2018 Summary of Advances Nominations: January – December 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.
Geraldine Dawson	Ozonoff S, Young GS, Brian J, Charman T, Shephard E, Solish A, Zwaigenbaum L. **Diagnosis of Autism Spectrum Disorder After Age 5 in Children Evaluated Longitudinally Since Infancy.** J Am Acad Child Adolesc Psychiatry. 2018 Nov;57(11):849-857.e2. [PMID: 30392626]
	ASD is manifest after age 5 in some children.
David Mandell	Sacrey LR, Zwaigenbaum L, Bryson S, Brian J, Smith IM, Roberts W, Szatmari P, Vaillancourt T, Roncadin C, Garon N. **Parent and clinician agreement regarding early behavioral signs in 12- and 18-month-old infants at-risk of autism spectrum disorder.** Autism Res. 2018 Mar;11(3):539-547. [PMID: 29356441]

	Even expert clinicians using standardized measures in a high-risk sample miss important infant and toddler behaviors that could assist in making a diagnosis of autism. The study findings suggest that we need better strategies for eliciting and incorporating parent feedback into the screening and diagnostic process.
Joshua Gordon	Wolff JJ, Dimian AF, Botteron KN, Dager SR, Elison JT, Estes AM, Hazlett HC, Schultz RT, Zwaigenbaum L, Piven J; IBIS Network. **A longitudinal study of parent-reported sensory responsiveness in toddlers at-risk for autism.** J Child Psychol Psychiatry. 2018 Oct 23. [PMID: 30350375]
	We know relatively little about the relationship between sensory-related features and restricted and repetitive behaviors in ASD during the first year of a child's life. In this study supported by NIMH and NICHD, investigators collected prospective, longitudinal parent-reported data using the Sensory Experiences Questionnaire (SEQ) for 331 high-risk toddlers with older sibling previously diagnosed with ASD and 135 low-risk controls without ASD. The findings showed significantly higher SEQ scores for the high-risk ASD group that received a confirmed clinical diagnosis of ASD from age 12 months, with more pronounced differences across the 12-24 month interval, suggesting that differences in sensory responsivity may be evident in high-risk infants later diagnosed with ASD in early toddlerhood, and that the magnitude of these differences increases over the second year of life.

Question 2 (Underlying Biology)

David Amaral; Walter Koroshetz	Avino TA, Barger N, Vargas MV, Carlson EL, Amaral DG, Bauman MD, Schumann CM. **Neuron numbers increase in the human amygdala from birth to adulthood, but not in autism.** Proc Natl Acad Sci USA. 2018 Apr 3;115(14):3710-3715. [PMID: 29559529]
	The authors report the results of a stereological analysis of the number of neurons in amygdala nuclei of 52 human postmortem brains ranging from 2 to 48 years of age [24 neurotypical and 28 autism spectrum disorder (ASD)]. In neurotypical development, the number of mature neurons in the basal and accessory basal nuclei increases from childhood to adulthood, coinciding with a decrease of immature neurons within the paralaminar nucleus. Individuals with ASD, in contrast, show an initial excess of amygdala neurons during childhood, followed by a reduction in adulthood across nuclei. This suggests that there is a dysregulation of neuronal maturation in the amygdala, a structure commonly implicated in the neuropathology of ASD.
	The amygdala plays a central role in emotion and social behavior, and it develops slowly, typically growing by 40% from youth to adulthood. In this study, researchers looked at the developmental growth trajectory of the amygdala in postmortem brains from 52 individuals with or without ASD. In neurotypical development, the number of mature neurons in the basal and accessory basal nuclei of the amygdala increased from childhood to adulthood. In contrast, individuals with ASD had an initial excess of

	amygdala neurons during childhood followed by a reduction in adulthood. These differences in amygdala growth patterns may contribute to altered emotional development and may be associated with volumetric changes observed in brain imaging studies in ASD and other neurodevelopmental or neuropsychiatric disorders.
Walter Koroshetz	Deneault E, White SH, Rodrigues DC, Ross PJ, Faheem M, Zaslavsky K, Wang Z, Alexandrova R, Pellecchia G, Wei W, Piekna A, Kaur G, Howe JL, Kwan V, Thiruvahindrapuram B, Walker S, Lionel AC, Pasceri P, Merico D, Yuen RKC, Singh KK, Ellis J, Scherer SW**. Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons.** Stem Cell Reports. 2018 Nov 13;11(5):1211-1225. [PMID: 30392976]
	In this paper, researchers present a new CRISPR-based method for systematically knocking out ASD-associated genes in human induced pluripotent stem cells, producing a new resource for studying disease mechanisms and testing potential therapies. They report that knocking out 10 different genes led to different neurophysiological effects in neurons, but to overall similar defects at the level of connectivity and network activity, adding to evidence for common functional phenotypes in ASD despite broad genetic heterogeneity.
Walter Koroshetz	Greenblatt EJ, Spradling AC. **Fragile X mental retardation 1 gene enhances the translation of large autism-related proteins.** Science. 2018 Aug 17;361(6403):709-712. [PMID: 30115809]
	Mutations in the fragile X mental retardation 1 gene (FMR1) cause Fragile X Syndrome, the most common inherited form of intellectual disability and a leading monogenic cause of autism. FMR1 regulates messenger RNA (mRNA) translation, and this paper, researchers report new and surprising findings about the functional targets of such regulation. In fruit fly oocytes, they found that FMR1 enhances translation of mRNAs that overlap previously identified FMR1 targets, in contrast to prior suggestions that FMR1 inhibits overall translation. The researchers also found that targeted transcripts were longer than average, pointing to preferential FMR1 regulation of large proteins.
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; David Amaral	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.
	It is well established that there is a male predominance of diagnoses for ASD of something like 4:1. The explanation for this has not been clear. The current paper looks at a variety of parameters of male and female mice that have the same mutation of the chd8 gene. The authors find that the behavioral abnormalities are greater in the male compared to the female mice with the mutation. Moreover, the mutation produces opposite electrophysiological changes in the hippocampus of male and female mice. Finally, the downstream effects of the mutation on other genes is also sexually dimorphic. If this study is replicated, it will go some way towards explaining why there are more boys than girls with ASD.
Joshua Gordon	Karalunas SL, Hawkey E, Gustafsson H, Miller M, Langhorst M, Cordova M, Fair D, Nigg JT. **Overlapping and Distinct Cognitive Impairments in Attention-Deficit/Hyperactivity and Autism Spectrum Disorder without Intellectual Disability.** J Abnorm Child Psychol. 2018 Nov;46(8):1705-1716. [PMID: 29450820]
	The current study, supported by NIMH, examined shared and distinct cognitive impairments in children (ages 7-15 years) with ADHD and ASD, a using both continuous symptom measures and empirically-defined categorical groups (ADHD, n=509; ASD, n=97; and TD controls, n=301). The findings showed that certain cognitive impairments in ASD (i.e., processing speed, working memory, and response inhibition) were independent of ADHD symptoms; while select impairments in ADHD were independent of ASD symptoms. Moreover, differences in reaction time on cognitive

	measures were distinct in that children with ASD showed consistently slower reaction times on fasts tasks, indicating a preference for accuracy over speed, relative to children with ADHD and controls. The study's findings indicate a phenotypic model in which certain cognitive impairments reflect shared liability between ASD and ADHD children, but are not attributable to comorbid symptom profiles between the two disorders.
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)	
Stuart Shapira	Andrews SV, Sheppard B, Windham GC, Schieve LA, Schendel DE, Croen LA, Chopra P, Alisch RS, Newschaffer CJ, Warren ST, Feinberg AP, Fallin MD, Ladd-Acosta C. **Case-control meta-analysis of blood DNA methylation and autism spectrum disorder.** Mol Autism. 2018 Jun 28;9:40. [PMID: 29988321]
	In this study, researchers used SEED data and Simons Simplex Collection data to generate epigenome-wide array DNA methylation data in children with and without ASD. Results suggest a potential role of genetic factors in contributing to DNAm differences in ASD. Additionally, among the seven sites achieving suggestive statistical significance, the authors observed consistent and stronger effects at the same sites in a previous brain-based

	analysis. Thus, the findings from this analysis suggest the potential to observe epigenetic disease associations from blood-based samples.
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.
Alison Singer; Joshua Gordon	Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Buil A, Werge TM, Liu C, White KP; CommonMind Consortium; PsychENCODE Consortium; iPSYCH-BROAD Working Group, Horvath S, Geschwind DH. **Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap.** Science. 2018 Feb 9;359(6376):693-697. [PMID: 29439242]
	This study showed that autism, schizophrenia and bipolar disorder share some similarities in the patterns of gene expression in the brain. These findings were only possible by looking at brain tissue of individuals affected with these conditions and comparing gene transcription. While the profiles were not exact, the patterns looked similar enough that it's highly probable they share a similar genetic etiology. Such similarities were not seen between autism and major depression or alcoholism. This provides even more understanding on why schizophrenia, bipolar disorder and autism overlap in terms of some symptoms.
	In this NIMH-funded study, a team of investigators examined gene expression in postmortem brains of people who had been diagnosed with autism spectrum disorder (ASD) (n=50), schizophrenia (n=159), bipolar disorder (n=94), major depressive disorder (n=87), or alcoholism (n=17), and matched controls (n=293). The results revealed for the first time that disorders with a large overlap in genetic risk factors also had a large overlap in patterns of gene expression, shared dysfunction in similar molecular pathways, and similar impacts on synapse and neuro-immune functions for individuals with autism, schizophrenia, and bipolar disorder. This study also highlights the significant benefits of team-oriented scientific collaboration in that the data were drawn from the PsychENCODE consortium, a data-sharing collaboration of NIMH grantees.
Walter Koroshetz	Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, Won H, van Bakel H, Varghese M, Wang Y, Shieh AW, Haney J, Parhami S, Belmont J,

	Kim M, Moran Losada P, Khan Z, Mleczko J, Xia Y, Dai R, Wang D, Yang YT, Xu M, Fish K, Hof PR, Warrell J, Fitzgerald D, White K, Jaffe AE; PsychENCODE Consortium, Peters MA, Gerstein M, Liu C, Iakoucheva LM, Pinto D, Geschwind DH. **Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder.** Science. 2018 Dec 14;362(6420). [PMID: 30545856]
	The PsychENCODE Consortium, funded by NIMH, is a collaboration between 15 research institutes focused on understanding how variation in regulatory genomic elements contribute to neuropsychiatric disorders. Here, in one of several new papers, consortium researchers analyzed genotypes and RNA sequencing in brain samples from 1695 individuals with autism spectrum disorder (ASD), schizophrenia, and bipolar disorder, as well as controls. They found differential splicing or expression in over 25% of the transcriptome (RNA), with disease-associated changes in cell types and pathways previously linked to ASD and other diseases, and in previously unidentified neural-immune mechanisms. Importantly, PsychENCODE data are now publicly available as a valuable research resource for further studies.
Geraldine Dawson	Janecka M, Kodesh A, Levine SZ, Lusskin SI, Viktorin A, Rahman R, Buxbaum JD, Schlessinger A, Sandin S, Reichenberg A. **Association of Autism Spectrum Disorder With Prenatal Exposure to Medication Affecting Neurotransmitter Systems.** JAMA Psychiatry. 2018 Dec 1;75(12):1217-1224. [PMID: 30383108]
	Examined in a large sample the association of early-life interference with different neurotransmitter systems by prenatal medication exposure on the risk of ASD in offspring.
Linda Birnbaum	Kalkbrenner AE, Windham GC, Zheng C, McConnell R, Lee NL, Schauer JJ, Thayer B, Pandey J, Volk HE. **Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study.** Environ Health Perspect. 2018 Mar 12;126(3):037004. [PMID: 29553459]
	This publication represents an advance for studying air pollution as a risk factor for autism on multiple fronts, both in the design and the exposures assessed. Firstly, the authors addressed unmeasured family-level confounding by using a multiplex family (two or more siblings with an ASD diagnosis)-based design with continuous measures of ASD-related traits and severity as well as diagnosis. Secondly, the number of air toxics assessed for association with risk of diagnosis was larger than previous (155 air toxics), going well beyond the most well studied air pollutant associated with autism, PM2.5. Lastly, since air pollution represents a mixture and risk associated with a specific air toxic may be confounded by exposure to other air pollutants, a subset of chemicals was examined using two-pollutant models. Using this novel study design and this wider range of air toxic exposures, the authors were able to identify novel air pollutants associated with both risk for and severity of autism diagnosis.

Stuart Shapira	Schieve LA, Tian LH, Drews-Botsch C, Windham GC, Newschaffer C, Daniels JL, Lee LC, Croen LA, Fallin MD. **Autism spectrum disorder and birth spacing: Findings from the study to explore early development (SEED).** Autism Res. 2018 Jan;11(1):81-94. [PMID: 29164825]
	There have been a few previous studies of ASD and birth spacing but they had a number of methodological limitations. In this study researches performed a much more comprehensive analysis using a large sample from the Study to Explore Early Development (SEED). In addition to examining the basic associations, they had data to assess ASD subtypes, to assess and compare associations for ASD and other non-ASD developmental disabilities (DDs), and to examine several factors possibly in the causal pathway. They report positive associations between ASD and both short (<18 months) and long (60+ months) birth spacing. These associations were unique to ASD as there were no associations between other DDs and either short or long birth spacing. Also, associations were strongest for ASD cases with the highest symptom severity scores. Associations were unchanged after controlling for sociodemographic factors and further controlling for factors potentially related to the causal pathway – unplanned pregnancy, maternal infertility disorders, maternal complications in pregnancy. These findings extend those from previous studies and further inform recommendations on optimal pregnancy spacing.
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 Oct;73:310-319. [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.
David Mandell	Nevill RE, Lecavalier L, Stratis EA. **Meta-analysis of parent-mediated interventions for young children with autism spectrum disorder.** Autism. 2018 Feb;22(2):84-98. [PMID: 29490483]
	This paper shows that the effects associated with parent-mediated intervention, while statistically significant, are small. Given that the intervention strategies that are being taught are the same as those demonstrated to have larger effects in clinician-mediated interventions, it suggests that either we are not good at teaching parents to implement these interventions, or that it is too much of a burden to place on parents, and we should consider clinician-implemented interventions as a more effective alternative.
Alison Singer	Stedman A, Taylor B, Erard M, Peura C, Siegel M. **Are Children Severely Affected by Autism Spectrum Disorder Underrepresented in Treatment Studies? An Analysis of the Literature.** J Autism Dev Disord. 2018 Dec 10. [PMID: 30536112]
	Despite significant advances in autism research, experts have noted that children severely affected by autism spectrum disorder (ASD) appear to have been understudied. Rigorous analysis of this observation has been limited, and the representation of severity has not been well-described. This study assessed three domains of severity (communication ability, cognitive functioning, and adaptive functioning) in 367 treatment studies of children with ASD published 1991–2013. The study found that the proportion of studies that included the severely affected population has decreased significantly over time. There was also wide variability in measurement and reporting. Inadequate representation of the full autism spectrum in the literature could lead to an unbalanced picture of ASD and leave behind those with arguably the greatest needs.
Question 5 (Services)	
David Mandell	Kennedy-Hendricks A, Epstein AJ, Mandell DS, Candon MK, Marcus SC, Xie M, Barry CL. **Effects of State Autism Mandate Age Caps on Health Service Use and Spending Among Adolescents.** J Am Acad Child Adolesc Psychiatry. 2018 Feb;57(2):125-131. [PMID: 29413145]
	Eleven states place age caps on their autism insurance mandates. This study shows that those age caps matter, and they reduce access to care for adolescents in those states relative to other states. Another important finding is that service use went down, on average, in all states, suggesting that there continue to be gaps in the healthcare system for adolescents with ASD, even when coverage for care is not an issue.

David Mandell	Rubenstein E, Daniels J, Schieve LA, Christensen DL, Van Naarden Braun K, Rice CE, Bakian AV, Durkin MS, Rosenberg SA, Kirby RS, Lee LC. **Trends in Special Education Eligibility Among Children With Autism Spectrum Disorder, 2002-2010.** Public Health Rep. 2018 Jan/Feb;133(1):85-92. [PMID: 29257937]
	A third of children who meet research criteria for autism aren't in the autism category of special education. It is likely that this results in less specific and perhaps poorer educational care. The study begs the question of why these kids aren't in the autism category, how being in a different category affects the services they receive, and how the health care and education systems should be sharing information and supporting each other in making sure kids with autism are identified and receive appropriate care.
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.
Alison Singer	Zerbo O, Modaressi S, Goddard K, Lewis E, Fireman BH, Daley MF, Irving SA, Jackson LA, Donahue JG, Qian L, Getahun D, DeStefano F, McNeil MM, Klein NP. **Vaccination Patterns in Children After Autism Spectrum Disorder Diagnosis and in Their Younger Siblings.** JAMA Pediatr. 2018 Mar 26. [PMID: 29582071]
	In a matched cohort study of 3729 children with autism spectrum disorder and 592,907 children without autism spectrum disorder, the study found that children with autism spectrum disorder were less likely to be fully vaccinated for vaccines recommended between ages 4 and 6 years. The younger siblings of children with autism were also less likely to be fully vaccinated for vaccines recommended at any age. *This means that children with autism spectrum disorder and their younger siblings are at increased risk of vaccine-preventable diseases.*

Joshua Gordon	Zerbo O, Qian Y, Ray T, Sidney S, Rich S, Massolo M, Croen LA. **Healthcare Service Utilization and Cost Among Adults with Autism Spectrum Disorders in a U.S. Integrated Healthcare System.** Autism in Adulthood. Published online 1 Apr 2018. http://doi.org/10.1089/aut.2018.0004
	The researchers compared healthcare utilization patterns and cost among insured adults with autism spectrum disorder (ASD), adults with attention-deficit and hyperactivity disorder (ADHD), and adults with neither condition (general population [GP] controls). Adults with ASD had significantly higher rates of utilization across most healthcare service areas compared with adults with ADHD or GP; however, women with ASD were significantly less likely to have gynecology visits and have screening for cervical cancer.
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; David Amaral	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)

Stuart Shapira	Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Robinson Rosenberg C, White T, Durkin MS, Imm P, Nikolaou L, Yeargin-Allsopp M, Lee LC, Harrington R, Lopez M, Fitzgerald RT, Hewitt A, Pettygrove S, Constantino JN, Vehorn A, Shenouda J, Hall-Lande J, Van Naarden Braun K, Dowling NF. **Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014.** MMWR Surveill Summ. 2018 Apr 27;67(6):1-23. [PMID: 29701730]
	This report includes findings from the ADDM Network, on the basis of 2014 data reported from 11 sites. The overall ASD prevalence estimate of 16.8 per 1,000 children aged 8 years in 2014 is higher than previously reported estimates from the ADDM Network. Consistent with reports from previous ADDM surveillance years, findings from 2014 were marked by variation in ASD prevalence when stratified by geographic area, sex, and level of intellectual ability. In contrast, the differences in prevalence estimates between black and white children previously reported in ADDM ASD surveillance reports, are shown to have diminished in most sites, in this latest 2014 report. Differences between non-Hispanic white children and Hispanic children remained notable, however. New in the 2014 report, results from application of the DSM-IV-TR and DSM-5 case definitions were similar, overall and when stratified by sex, race/ethnicity, DSM-IV-TR diagnostic subtype, or level of intellectual ability.
Stuart Shapira	Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, Perrin JM, Shattuck P, Kuhlthau KA, Harwood RL, Lu MC. **The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children.** Pediatrics. 2018 Dec;142(6). [PMID: 30478241]
	Previous studies over the last 20 years have shown an increasing prevalence of ASD among US children. Moreover, families of children with ASD have reported greater health care needs and challenges compared with children with other emotional or behavioral conditions. In this study, researchers present new nationally representative data on the prevalence of ASD, reported health care challenges, and estimates on ASD specific behavioral and medication treatments. The estimated prevalence of US children 3-17

	years of age with parent-reported diagnosis of ASD in 2016 was 2.50% (1 in 40) in this most recent prevalence report. The 2016 NSCH also offers the first opportunity to provide national estimates on ASD-specific drug and behavioral treatments. In this study, 27% of children with ASD were taking medication for ASD-related symptoms, and 64% received behavioral treatments in the last 12 months, with variations by sociodemographic characteristics and co-occurring conditions.
Geraldine Dawson	McDonnell CG, Boan AD, Bradley CC, Seay KD, Charles JM, Carpenter LA. **Child maltreatment in autism spectrum disorder and intellectual disability: results from a population-based sample.** J Child Psychol Psychiatry. 2018 Oct 19. [PMID: 30368827]
	Population-based study finds that children with ASD and/or ID are at heightened risk for maltreatment.
Geraldine Dawson	Schendel DE, Thorsteinsson E. **Cumulative Incidence of Autism Into Adulthood for Birth Cohorts in Denmark, 1980-2012.** JAMA. 2018 Nov 6;320(17):1811-1813. [PMID: 30398592]
	One of the few studies on incidence of autism in adults.