2019 Summary of Advances Nominations: April – July 2019

Question 1 (Screening and Diagnosis)	
Walter Koroshetz	Pierce K, Gazestani VH, Bacon E, Barnes CC, Cha D, Nalabolu S, Lopez L, Moore A, Pence-Stophaeros S, Courchesne E. **Evaluation of the Diagnostic Stability of the Early Autism Spectrum Disorder Phenotype in the General Population Starting at 12 Months.** JAMA Pediatr. 2019 Apr 29. [PMID: 31034004]
	Early ASD diagnosis can facilitate early intervention, but the diagnostic stability of ASD in children younger than 18 months is not known. This prospective study followed 1269 toddlers diagnosed with ASD after initial referral through a universal screening program and found that ASD diagnosis becomes stable starting at 14 months of age. In this study, 23.8% of children were diagnosed with ASD after receiving a non-ASD diagnosis at their initial evaluation, and only 1.8% of children initially diagnosed with ASD transitioned to a final diagnosis of typical development.
Question 2 (Underlying Biology)	
Louis Reichardt	Avagliano Trezza R, Sonzogni M, Bossuyt SNV, Zampeta FI, Punt AM, van den Berg M, Rotaru DC, Koene LMC, Munshi ST, Stedehouder J, Kros JM, Williams M, Heussler H, de Vrij FMS, Mientjes EJ, van Woerden GM, Kushner SA, Distel B, Elgersma Y. **Loss of nuclear UBE3A causes electrophysiological and behavioral deficits in mice and is associated with Angelman syndrome.** Nat Neurosci. 2019 Jun 24. [PMID: 31235931]
	This paper shows the surprising importance of Ube3A in the nucleus in reproducing rodents the phenotypes of Angelman Syndrome. Ube3A has before been assumed to exert its actions at the synapse.
Walter Koroshetz	Pagani M, Bertero A, Liska A, Galbusera A, Sabbioni M, Barsotti N, Colenbier N, Marinazzo D, Scattoni ML, Pasqualetti M, Gozzi A. **Deletion of Autism Risk Gene Shank3 Disrupts Prefrontal Connectivity**. J Neurosci. 2019 Jul 3;39(27):5299-5310. [PMID: 31061091]
	Mutations affecting the synaptic scaffolding protein SHANK3 are linked to language and communication impairments in Phelan-McDermid syndrome and other forms of ASD. In this study of mice lacking the Shank3B gene, the authors find disrupted functional connectivity and abnormal gray matter anatomy in the prefrontal cortex, and they show that these abnormalities correlate with socio-communicative deficits. The observations add to other research in people and animal models suggesting that disrupted functional connectivity in higher-level cortical areas may be a shared mechanism across different forms of ASD.
Walter Koroshetz	Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mazmanian SK. **Human Gut**

	Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell. 2019 May 30;177(6):1600-1618.e17. [PMID: 31150625]
	Prior studies have suggested that the gut microbiome may differ between typically developing individuals and those with ASD. Here, the authors transplanted gut microbiota from human donors with or without ASD into germ-free mice and showed that gut colonization with ASD-donor microbiota induced ASD-like behaviors and alternative splicing of ASD-relevant genes in the brain. Treating an ASD mouse model with certain microbial metabolites improved behavioral abnormalities and modulated neuronal excitability in the brain. Although further study should determine whether these findings apply to ASD in people, the results add to research suggesting a role for gut-brain connections in ASD.
Joshua Gordon	Velmeshev D, Schirmer L, Jung D, Haeussler M, Perez Y, Mayer S, Bhaduri A, Goyal N, Rowitch DH, Kriegstein AR. **Single-cell genomics identifies cell type-specific molecular changes in autism.** Science. 2019 May 17;364(6441):685-689. [PMID: 31097668]
	Despite the clinical and genetic heterogeneity of autism, this disorder has been shown to converge and affect specific cellular pathways in the patients brains. In the current study the research team took advantage of recent methodological advances to further try and understand the distinct roles of the array of cortical brain cells in autism pathology. They performed single-nucleus RNA sequencing of cortical tissue from patients with autism to identify autism-associated transcriptomic changes in specific cell types. Results identified that synaptic signaling of upper-layer excitatory neurons and the molecular state of microglia are preferentially affected in autism. Moreover, findings point to, a correlation between dysregulation of specific groups of genes in cortico-cortical projection neurons and the clinical severity of autism. These findings suggest that molecular changes in upper-layer cortical circuits are linked to behavioral manifestations of autism and provide preliminary findings on regional cell specific disfunction in this disorder.
Question 3 (Risk Factors)	
Diana Bianchi	Bai D, Yip BHK, Windham GC, Sourander A, Francis R, Yoffe R, Glasson E, Mahjani B, Suominen A, Leonard H, Gissler M, Buxbaum JD, Wong K, Schendel D, Kodesh A, Breshnahan M, Levine SZ, Parner ET, Hansen SN, Hultman C, Reichenberg A, Sandin S. **Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort.** JAMA Psychiatry. 2019 Jul 17. [PMID: 31314057]
	This study focuses on the relative importance of inherited vs non-inherited causes of autism using population data from the 5 MINERvA countries, i.e., Denmark, Finland, Sweden, Israel, and Western Australia, the largest family-based database for autism research. The analysis applied to full

	birth cohorts of children born between January 1, 1998, and December 31, 2011 (N=2,001,631). The heritability of ASD was estimated to be about 80%.
Geraldine Dawson	Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, Pallesen J, Agerbo E, Andreassen OA, Anney R, Awashti S, Belliveau R, Bettella F, Buxbaum JD, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Christensen JH, Churchhouse C, Dellenvall K, Demontis D, De Rubeis S, Devlin B, Djurovic S, Dumont AL, Goldstein JI, Hansen CS, Hauberg ME, Hollegaard MV, Hope S, Howrigan DP, Huang H, Hultman CM, Klei L, Maller J, Martin J, Martin AR, Moran JL, Nyegaard M, Nærland T, Palmer DS, Palotie A, Pedersen CB, Pedersen MG, dPoterba T, Poulsen JB, Pourcain BS, Qvist P, Rehnström K, Reichenberg A, Reichert J, Robinson EB, Roeder K, Roussos P, Saemundsen E, Sandin S, Satterstrom FK, Davey Smith G, Stefansson H, Steinberg S, Stevens CR, Sullivan PF, Turley P, Walters GB, Xu X; Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium; BUPGEN; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium; 23andMe Research Team, Stefansson K, Geschwind DH, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Neale BM, Daly MJ, Børglum AD. **Identification of common genetic risk variants for autism spectrum disorder**. Nat Genet. 2019 Mar;51(3):431-444. [PMID: 30804558]
	With a marked sample-size increase from a unique Danish population resource, the authors report a genome-wide association meta-analysis of 18,381 individuals with ASD and 27,969 controls that identified five genome-wide-significant loci. They identified seven additional loci shared with other traits at equally strict significance levels, and also found both quantitative and qualitative polygenic heterogeneity across ASD subtypes. These results highlight biological insights, particularly relating to neuronal function and corticogenesis, and establish that GWAS performed at scale will be much more productive in the near term in ASD.
Question 4 (Treatments and Interventions)	
Alison Singer	Nahmias AS, Pellecchia M, Stahmer AC, Mandell DS. **Effectiveness of community-based early intervention for children with autism spectrum disorder: a meta-analysis.** J Child Psychol Psychiatry. 2019 Jun 17. [PMID: 31206690]
	This study used a meta-analysis approach to examine how clinic-based interventions were working in real world, community-based settings. Unfortunately, the effect sizes for improvement across multiple outcomes across the same intervention were significantly smaller in community-based settings than in research settings. There may be many reasons for this, but the message is clear: we need to do a better job implementing research findings in the community.
Larry Wexler	Sam AM, Cox AW, Savage MN, Waters V, Odom SL. **Disseminating Information on Evidence-Based Practices for Children and Youth with Autism Spectrum Disorder: AFIRM.** J Autism Dev Disord. 2019 Feb 28. [PMID: 30820727]

	The AFIRM modules were created to educate practitioners on the identified evidence-based practices for students with autism. This study sought to identify who uses the AFIRM modules, what knowledge gains did they make, and their perception of the modules. Results indicate AFIRM is used across the country and the nation with users from various practitioner roles (i.e., SLPs, general education, special education, administrators, and interventionists). Gains were seen in modules completed with practitioners indicating they felt the modules were useful and relevant to their work. These modules align with IAAC's goal of supporting school-based interventions by disseminating learning modules teaching how to implement evidence-based practices in the school.
Question 5 (Services)	
Joshua Gordon	Barry CL, Kennedy-Hendricks A, Mandell D, Epstein AJ, Candon M, Eisenberg M. **State Mandate Laws for Autism Coverage and High-Deductible Health Plans**. Pediatrics. 2019 Jun;143(6). [PMID: 31092588]
	While most states now have legislative mandates requiring health insurers to cover medical and intervention services for children with ASD, the increasing shift by employers to high deductible health plans (HDHP) may impact access to services among individuals with ASD in families utilizing HDHPs. Using insurance claim data from three large national health insurers (United Healthcare, Aetna, and Humana from 2008-2012), the researchers found that relative to children with in ASD in traditional or low deductible plans, health care spending for children with ASD in HDHPs was higher for mandated ASD services. However, the higher spending of services was attributed to the higher costs of services in HDHPs and not through out of pocket spending on the part of families.
Alison Singer	Brookman-Frazee L, Roesch S, Chlebowski C, Baker-Ericzen M, Ganger W. **Effectiveness of Training Therapists to Deliver An Individualized Mental Health Intervention for Children With ASD in Publicly Funded Mental Health Services: A Cluster Randomized Clinical Trial.** JAMA Psychiatry. 2019 Mar 6. [PMID: 30840040]
	This was a randomized clinical trial looking at a mental health intervention delivered in community settings in children with autism. Community providers were trained to deliver a protocol which was shown to reduce challenging behaviors. It's important because the only way people with autism and their families are going to receive the services they need is if there is an evidence base that certain interventions can be delivered by community health care providers. This study shows that is possible, and targets behaviors that are most disruptive in school settings.
Joshua Gordon	LaClair M, Mandell DS, Dick AW, Iskandarani K, Stein BD, Leslie DL. **The effect of Medicaid waivers on ameliorating racial/ethnic disparities among children with autism.** Health Serv Res. 2019 Aug;54(4):912-919. [PMID: 31132161]

	Families and individuals with ASD often experience financial difficulties in meeting their service needs related an autism diagnosis, especially among ethnically diverse and low-income households. And many states have used the availability of Medicaid Home and Community-based Services (HCBS) waivers to bridge the gap in unmet needs and services. HCBS waivers can be used to expand Medicaid coverage to include more services for individuals with ASD, and expand eligibility to include individuals who would not typically qualify for Medicaid. Using data from data from several waves of the National Survey of Children's Health (2003, 2007, & 2011) and the National Survey of Children with Special Health Care Needs (2005 & 2010), the findings showed that states with more generous HCBS waivers, showed a significantly reduced odds of having unmet need for black children with ASD compared with white children with ASD; and unmet needs among black children with ASD were roughly cut in half or approximately 13%.
Question 6 (Lifespan Issues)	
David Mandell	Laxman DJ, Taylor JL, DaWalt LS, Greenberg JS, Mailick MR. **Loss in Services Precedes High School Exit for Teens with Autism Spectrum Disorder: A Longitudinal Study.** Autism Res. 2019 Apr 29. [PMID: 31033222]
	In this research, the authors studied changes in the number of services received before and after high school exit in a large sample of individuals with ASD. With each passing year during high school, individuals with ASD received fewer services. At the time of high school exit, there was a sharp drop in the number of services received, particularly for those with co-occurring intellectual disability. This study found not only that there is a post-high school service cliff, but also that the loss of services begins long before high school exit.
Question 7 (Infrastructure and Surveillance)	
Alison Singer	Russell G, Mandy W, Elliott D, White R, Pittwood T, Ford T. **Selection bias on intellectual ability in autism research: a cross-sectional review and meta-analysis.** Mol Autism. 2019 Mar 1;10:9. [PMID: 30867896]
	Although current global estimates suggest the proportion of the population with autism who have intellectual disability (ID) is approximately 50%, this study found a selection bias due to under-inclusion of populations with ID across all fields of autism research. The review covers all original research published in 2016 in autism-specific journals with an impact factor greater than 3. The results were stark: meta-analysis estimated 94% of all participants identified as being on the autism spectrum in the studies reviewed did not have ID (95% CI 0.91–0.97). Eight out of ten studies demonstrated selection bias against participants with ID. The reporting of participant characteristics was generally poor: information about participants' intellectual ability was absent in 38% of studies (n = 114). Where there was selection bias on ID, only 31% of studies mentioned lack of generalisability as a limitation.

	Autism research must be more transparent about the underlying severity and characteristics of the individuals being studied, and we must find strategies for inclusion for children and adults with severe forms of autism.