2017 Summary of Advances Nominations: October – December 2017
(Newly nominated since the October meeting)

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.
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.
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.
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.
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.
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.*
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.*
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.
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.
Question 4 (Treatments and Interventions)	
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.*
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.*
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)].
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)	
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.*
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.
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.
Question 6 (Lifespan Issues)	
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	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).
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	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.
Question 7 (Infrastructure and Surveillance)	