2018 Summary of Advances Nominations: April – October 2018

Question 1 (Screening and Diagnosis)	
David Amaral	Bosl WJ, Tager-Flusberg H, Nelson CA. **EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach.** Sci Rep. 2018 May 1;8(1):6828. [PMID: 29717196]
	This paper indicates that alterations in EEG activity can be used to predict an ASD diagnosis in infants at risk as early as 3 months. This raises the prospect that the EEG analyses used in the paper could be an early biomarker of autism risk.
Geraldine Dawson	Egger HL, Dawson G, Hashemi J, Carpenter KLH, Espinosa S, Campbell K, Brotkin S, Schaich-Borg J, Qiu Q, Tepper M, Baker JP, Bloomfield RA, and Sapiro G. **Automatic Emotion and Attention Analysis of Young Children at Home: A ResearchKit Autism Feasibility Study.** npj Digital Medicine. 2018 Jun 1;1(20). http://www.nature.com/articles/s41746-018-0024-6
	This study presents data from the first autism app built on ResearchKit's open-source platform. The entire study—from an e-Consent process to stimuli presentation and data collection—was conducted within an iPhone-based app available in the Apple Store. 1756 families with children aged 12–72 months old participated in the study, completing 5618 caregiver-reported surveys and uploading 4441 videos recorded in the child's natural settings. Usable data were collected on 87.6% of the uploaded videos. Automatic computer vision analysis coding identified significant differences in emotion and attention by age, sex, and autism risk status.
Geraldine Dawson	Hirai AH, Kogan MD, Kandasamy V, Reuland C, Bethell C. **Prevalence and Variation of Developmental Screening and Surveillance in Early Childhood.** JAMA Pediatr. 2018 Jul 9. [PMID: 29987317]
	Despite more than a decade of initiatives, rates of developmental screening and surveillance are shown in this article to remain low. State-level variation indicates continued potential for improvement.
Question 2 (Underlying Biology)	
Alison Singer	Handen BL, Mazefsky CA, Gabriels RL, Pedersen KA, Wallace M, Siegel M; Autism and Developmental Disorders Inpatient Research Collaborative (ADDIRC). **Risk Factors for Self-injurious Behavior in an Inpatient Psychiatric Sample of Children with Autism Spectrum Disorder: A Naturalistic Observation Study.** J Autism Dev Disord. 2018 Jan 24. [PMID: 29368233]
	Research on individuals with severe autism, including those who are minimally verbal, have intellectual disability or challenging behaviors, is uncommon because of challenges regarding consent and compliance with protocols. The Autism Inpatient Collection (AIC) was initiated so data on this

	understudied group could be collected. Using phenotypic data from the first 350 AIC participants, the authors found that lower IQ, greater social communication deficits, more stereotyped behavior and higher scores on the Repetitive Behavior Scale Revised, SIB subscale all increase the risk of SIB. The findings provide actionable information for ways to improve the lives of individuals with severe autism.
Linda Birnbaum	Jones KL, Pride MC, Edmiston E, Yang M, Silverman JL, Crawley JN, Van de Water J. **Autism-specific maternal autoantibodies produce behavioral abnormalities in an endogenous antigen-driven mouse model of autism.** Mol Psychiatry. 2018 Jun 28. [PMID: 29955164]
	This study is the first reported preclinical antigen-driven mouse model of maternal autoantibody related (MAR) ASD. The development of this model is an important step to advance our understanding of the underlying mechanisms of MAR ASD.
Geraldine Dawson	Jung H, Park H, Choi Y, Kang H, Lee E, Kweon H, Roh JD, Ellegood J, Choi W, Kang J, Rhim I, Choi SY, Bae M, Kim SG, Lee J, Chung C, Yoo T, Park H, Kim Y, Ha S, Um SM, Mo S, Kwon Y, Mah W, Bae YC, Kim H, Lerch JP, Paik SB, Kim E. **Sexually dimorphic behavior, neuronal activity, and gene expression in Chd8-mutant mice.** Nat Neurosci. 2018 Sep;21(9):1218-1228. [PMID: 30104731]
	This study demonstrates that a human CHD8 mutation leads to sexually dimorphic changes ranging from transcription to behavior in mice.
Walter Koroshetz	Qin L, Ma K, Wang ZJ, Hu Z, Matas E, Wei J, Yan Z. **Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition.** Nat Neurosci. 2018 Apr;21(4):564-575. [PMID: 29531362]
	The SHANK3 gene encodes a scaffolding protein located at certain excitatory synapses, and deletion or loss-of-function mutations in SHANK3 gene are causally linked to Phelan-McDermid syndrome, ASD, and intellectual disability. This study explores a strategy to alleviate social deficits in a mouse model of SHANK3 deficiency. Prior research has shown an enrichment of ASD-related mutations in chromatin remodeling pathways, which influence gene expression. Here, the authors show that social deficits in young Shank3-deficient mice are alleviated for up to 3 weeks by brief treatment with romidepsin, an FDA-approved cancer drug and inhibitor of a type of chromatin remodelers called class 1 histone deacetylases (HDAC). The authors also investigated the mechanisms underlying this therapeutic effect. They found that the histone deacetylase HDAC2 is upregulated in the prefrontal cortex of Shank3-deficient mice and that HDAC2 upregulation and social deficits were induced by increased nuclear localization of β-catenin, a Shank3-binding protein that regulates cell adhesion and transcription. Romidepsin treatment restored expression of many genes that are down-regulated in Shank3-deficient mice. In particular, romidepsin increased expression of the NMDA receptor subunit

	gene Grin2a and actin-regulatory genes, leading to restored NMDA-receptor function and actin filaments in Shank3-deficient mice. These findings advance understanding of the epigenetic mechanisms leading to social deficits linked to Shank3 deficiency and suggest potential therapeutic strategies.
Question 3 (Risk Factors)	
Geraldine Dawson	The Brainstorm Consortium. **Analysis of shared heritability in common disorders of the brain.** Science. 2018 Jun 22;360(6395). [PMID: 29930110]
	This large genetic analysis showed that psychiatric disorders share common variant risk, whereas neurological disorders appear more distinct from one another and from the psychiatric disorders. The study identified significant sharing between disorders and a number of brain phenotypes, including cognitive measures.
Joshua Gordon	Brandler WM, Antaki D, Gujral M, Kleiber ML, Whitney J, Maile MS, Hong O, Chapman TR, Tan S, Tandon P, Pang T, Tang SC, Vaux KK, Yang Y, Harrington E, Juul S, Turner DJ, Thiruvahindrapuram B, Kaur G, Wang Z, Kingsmore SF, Gleeson JG, Bisson D, Kakaradov B, Telenti A, Venter JC, Corominas R, Toma C, Cormand B, Rueda I, Guijarro S, Messer KS, Nievergelt CM, Arranz MJ, Courchesne E, Pierce K, Muotri AR, Iakoucheva LM, Hervas A, Scherer SW, Corsello C, Sebat J. **Paternally inherited cis-regulatory structural variants are associated with autism.** Science. 2018 Apr 20;360(6386):327-331. [PMID: 29674594]
	This study identified an association between paternally-inherited rare structural variants in noncoding segments of genes and the development of ASD. While previous have focused on genetic heritability or mutations in genes that code for the creation of proteins or other molecular products, the findings from this suggest that rare, inherited structural differences in the noncoding portions of genes also contribute to ASD. The researchers examined the contribution of structural variants in noncoding regions of DNA called cis-regulatory elements (CRE-SVs) to ASD. The findings revealed deletions in protein-coding areas of genes were transmitted more often from parents to offspring with autism than from parents to offspring without autism; and that CRE-SVs were transmitted more often from fathers to offspring with autism then from fathers to offspring without autism. Their results were also replicated in an independent follow-up experiment examining the genomes 1,771 families.
Linda Birnbaum	Brown AS, Cheslack-Postava K, Rantakokko P, Kiviranta H, Hinkka-Yli-Salomäki S, McKeague IW, Surcel HM, Sourander A. **Association of Maternal Insecticide Levels With Autism in Offspring From a National Birth Cohort.** Am J Psychiatry. 2018 Aug 16:appiajp201817101129. [PMID: 30111184]
	This is the first study using a biomarker to link high levels of maternal exposure to the insecticide DDT to increased risk of autism, particularly autism with co-morbid intellectual disability.

Geraldine Dawson	Chen S, Fragoza R, Klei L, Liu Y, Wang J, Roeder K, Devlin B, Yu H. **An interactome perturbation framework prioritizes damaging missense mutations for developmental disorders.** Nat Genet. 2018 Jul;50(7):1032-1040. [PMID: 29892012]
	By analyzing de novo missense mutation data from six disorders, the authors demonstrate that an interactome perturbation approach offers a generalizable framework for identifying and prioritizing missense mutations that contribute to the risk of human disease.
Linda Birnbaum	Curtin P, Austin C, Curtin A, Gennings C, Arora M; (for the Emergent Dynamical Systems Group), Tammimies K, Willfors C, Berggren S, Siper P, Rai D, Meyering K, Kolevzon A, Mollon J, David AS, Lewis G, Zammit S, Heilbrun L, Palmer RF, Wright RO, Bölte S, Reichenberg A. **Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder.** Sci Adv. 2018 May 30;4(5):eaat1293. [PMID: 29854952]
	This study is the first to show that dysregulation of metal cycling during prenatal and early postnatal periods, independent of metal concentration, is associated with autism diagnosis and that metrics of Zn-Cu cycling can be prospectively used to distinguish between cases and controls.
Geraldine Dawson; Walter Koroshetz	Short PJ, McRae JF, Gallone G, Sifrim A, Won H, Geschwind DH, Wright CF, Firth HV, FitzPatrick DR, Barrett JC, Hurles ME. **De novo mutations in regulatory elements in neurodevelopmental disorders.** Nature. 2018 Mar 29;555(7698):611-616. [PMID: 29562236]
	This study underscores the contribution of de novo mutations in regulatory elements to genetically heterogeneous neurodevelopmental disorders.
	A growing number of genetic mutations are associated with neurodevelopmental disorders including autism, but little is known about the role of mutations in non-coding regulatory elements, which affect the expression of genes. This study in 8,000 patients with severe developmental disorders shows that de novo mutations in regulatory elements active in the fetal brain are enriched in neurodevelopmental disorders. Overall, the authors estimate that 1-3% of patients without a diagnostic variant in a coding sequence carry disease-causing de novo mutations in fetal brain-active regulatory elements. They also estimate that only 0.15% of all possible mutations within highly conserved fetal brain-active regulatory elements cause neurodevelopmental disorders with a dominant mechanism. These findings provide one of the first robust estimates of the contribution of such mutations to neurodevelopmental disorders and highlight both challenges and opportunities for further research.
Geraldine Dawson	Tabouy L, Getselter D, Ziv O, Karpuj M, Tabouy T, Lukic I, Maayouf R, Werbner N, Ben-Amram H, Nuriel-Ohayon M, Koren O, Elliott E. **Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders.** Brain Behav Immun. 2018 May 19. pii: S0889-1591(18)30188-0. [PMID: 29787855]

	This study identifies bacterial species that are sensitive to an autism-related mutation, and further suggests a therapeutic potential for probiotic treatment.
Joshua Gordon	Werling DM, Brand H, An JY, Stone MR, Zhu L, Glessner JT, Collins RL, Dong S, Layer RM, Markenscoff-Papadimitriou E, Farrell A, Schwartz GB, Wang HZ, Currall BB, Zhao X, Dea J, Duhn C, Erdman CA, Gilson MC, Yadav R, Handsaker RE, Kashin S, Klei L, Mandell JD, Nowakowski TJ, Liu Y, Pochareddy S, Smith L, Walker MF, Waterman MJ, He X, Kriegstein AR, Rubenstein JL, Sestan N, McCarroll SA, Neale BM, Coon H, Willsey AJ, Buxbaum JD, Daly MJ, State MW, Quinlan AR, Marth GT, Roeder K, Devlin B, Talkowski ME, Sanders SJ. **An analytical framework for whole-genome sequence association studies and its implications for autism spectrum disorder.** Nat Genet. 2018 May;50(5):727-736. [PMID: 29700473]
	The contribution of rare variation in the noncoding portions of the genome is a potentially large and hitherto unexplored class of variation. Whole genome sequencing (WGS) could provide important insights into the biology underlying complex disorders. However, interpreting WGS data in the noncoding genome presents considerable unique challenges requiring a development of a standardized unbiased analytical approach. The current study focused on development of such an analytical pipeline to identify and determine the contribution of non-coding de-novo variation to psychiatric risk, specifically its association to ASD. These analyses focused on families with both affected and unaffected children (519 ASD cases, their unaffected sibling controls and both of their parents from SSC) and evaluated the association of different classes of both non-coding and coding variation with ASD. Results point to modest contribution of de novo noncoding variation in comparison to de novo coding variants in ASD. Promoting further studies to investigate the complex genetic risk architecture of ASD and providing a plausible analytical pipeline to be used in future research of the contribution of non-coding variation in psychiatric and other complex disorder risk.
Question 4 (Treatments and Interventions)	
Larry Wexler	Morgan L, Hooker JL, Sparapani N, Reinhardt VP, Schatschneider C, Wetherby AM. **Cluster randomized trial of the classroom SCERTS intervention for elementary students with autism spectrum disorder.** J Consult Clin Psychol. 2018 Jul;86(7):631-644. [PMID: 29939056]
	The purpose of this multi-site CRT was to determine the impact of a research-based classroom intervention to target active engagement in social, communication, and emotional regulation behaviors by kindergarten to second-grade children with ASD; school-based interventions are identified as a key area for research by the IACC. This is the first study to show positive effects on child outcomes for this intervention. The study consisted of approximately 200 treatment and control students across 70 schools in California, Florida, and Georgia from 2011-2014. The results

	showed significant positive effects on social interaction, communication, and social skills for treatment students.
Question 5 (Services)	
Larry Wexler	Waters CF, Amerine Dickens M, Thurston SW, Lu X, Smith T. **Sustainability of Early Intensive Behavioral Intervention for Children With Autism Spectrum Disorder in a Community Setting.** Behav Modif. 2018 Jul 1:145445518786463. [PMID: 30009626]
	The purpose of this quasi-experimental study was to determine the gains from a research-based parent- training intervention (Early Intensive Behavioral Intervention or EIBI) on IQ and adaptive behavior in children with ASD age 1.5 to 6 years old. The study extends the literature by examining whether outcomes first seem in a university-led project could be replicated with children outside the project, and extending the age range of the subjects up to 6 years old. The study consisted of approximately 100 treatment and control children in homes across five counties in northern California from 2006-2009. The results showed larger improvements in the EIBI (home) group than in the group receiving services only from the local public schools. The results are only suggestive of causal effect, due to a lack of random assignment and possible knowledge by outcome evaluators of which a child's group assignment. However, the study supports the possibility that children through kindergarten may attain significant improvement with scaled-up, intensive home interventions.
Question 6 (Lifespan Issues)	
Julie Lounds Taylor	Bal VH, Kim SH, Fok M, Lord C. **Autism spectrum disorder symptoms from ages 2 to 19 years: Implications for diagnosing adolescents and young adults.** Autism Res. 2018 Aug 12. [PMID: 30101492]
	This study followed 140 individuals with ASD from ages 2 to 19 years and examined changes in social-communication symptoms on the ADI-R over time by language level. The authors found evidence for some items/symptoms that stayed stable over time (e.g., impaired facial expression) and many others that improved over adolescence and adulthood (e.g., items related to non-verbal communication, deficits in development and maintenance of relationships for verbal individuals). Trajectories of change were highly related to the individual's language level. The authors suggest that the findings don't necessarily indicate ASD symptoms that are becoming milder over time, but instead that childhood symptoms of ASD might not be the best markers for ASD in young adulthood. Results of this study have potential implications for how we assess and diagnose ASD in adolescence and adulthood.
Geraldine Dawson	Davignon MN, Qian Y, Massolo M, Croen LA. **Psychiatric and Medical Conditions in Transition-Aged Individuals With ASD.** Pediatrics. 2018 Apr;141(Suppl 4):S335-S345. [PMID: 29610415]

	After controlling for sex, age, race, and duration of Kaiser Permanente Northern California membership, most psychiatric conditions were significantly more common in the ASD group than in each comparison group, and most medical conditions were significantly more common in the ASD group than in the attention-deficit/hyperactivity disorder and typical control groups but were similar to or significantly less common than the diabetes mellitus group.
Julie Lounds Taylor	Dudley KM, Klinger MR, Meyer A, Powell P, Klinger LG. **Understanding Service Usage and Needs for Adults with ASD: The Importance of Living Situation.** J Autism Dev Disord. 2018 Aug 25. [PMID: 30145735]
	In this study, researchers collected data from parents on a relatively large (n=274) sample of adults with ASD (age range 20-58, mean age of 35) who were diagnosed with ASD by TEACCH between 1969 and 2000. They found that - after controlling for a number of relevant factors – adults with ASD who were living at home were receiving fewer services and had more unmet service needs, relative to those living in supported settings. Caregivers of those living at home were 3 times more likely than caregivers of those in supported settings to say that services were too far away/unavailable, and they were unsure of where to find services. This is one of the first studies (to my knowledge) to examine the impact of living situation on service receipt – and points to the need for additional supports for adults with ASD living with family. An additional strength of this study is that the sample's average age is the mid-30s – a time of life that we know little about.
Question 7 (Infrastructure and Surveillance)	
There were no nominations covering Question 7 topics from April - October 2018.	