autism Dev Disord. 2017 May;47(5):1314-1322. [PMID: 28168677]
	This study comprises a randomized trial of a relatively inexpensive intervention to improve outcomes for poor and ethnic minority caregivers of children with autism. The study found that the intervention increased parent knowledge of autism and reduced parent stress, but had no effect on service use, suggesting that interventions like these may be necessary but not sufficient for improving overall parent and child outcomes.
Laura Kavanagh	Kuhlthau KA, McDonnell E, Coury DL, Payakachat N, Macklin E. **Associations of quality of life with health-related characteristics among children with autism**. Autism. 2017 Jul 1:1362361317704420. [Epub ahead of print] [PMID: 28691502]
	Justification for Nomination: Most previous studies about a child with Autism Spectrum Disorder's (ASD) quality of life focus primarily on the behavioral problems associated with the disorder. The current study examined the relationship between a child with ASD's quality of life and both behavioral and physical health conditions such as sleep and digestive problems. This study aimed at understanding the relationship between the broader physical health problems children with ASD might experience in relation to these children's health-related quality of life. By looking at both cross-sectional and longitudinal data from the Autism Treatment Network

	registry, researchers were able to get a more holistic view at how physical ailments effect quality of life for children with ASD. *Scientific Insights: This study showed that baseline physical health and mental health characteristics are associated with health-related quality of life in children with ASD. More specifically, bipolar disorder, sleep problems, and gastrointestinal issues such as constipation, acid reflux, and abdominal pain were associated with a lower health-related quality of life. By increasing focus on these co-occurring conditions, clinicians may improve the health-related quality of life of their patients with ASD. Optimal treatment of underlying medical conditions could also potentially help children with autism benefit more from behavioral interventions since co-existing conditions may interfere with learning progress, health, and health-related quality of life.* *Significant Impact: The results of this study indicate that both behavioral problems and physical health conditions are associated with a lower quality of life for this population of children. Clinicians should screen for these factors as they work with families and children on treatment plans.*
David Mandell	Leslie DL, Iskandarani K, Velott DL, Stein BD, Mandell DS, Agbese E, Dick AW. **Medicaid waivers targeting children with autism spectrum disorder reduce the need for parents to stop working**. Health Aff (Millwood). 2017 Feb 1;36(2):282-288. [PMID: 28167717]
	This paper is emblematic of a body of work coming from this group that merges Medicaid claims data with national survey data and uses ecological associations to examine the effects of different state Medicaid policies on child and family outcomes. This particular study examines the effect of the generosity of Medicaid waivers on parents' workforce participation. Prior research has demonstrated that mothers of children with autism are much more likely than parents of other children to drop out of the workforce. The present study finds that parents of children with autism who live in states with more generous Medicaid waivers are more likely to stay in the workforce, suggesting that these state policies have important economic implications beyond the immediate care for which they pay.
Larry Wexler	Odom SL, Cox A, Sideris J, Hume KA, Hedges S, Kucharczyk S, Shaw E, Boyd BA, Reszka S, Neitzel J. **Assessing quality of program environments for children and youth with autism: Autism Program Environment Rating Scale (APERS)**. J Autism Dev Disord. 2017 Nov 20. [PMID: 29159578]
	The purpose of this study was to examine the psychometric properties of the Autism Program Environment Rating Scale (APERS), an instrument designed to assess quality of program environments for students with autism spectrum disorder (ASD). It is important to have an understanding of the quality of environments where students with ASD are served because the environment forms the foundation for implementing evidence-based practices. There are no other psychometrically validated tools in the field to

	assess the quality of school-based programs for students with ASD. Therefore, this tool meets a need in the field by providing essential information schools can use to provide more effective programs for children and youth with ASD.
Geraldine Dawson *Laura Kavanagh*	Zuckerman KE, Lindly OJ, Reyes NM, Chavez AE, Macias K, Smith KN, Reynolds A. **Disparities in diagnosis and treatment of autism in Latino and non-Latino white families**. Pediatrics. 2017 May;139(5). pii: e20163010. [PMID: 28557734]
	Study compared barriers to autism spectrum disorder (ASD) diagnosis and current ASD-related service use among non-Latino white (NLW) families and Latino families with English proficiency (L-EP) or limited English proficiency (L-LEP). English proficiency was an important marker for barriers to ASD diagnosis and treatment in Latinos. Increasing ASD-related knowledge and provider trust may decrease disparities in the diagnosis and treatment of ASD among US Latinos.
	Brief (3-5 sentences) justification for nomination: Health inequalities in children with Autism Spectrum Disorder (ASD) have been widely reported in families with low SES and from minority communities. For example, children from minority groups tend to receive a diagnosis of ASD later than White children. Understanding barriers to access to diagnosis and treatment is a paramount goal to provide better services to these communities. *Scientific insights: These findings indicated that more than 50% of families tend to experience the following barriers when trying to get an ASD diagnosis, including stress of the diagnostic process, lack of knowledge about ASD, understanding medical system, knowing where to go for help, providers' views on child's behaviors, long waits for evaluations, family members' views on child's behaviors, lack of comfort of appointment for children, and lack of help with care coordination. Moreover, Latino families who had limited English proficiency (L-LEP) tended to experience more barriers than White families who were English proficient (EP). Children from (L-LEP) families also had fewer ASD therapy hours and more unmet therapy needs than children from EP families. Finally, barriers and treatment services of Latino families who were English proficient (L-EP) were more similar to EP families than L-LEP families.* *Significant impact: English proficiency appears to be an important factor for barriers to ASD diagnosis and treatment in the Latino communities. Inequalities in ASD diagnosis might be decreased if the identified barriers are addressed to facilitate access to services in these communities.*
Question 6 (Lifespan Issues)	
Julie Lounds Taylor	Bishop-Fitzpatrick L, Smith DaWalt L, Greenberg JS, Mailick MR. **Participation in recreational activities buffers the impact of perceived stress on quality of life in adults with autism spectrum disorder**. Autism Res. 2017 May;10(5):973-982. [PMID: 28244233]

	Although the sample is small (60), they found that parent-reported AND self-reported recreational activities buffered the effects of stress on quality of life. Interestingly, it was recreational activities that were important and not social activities. It gives some food for thought about what interventions might be more or less important to improve self-perceived quality of life.
Geraldine Dawson	Chan W, Smith LE, Hong J, Greenberg JS, Lounds Taylor J, Mailick MR. **Factors associated with sustained community employment among adults with autism and co-occurring intellectual disability**. Autism. 2017 Jul 1:1362361317703760. [PMID: 28691500]
	This study utilized longitudinal data to explore the impact of contextual influences, family factors, and individual characteristics on sustained employment over approximately 18 months (N = 105). Very few adults with autism spectrum disorder and intellectual disability achieved sustained employment (14.3%). The results indicated that more independent daily living skills, a higher family income, a larger maternal social network, an inclusive school environment in early childhood, and currently living in an area with a larger population size were associated with significantly greater odds of sustaining employment. Follow-up analyses suggested that managing personal care is particularly important for employment.
Julie Lounds Taylor	Ditchman NM, Miller JL, Easton AB. **Vocational rehabilitation service patterns: an application of social network analysis to examine employment outcomes of transition-age individuals with autism**. Rehabil Counseling Bull. 2017 May 31. [http://journals.sagepub.com/doi/abs/10.1177/0034355217709455]
	There have been a handful of studies that have used vocational rehabilitation databases to determine which individual services are associated with employment outcomes at case closure. This study also uses the voc rehab database (i.e., the Rehabilitative Service Databases), but instead of looking at individual contribution of services, they used social network analysis to examine patterns/combinations of services that might facilitate employment outcomes for adults with ASD in the VR system. Using this method, they were able to identify six "core services" (assessment, job placement assistance, counseling, job search assistance, on-the-job support, transportation) – for every one increase in core services, the odds of successful employment were 1.54 times greater. This study is interesting because it takes an innovative approach to understanding service effectiveness.
Julie Lounds Taylor	Eack SM, Hogarty SS, Greenwald DP, Litschge MY, Porton SA, Mazefsky CA, Minshew NJ. **Cognitive enhancement therapy for adult autism spectrum disorder: Results of an 18-month randomized clinical trial**. Autism Res. 2017 Dec 29. [Epub ahead of print] [PMID: 29286586]
	Although the sample size is small (n = 54), this is a promising randomized controlled trial examining the effects of cognitive enhancement therapy on

	neurocognitive and social-cognitive outcomes. The design was rigorous, with a stringent control group (support groups with a therapist). Both groups improved in social-cognitive functioning, but the intervention group had greater increased than the control group in neurocognitive functioning. They were also more likely to be competitively employed. This therapy seems like a promising approach, and I liked the attempt link improvements made in therapy to "real-world" outcomes (employment).
Joshua Gordon	Guan J, Li G. **Injury mortality in individuals with autism**. Am J Public Health. 2017 May;107(5):791-793. [PMID: 28323463]
	Researchers identified individuals with a diagnosis of autism who died between 1999 and 2014 by screening causes of death in the multiple cause-of-death data files in the National Vital Statistics System based on the ICD-10. During the study period, 1367 deaths (1043 males and 324 females) in individuals with autism were recorded in the United States. The mean age at death for individuals with autism was 36.2 years (SD = 20.9 years), compared with 72.0 years (SD = 19.2 years) for the general population. Of the deaths in individuals with autism, 381 (27.9%) were attributed to injury, with suffocation being the leading cause of injury mortality, followed by asphyxiation (n = 78; PMR = 13.50; 95% CI = 10.68, 16.85) and drowning (n = 74; PMR = 39.89; 95% CI = 31.34, 50.06). The researchers concluded that individuals with autism appear to be at substantially heightened risk for death from injury. *Limitations of the study noted by the researchers: First, in the absence of population data on autism, we were unable to calculate the death rates and cause-specific standardized mortality ratios. Instead, we relied on proportionate mortality analysis to explore the relative burden of injury mortality in individuals with autism. In proportionate mortality analysis, a cause-specific PMR is influenced by changes in the number of deaths from the specific cause or the number of deaths from all other causes. Consequently, the heightened PMR from injury observed in individuals with autism may not necessarily measure the excess risk of injury mortality in individuals with autism as compared with the general population. Second, our study was limited to death certificate data. The accuracy of data on death certificates filed by medical examiners and coroners varies with the cause of death and the types of disease. Therefore, autism as a contributing cause of death is likely underreported.*
David Mandell *Julie Lounds Taylor*	Liu G, Pearl AM, Kong L, Leslie DL, Murray MJ. **A profile on emergency department utilization in adolescents and young adults with autism spectrum disorders**. J Autism Dev Disord. 2017 Feb;47(2):347-358. [PMID: 27844247]
	Prior studies have shown that children with ASD use emergency medical services more than other children. This study focuses specifically on adolescents, an understudied group. This study estimates that risk as four-fold, and greater for those who are older or live in rural areas. The use of the ED for females with autism is increasing over time. To the extent that

	ED use represents a failure of the health care system to provide more timely and less restrictive services, this study shows the importance of developing crisis prevention and management services for these groups.
Julie Lounds Taylor	Mandy W, Clarke K, McKenner M, Strydom A, Crabtree J, Lai MC, Allison C, Baron-Cohen S, Skuse D. **Assessing autism in adults: an evaluation of the Developmental, Dimensional and Diagnostic Interview-Adult Version (3Di-Adult)**. J Autism Dev Disord. 2017 Nov 7. [Epub ahead of print] [PMID: 29116420]
	It would be interesting to hear from clinicians with more experience in diagnosis, but this study seems very promising. ASD Diagnosis is difficult in adulthood; informant interviews ask the informant about behaviors that occurred in early childhood, which can be very hard to recall. And they are very long. This study describes the validation of a new informant-report diagnostic measure of ASD, developed specifically for adults. It can be done over the phone, and administration time averaged 50 minutes for adults with ASD (lower for other groups). Sensitivity and specificity when compared to adults without any condition and adults with mental health conditions was very good (.95 sensitivity .92 specificity). Scores were not dependent on age or gender (or IQ, although those with intellectual disability were excluded). Although the sample size here was small, if these results were replicated in a larger sample, I could see this measure being commonly used.
David Mandell *Julie Lounds Taylor*	Nathenson RA, Zablotsky B. **The transition to the adult health care system among youths with autism spectrum disorder**. Psychiatr Serv. 2017 Jul 1;68(7):735-738. [PMID: 28292222]
	In this administrative database study in one state, use of all services except emergency services decreased with age for youth with ASD. The fact that ED service use does not increase with age suggests that need is still there, but that services are not accessible for this group.
David Mandell	Sasson NJ, Morrison KE. **First impressions of adults with autism improve with diagnostic disclosure and increased autism knowledge of peers**. Autism. 2017 Oct 1:1362361317729526. [PMID: 29039208]
	First study to demonstrate that disclosure of autism diagnosis in adults can improve the perceptions of others.
Julie Lounds Taylor	Taylor JL, DaWalt LS. **Brief report: postsecondary work and educational disruptions for youth on the autism spectrum**. J Autism Dev Disord. 2017 Sep 9. [PMID: 28889215]
	Nearly all studies of employment outcomes use data collected at one point in time, and thus cannot speak to issues around maintaining vocational positions once obtained. This study, using detailed longitudinal data collected from a small sample (n = 36), examined the proportion of youth with ASD who experienced instability in vocational/education in the first 2-3 after high school exit, as well as whether behavioral and family factors

	measured in high school distinguished those who did versus did not experienced instability. Although most youth transitioned into some sort of post-secondary activity, 50% experienced instability in those activities. Maternal and family functioning – and not the characteristics of the youth with ASD – distinguished those who did versus did not experience instability. This study suggests that the factors that predict whether youth with ASD get a job or go to college might be different from the factors that predict maintaining those activities.
Julie Lounds Taylor	Van Schalkwyk GI, Marin CE, Ortiz M, Rolison M, Qayyum Z, McPartland JC, Lebowitz ER, Volkmar FR, Silverman WK. **Social media use, friendship quality, and the moderating role of anxiety in adolescents with autism spectrum disorder**. J Autism Dev Disord. 2017 Jun 14. [PMID: 2861685]
	This study examined social media use, anxiety, and friendship quality in 44 adolescents with ASD and 56 clinical comparison controls. More time on social media and greater social media utility was associated with higher friendship quality as rated by both parents and adolescent with ASD – particularly for those with lower parent-rated anxiety. There were no relationships between friendship quality and social media use for control group adolescents. This study suggests that adolescents with ASD may be a unique subgroup in terms of their capacity to benefit from social media.
Question 7 (Infrastructure and Surveillance)	
Joshua Gordon	Durkin MS, Maenner MJ, Baio J, Christensen D, Daniels J, Fitzgerald R, Imm P, Lee LC, Schieve LA, Van Naarden Braun K, Wingate MS, Yeargin-Allsopp M. **Autism spectrum disorder among US children (2002-2010): socioeconomic, racial, and ethnic disparities**. Am J Public Health. 2017 Nov;107(11):1818-1826. [PMID: 28933930]
	ASD prevalence and 95% confidence intervals (CIs) were computed from population-based surveillance, census, and survey data. SES categories were defined using area-level education, income, and poverty indicators. ASD was ascertained in 13,396 of 1,308,641 8-year-old children under surveillance. The prevalence of ASD increased with increasing SES during each surveillance year among White, Black, and Hispanic children. The prevalence difference between high- and low-SES groups was relatively constant over time (3.9/1000 [95% CI = 3.3, 4.5] in 2002 and 4.1/1000 [95% CI = 3.6, 4.6] in the period 2006-2010). Significant racial/ethnic differences in ASD prevalence remained after stratification by SES. A positive SES gradient in ASD prevalence according to US surveillance data prevailed between 2002 and 2010, and racial and ethnic disparities in prevalence persisted during this time among low-SES children.
Geraldine Dawson	Hoffman K, Weisskopf MG, Roberts AL, Raz R, Hart JE, Lyall K, Hoffman EM, Laden F, Vieira VM. **Geographic patterns of autism spectrum disorder among children of Nurses' Health Study II women**. Am J Epidemiol. 2017 Oct 1;186(7):834-842. [PMID: 28525627]

	Analyses included 13,507 children born from 1989-1999 (486 with ASD). The study explored relationships between ASD and residential location at both birth and age 6 years (i.e. closer to average diagnosis age). Using the residential address at age 6 produced similar results; however, areas of significantly decreased ASD odds were observed in the Southeast, where children were half as likely to have ASD. These results may indicate that diagnostic factors are driving spatial patterns; however, it is possible that other environmental factors are influencing distributions.
Walter Koroshetz	Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Paneth N, Leviton A, Kuban KC. **Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years**. Autism Res. 2017 Feb;10(2):224-232. [PMID: 27220677]
	This study evaluated 889 10-year-old children from the Extremely Low Gestational Age Newborn (ELGAN) birth cohort (delivered at 23-27 weeks' gestation in 2002-2004) to assess prevalence of ASD in extremely pre-term children versus the general population. Children were first screened using the Social Communication Questionnaire, then further evaluated with the ADI-R, and final diagnosis was made with the ADOS-2. Prevalence of 7.1% was found, and the analyses revealed an inverse relationship between ASD risk and gestational age. Forty percent of ASD children had intellectual disability, and the male to female ratio was 2.1:1, which is lower than the 4:1 ratio observed in the general population. This study underscores the need for enhanced ASD screening for preterm children, and for further exploration of the relationship between risk factors associated with preterm birth that may play a role in ASD etiology.
Geraldine Dawson	Loomes R, Hull L, Mandy WPL. **What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis**. J Am Acad Child Adolesc Psychiatry. 2017 Jun;56(6):466-474. [PMID: 28545751]
	The purpose of this study was to derive the first systematically calculated estimate of the relative proportion of boys and girls with autism spectrum disorder (ASD) through a meta-analysis of prevalence studies conducted since the introduction of the DSM-IV and the International Classification of Diseases, Tenth Revision. Of children meeting criteria for ASD, the true male-to-female ratio is not 4:1, as is often assumed; rather, it is closer to 3:1. There appears to be a diagnostic gender bias, meaning that girls who meet criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis.