

2017 Summary of Advances Nominations: April – July 2017

Question 1 (Screening and Diagnosis)	
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]
	<p>Funded by NIMH and NICHD; highlighted in NIMH and NIH press releases, as well as Dr. Collins' blog:</p> <ul style="list-style-type: none"> • 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/
Question 2 (Underlying Biology)	
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 12. [Epub ahead of print] [PMID: 28700580]
	<i>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.</i>
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]
	<i>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</i>

	<p><i>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.</i></p>
<p>Walter Koroshetz</p>	<p>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]</p> <p><i>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.</i></p>
<p>Question 3 (Risk Factors)</p>	
<p>Linda Birnbaum</p>	<p>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]</p> <p><i>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.</i></p> <p><i>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</i></p>

	<p><i>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.</i></p>
Linda Birnbaum	<p>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]</p> <p><i>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.</i></p> <p><i>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).</i></p>
Linda Birnbaum	<p>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 Apr 27. [Epub ahead of print] [PMID: 28448694]</p> <p><i>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.</i></p> <p><i>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</i></p>

	<i>high levels of CNVs and ozone, an oxidizing agent, may converge on oxidative and cellular stress pathways to potentiate ASD risk.</i>
Joshua Gordon	<p>Lim ET, Uddin M, De Rubeis S, Chan Y, Kamumbu AS, Zhang X, D'Gama AM, Kim SN, Hill RS, Goldberg AP, Poultney C, Minschew NJ, Kushima I, Aleksic B, Ozaki N, Parellada M, Arango C, Penzol MJ, Carracedo A, Kolevzon A, Hultman CM, Weiss LA, Fromer M, Chiochetti 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]</p> <p><i>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.</i></p>
Geraldine Dawson	<p>Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S. Autism risk following antidepressant medication during pregnancy. Psychol Med. 2017 May 22:1-10. [Epub ahead of print] [PMID: 28528584]</p> <p><i>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.</i></p>
Geraldine Dawson Alison Singer	<p>Weiner DJ, Wigdor EM, Ripke S, Walters RK, Kosmicki JA, Grove J, Samocha KE, Goldstein JL, 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 May 15. [Epub ahead of print] [PMID: 28504703]</p> <p><i>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</i></p>

	<p><i>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.</i></p>
	<p><i>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.</i></p>
<p>Question 4 (Treatments and Interventions)</p>	
<p><i>Alison Singer</i></p>	<p>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 Jun 2. [Epub ahead of print] [PMID: 28574669]</p> <p><i>Another randomized clinical trial – multisite no less – shows the effectiveness of targeting very early behaviors for the treatment of autism.</i></p>
<p><i>Larry Wexler</i></p>	<p>Commons ML, Adhikari D, Giri S, Weinberg M, Baran JJ, Malik E. Measuring developmental outcomes in autism spectrum disorder (ASD). Behav Dev Bull. 2017 Apr;22(1):197-208.</p> <p><i>Commons and colleagues created a behavior-developmental scale to predict performance in students with Autism Spectrum Disorder (ASD). Forty-two children were given the Autism Developmental Task Sequence (ADTS). Using the Rasch Analysis, researchers ascertained the order of hierarchical complexity (MHC) of various tasks, including the behavioral developmental difficulty of task items. The scale derived from the Rasch Analysis will help create interventions and provide diagnostic data. Furthermore, this tool could improve progress monitoring strategies for children with ASD. In turn, such improvements could strengthen the design of behavioral and educational materials.</i></p>
<p><i>Larry Wexler</i></p>	<p>Corbett BA, Blain SD, Ioannou S, Balsler 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]</p> <p><i>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</i></p>

	<p><i>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.</i></p>
Geraldine Dawson	<p>Sathe N, Andrews JC, McPheeters ML, Warren ZE. Nutritional and dietary interventions for autism spectrum disorder: a systematic review. Pediatrics. 2017 May 26. [Epub ahead of print] [PMID: 28562286]</p> <p><i>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</i></p>
Larry Wexler	<p>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]</p> <p><i>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.</i></p>
Larry Wexler	<p>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]</p> <p><i>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</i></p>

	<p><i>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 than a child's individualized need) can significantly impact their developmental trajectory and their academic success.</i></p>
Geraldine Dawson	<p>Weitlauf AS, Sathe N, McPheeters ML, Warren ZE. Interventions targeting sensory challenges in autism spectrum disorder: a systematic review. Pediatrics. 2017 May 26. [Epub ahead of print] [PMID: 28562287]</p> <p><i>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.</i></p>
Question 5 (Services)	
Larry Wexler	<p>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]</p> <p><i>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.</i></p>
Larry Wexler	<p>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]</p> <p><i>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</i></p>

	<p>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.</p>
Geraldine Dawson	<p>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]</p> <p>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.</p>
Question 6 (Lifespan Issues)	
	<p>There were no nominations under Question 6 from April - July 2017.</p>
Question 7 (Infrastructure and Surveillance)	
Geraldine Dawson	<p>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 May 19. [Epub ahead of print] [PMID: 28525627]</p> <p>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.</p>
Geraldine Dawson	<p>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]</p> <p>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.</p>