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**COMMENTARY**

Gaps in current autism research:
The thoughts of the Autism Research Editorial Board and Associate Editors

In advance of the 2019 INSAR Conference in Montreal, Quebec, Canada, I asked the members of the Autism Research Editorial Board and the Associate Editors to write short (approximately 300 word) mini-commentaries on what they considered to be the current gaps in research on autism spectrum disorder. The responses and styles were diverse and reflect research gaps ranging from basic biology to treatment trials to services for transition to adulthood. They reflect thoughts from countries around the world. While each of the contributions was done entirely independently, it is interesting how the theme of heterogeneity is found in many of them. There is also increasing concern over the lack of research on socioeconomic and cultural factors related to the diagnosis and treatment of autism spectrum disorder. We hope that these comments will provide food for thought.

I would like to thank the staff at Wiley, Ms. Christine (Chrissy) Murray and Victoria Scheibe for valuable help in producing this Commentary.

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Over the years I have become convinced that the genesis of autism spectrum disorder (ASD) occurs prenatally. There are many potential causes and both genetic and environmental factors appear to be at play. It is equally clear that the characteristics of ASD in a particular individual may change substantially throughout life. Autism severity may increase or decrease and co-morbid conditions such as gastrointestinal (GI) distress or epilepsy may decrease or appear without warning. While there are a number of large-scale genetic studies under way, these rarely take environmental factors into consideration. Environmental studies are increasingly collecting data from families early during, or even before pregnancy, but generally are unable to comprehensively evaluate brain and behavioral development of the offspring. Thus, one major gap that I believe still exists is a large-scale, longitudinal survey of families that begins prior to pregnancy and then follows children into at least adolescence. The study that I have in mind would collect detailed environmental data, would carry out sophisticated genetic analysis of the family and then equally comprehensively document brain development using magnetic resonance imaging and behavioral development using sophisticated behavioral probes. Of course to provide the most comprehensive picture of ASD, participants with all levels of severity would be included and the cohort would be sex
balanced. The hope would be that this would go some way towards defining predictors of improvement as well as emerging medical problems such as epilepsy. Expensive? Yes, but if we finally started to have some definitive answers about the trajectories of ASD, it might save money in the long run. Beyond this, I believe that there is a gap in trying to determine how the core and comorbid features of ASD are linked. For example, the amygdala is clearly involved in the neural alterations associated with ASD. And, the amygdala can also influence gastric secretion and gastrointestinal problems. What is not known is whether there is a link between alterations in the amygdala and GI problems in ASD. Does one cause the other? Is the presence of abnormal amygdala structure or function a predictor of GI problems? Finally, there is an enormous gap in understanding the neural alterations in the autistic brain at the cellular and circuit levels. It is the hope of those involved in Autism BrainNet (autismbrainnet.org) that an increase in the availability of postmortem brain specimens will encourage researchers to begin to fill this gap.

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Mind the Gap, Mind the Heterogeneity
A major shortcoming of most research in the autism realm has been the failure to take into account the heterogeneity of the Autism Spectrum Disorder (ASD) category when designing studies. Most studies -- be they genetic, neurobiological, or behavioral— have compared an ASD group to a typically developing group. Findings are rarely replicated and any group mean differences observed are then attributed to all members of the group despite the invariable large overlap in individual data points across groups. Though many have recommended a more dimensional, fractionable, Research Domain Criteria approach, this strategy has not been widely adopted. Instead, genetic studies continue to search for risk variants of small effect in complex groups, biological research proceeds in its attempt to find unitary underlying commonalities in members of the ASD category, and early detection research continues to search in vain for markers with clinically useful specificities and sensitivities. On the one hand, this state of affairs can be attributed to an understandable attachment to diagnostic and categorical labels. On the other, the paucity of validated dimensional instruments for the multiple relevant dimensions presents a practical obstacle. Also, the power of the language of “disorder” and “symptoms”, and the influence of the implicit medical model, should not be underestimated.

While no one expects the journal Autism Research to be renamed Social Atypicality Research, autism research might benefit from a thorough and continuing consideration of how the term “autism” is used, applied and defined, and how it can mislead. Only when the behavioral dimensions relevant to the social atypicality realm are fully characterized, and we have some idea how they interact within a particular individual, will we be able to discern genetic and biological underpinnings, and predict and possibly
alter development. In short, in social atypicality research we need to be focused on characterization rather than categorization.

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Despite a welcome recent shift, a very small proportion of ASD research focuses on the needs of affected adults, despite these individuals constituting the bulk of the ASD population and incurring over 90% of ASD related costs. The significance of this research gap is amplified by the relative lack of services for adults with ASD, which is particularly marked for those with intellectual abilities within the typical range.

Three broad research areas stand out. First, the strong associations between ASD and diverse comorbid mental health conditions is now well documented and the reasons for these associations represent a research field in their own right. Arguably it is the association with anxiety disorders that causes the greatest overall impairment, and although many individuals with comorbid anxiety will show a positive response to psychotherapy and/or pharmacology, residual levels of anxiety can remain troublingly high. Consequently, there is a pressing need to understand the neurobiological basis of anxiety in this population in order to facilitate discovery of new antianxiety drugs or drug repurposing. Additionally there appear to be systemic barriers to adults with ASD obtaining equitable access to adult mental health services across many different countries. The overall problem is widely recognized, but there has been almost no attempt to identify the underlying obstacles to service access; is the main issue limited knowledge amongst mental health professionals about ASD in adulthood, or a belief that a super specialized skill set is required to manage these individuals, and to what extent are the barriers facing adults with ASD the same as or different from those facing adults with intellectual disability?

Secondly, success in higher education or the workplace still eludes many adults with ASD. Both entry into higher education and graduation rates are relatively low compared to the general population and the issue is becoming more pressing as a greater proportion of adolescents with ASD can now benefit from higher education and recent changes in the nature of work require an increasingly well-trained workforce. There has been a welcome increase in higher education related research in the last three years, much of it documenting the utility of focused support and peer mentoring schemes. Nevertheless, approaches still vary widely between institutions and are not always based on empirical evidence. What are the best ways to support adult learners with ASD and to help them achieve optimal outcomes? And how can we answer these questions unless we develop standardized assessment tools to identify individual strengths, weaknesses and needs at entry into higher education. Even on graduating from higher education, employment levels of adults with ASD still do not attain those of the general population and overall employment rates for affected adults remain abysmal. Focused government initiatives have had modest impact on employment rates
or the dual scourges of underemployment or a job rather than a career. There appear to
be multiple barriers to employment, but little guidance from the current research
literature as to which of these deserve most attention. Does the way forward lie in giving
individuals with ASD enhanced training on pre-employment skills, or in offering
incentives to employers? And, when individuals are employed, should maximizing their
skills be left to employers alone or is outside ASD expertise or advocacy also required?

Finally, adult relationships are protective for both psychological and physical health, but
in the context of ASD, we simply do not know the number and quality of extra-familial
relationships that are sufficient for good health and high quality of life. Concern about
social isolation is a common worry of parents of individuals with ASD and there is a gap
in our understanding about how best to help individuals develop relationships that are
both enjoyable and sustainable.

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There are a number of gaps in autism research that are sprinkled throughout several
different domains, from genetics, to neuroscience, to intervention. Even in areas that
have been well studied, gaps remain. These pockets of gaps are reflective of the gaps
in adaptive skills observed in many children with autism, in which some skills are intact,
but others (even more foundational adaptive skills) are not developed.

One primary gap concerns intervention. In order to hasten the pace of intervention
research we need objective markers to monitor treatment outcome. A major obstacle
concerns our limited ability to monitor treatment progress in an objective, quantitative,
and efficient manner. Relatedly, we also need to establish more specific, reliable
predictors for who will positively respond to different types of intervention. We need to
know who will respond to which type of empirically supported treatment approach. And,
clearly we need to identify new treatments for those individuals who are not responding
to existing interventions.

A second major gap concerns the etiology of autism. While significant gains have been
made in autism genetics through collaborative efforts, the assembly of large cohorts,
and new sequencing advances, there still exist major gaps. These gaps are in the
identification of which genes and genetic events are contributing to autism risk, how
structural variation and common variation intersect, and how genetic risk interacts with
environmental or other background risk. This foundational gap in understanding etiology
impedes progress in understanding the pathophysiology and mechanism.

A third major gap concerns the identification of novel, efficient diagnostic processes.
Given that an autism diagnosis currently serves as a gateway to services for many,
immediate access to diagnostic evaluation is critical. We need to identify, novel, valid
diagnostic approaches to hasten an individual’s access to services.
Despite many years of calls for more longitudinal research, this critical gap remains. Much has been learned from existing longitudinal cohorts, but there is now a pressing need to recruit contemporary cohorts of children diagnosed with ASD and follow them into adulthood. It is clear that attempts to subtype within ASD are not likely to be successful unless we can subtype by trajectories. Our ability to offer information to parents and policy makers about what children diagnosed today need now, and what they will need in 10 or 20 or 30 years, is dependent on recruitment of new longitudinal cohorts. These efforts would also be enhanced by increased collaboration between experts in assessment and treatment, as well as in-the-moment coordination between clinical researchers and those interested in neurobiology and genetics (e.g., genetic testing for children with ASD enrolled in longitudinal studies).

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Autism research is thriving with many informative and well-constructed studies in a variety of fields, including early detection and intervention, imaging and genetic studies. Numerous mouse models (studying developmental processes, behavior, physiology, etc. are attempting to demonstrate that single gene mutations can cause autism-related functions and then “rescue” those deficits with compounds that target receptors in particular pathways. The problem is providing convincing evidence that findings are truly translational in nature. Do genes act differently in humans versus mice? What about gene variants in humans causing up- or down-regulated gene expression and/or epigenetic effects? The challenge to neuroscientists is to build viable well thought out models with translational value. For human studies, increasing iPSC studies can examine development of human autism cell types in an attempt to identify from very early on whether neurite outgrowth, synapse formation and ultimately circuitry develops normally in autism lines versus controls. Now that Autism BrainNet is operative, more researchers should compose viable experiments and aims in postmortem ASD cases versus controls in specific brain areas where studies have identified structural/functional changes. Now that more ASD cases are available to researchers, studies can potentially include males versus females and/or in children versus adults For the first time, the "n" for postmortem cases has doubled, making postmortem studies informative and possibly providing better evidence despite the high variability in any ASD study. As imaging techniques improve in resolution for both white matter tracts and gray matter changes and/or functional differences, more studies in idiopathic autism cases are needed as most imaging studies have been carried out in high functioning subjects. In summary, many strides have been made in recent years toward better understanding of the underlying mechanisms and toward identifying changes in area
activation and behavior. What is lacking is better animal models with translational value and more human-based studies that cover a range of individuals on the spectrum, in an attempt to obtain a wider understanding of structural/functional changes and how to best approach improving the lives of people with ASD and their families.

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In the last 20 years, there has been notable progress towards identifying early signs and studying their predictive value. Currently, it is possible to identify some children at risk of ASD before 24 months in low-risk populations and 12 months (or sometimes earlier) in high-risk groups (siblings of children with ASD). However, the greatest gaps for people who later will develop ASD are found in the first year of life. The age of 12 months seems to be a difficult frontier to overcome, especially for population screening, as behavioral indicators alone are not enough. Only some early biomarkers are currently being studied (mainly in samples at genetic risk), which could potentially be useful in an early identification protocol (Emerson et al., 2017; Hazlett et al., 2017; Samango-Sprouse et al., 2015). For that reason, a priority will be to move towards the identification of neuropathological processes in early brain development, including the prenatal phase (Muhle, Reed, Stratigos, & Veenstra-VanderWeele, 2018). There are several studies on early biomarkers but only a few have proven some predictive value to improve early detection and diagnosis. In addition, it has been suggested that biomarkers are needed to stratifying different subgroups of subjects within the spectrum (Pelphrey, 2017) and studies are needed to combine these biomarkers with early behavioral indicators. Further research in this area is also essential in order to develop accurate measures that help to assess progress on early interventions (behavioral or pharmacological). Finally, another important aspect to highlight is how to transfer the knowledge about risk factors, biomarkers and behavioral signs into practical application for the professionals working with people with ASD.

References

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Tackling heterogeneity

Whilst recognition of the variability and heterogeneity of autism, from its aetiological causes to its varied presentation between individuals and within an individual across the developmental time course, is to be welcomed it continues to present pervasive challenges to autism science and clinical progress. So many of the scientific paradigms that we use in fields as diverse as genetics to neuroimaging to intervention trials traditionally ‘work better’ if one is studying a more homogeneous group of individuals. To some degree the heterogeneity issue places limits on critical aspects of a mature clinical science, including replication and generalisation of findings, that lessen the impact of the work that we do to improve the lives of individuals with autism. Whilst autism is not alone in medical conditions in facing such challenges, we need to embrace heterogeneity by adopting new and paradigm-shifting approaches that are barely emerging. This places an onus on all stakeholders in the autism research field – from research funders to research participants and, of course, including research scientists – to develop these new paradigms to accelerate the pace of much-needed change. I’m not sure what the answers will be but the challenge will not recede without creativity, application and a little good fortune.

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As new potential treatments for improving outcomes and quality of life for individuals with autism are developed, robust methods for evaluating their efficacy are critical for moving the field forward. While the need for more effective treatment is urgent, we struggle with the ability to design and carry out well-designed clinical trials. Part of that difficulty arises from the fact that autism spectrum disorder (ASD) is inherently phenotypically and biologically complex, and both behavior and biology change across development. Adding to phenotypic and biological complexity is the variability in environmental effects, including the influences of multiple interventions over time.
To improve our ability to evaluate new autism treatments, research is needed to address a wide range of issues that affect how ASD clinical trials should be designed to optimally determine efficacy. These include: the need for natural history studies that incorporate clinical trial outcome measures so that studies can be adequately powered to separate changes reflecting treatment response from developmental changes; standardized approaches for assessing and accounting for a wide range of confounding factors, such as use of other interventions during the clinical trial, and the presence of co-morbidities, genetic and other biological features that might be related to treatment response; methods for addressing the large placebo effect inherent in most ASD clinical trials; commonly agreed upon standards for outcome measures and rater training; and the development and validation of more sensitive, objective, and reliable biomarkers and outcome measures. With respect to outcome measures, research on the use of digital behavioral measures have the potential to offer more precise, objective, scalable quantification of behavioral outcomes. In summary, given the pressing need for more effective treatments across the lifespan, research leading to improved methodology for autism clinical trials should be a high priority.

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The ASD Research GAP in low- and middle-income countries

A recent study of the global burden of developmental disabilities in under 5-year olds (GRDDC, Lancet Global Health) identified that 95% of all under 5-year olds with developmental disabilities (including ASD), live in low- and middle-income countries (LMIC). Strikingly, sub-Saharan Africa (SSA) and South-East Asia showed the greatest rise in developmental disabilities over the last 30 years of all global regions. In stark contrast to this growing recognition and rapidly growing need, very little ASD research is conducted in LMIC. A scoping review of ASD research in SSA showed, for instance, that less that 1% of the world’s ASD research originated from SSA (Franz et al., Autism Research, 2017).

LMIC represent not only low socio-economic status, but are also characterized by highly diverse, multilingual and multicultural communities. South Africa is an interesting case example: the country has a population of 55 million people who speak 11 official languages, is categorized by the World Bank as an ‘upper-middle’ income country, but is also the nation with the highest Gini coefficient, suggesting the greatest socio-economic disparities. Associated with this comes some of the greatest health disparities in the world (Franz et al., 2018). ASD services in the country are highly limited, exist almost exclusively in urban communities, and provide little more than diagnostic services to the majority of the population, who cannot afford to pay for (mostly non-evidence-based) interventions (de Vries, 2016; Franz et al, 2017; Franz et al, 2018).
In the scoping review on ASD in SSA, Franz and colleagues (2017) identified major gaps in almost all areas of research. Notable gaps included the absence of any epidemiological studies of ASD, no early intervention studies, no research on adults with ASD, and virtually no knowledge of health and education systems, use of technology, or perspectives of stakeholders. Research, on the whole, was of relatively poor quality (Franz et al., 2017).

It seems clear that ASD and related developmental disabilities represent one of the major challenges of the 21st century. Much is required to understand the ASD research gaps in parts of the world where most people with ASD live. A global, collaborative research effort will be required to understand the needs of these culturally, linguistically and socio-economically diverse communities, systems and stakeholders, and specific efforts should be made by the global ASD research community to support advocacy for ASD research and capacity-building of local researchers in LMIC.

References


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It’s time for autism neural stem cell research

Since autism is a uniquely human disorder, understanding its pathogenesis will require investigation of etiological factors, like genes and environment, in the human brain. A major challenge, and significant gap, is that many contributory factors act during early
brain development, a prenatal period that is difficult to access and study. Evidence of early fetal developmental dysregulation comes from studies of postmortem tissue and MRI imaging. Moreover, newer genetic studies suggest autism risk genes largely converge on the developing cerebral cortex between gestational weeks 8 and 24, when neural precursor cells (NPCs) are undergoing proliferation, migration, and initial differentiation. No doubt, tremendous progress in understanding the roles of genetic factors has derived from mouse models where expression of specific risk genes is manipulated eg. the monogenic syndromes that exhibit autism symptoms, such as Rett, Fragile X, Tuberous Sclerosis, and high penetrance copy number variants, like 16p11.2.

However, the majority (80%) of autism is genetically undefined (idiopathic) and monogenic risk genes contribute little, so genetic models cannot be generated. Further, even when mouse models have been analyzed for behavior, structure, neural circuits, and synaptic functions, the earliest periods of cortical neurogenesis have been neglected, missing the time and place where convergent genetic analyses point. It is also obvious that animal models can only take us so far: Neurons in the mouse cerebral cortex are generated in only 6 days, whereas the same process takes 6 months (1st & 2nd trimesters) in humans. Thus, to overcome these developmental, genetic, and functional differences between animals and humans, we should now focus our attention on human NPCs generated from individuals with autism, both idiopathic and genetically-defined, in which the person-specific genetic signature and family background are maintained. The advent of human induced pluripotent stem cell (iPSC) technology now allows us to create the diverse stages of developing NPCs and more mature neurons. This revolution is now well underway in academia and industry with the expectation that we will identify neurobiological pathways and mechanisms underlying genetic and environmental contributions to human disease. In turn, we hope to identify autism subgroups based on etiological pathways at cellular and circuit levels that can be targets for therapeutic interventions. This approach, already beneficial in cancer, warrants further development and support as we struggle with the incredible heterogeneity of autism spectrum disorders.

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Despite calls for more research on adolescents and adults, and a new journal dedicated to adults, there remains limited empirical research on the presentation of autism in adults and how its' features impact their lives. Without this knowledge, we can do little to progress and provide evidence-based supports to improve the quality of lives of those living with autism.

Of particular need is research that is co-produced with autistic researchers, and we need to focus on not just research on adulthood but training autistic scholars to contribute to these research efforts. Listed below are topics begging empirical attention.
Aging and autism (with particular attention to vulnerability to medical disease; and service provision)

Parenting with autism

Drug and alcohol use in autism

Self-injury and autism (see work by Chris Oliver)

Autism and the criminal justice system

RRBs in adulthood (with attention on the presentation of circumscribed interests in adults)

Good empirical research on employment to enhance understanding of enables and barriers to employment and good alternatives for recruitment and employee retention

Inter-relationships of comorbid conditions and their relationship to core autism symptomatology and outcomes across the lifespan (as well as intervention for co-morbid conditions)

Minimally verbal autistic people and those with severe autism overlooked across all stages of development and inquiry

One of the overarching gaps is advancement of theory in autism research - whereby having criticized much of what was available which was found to be of little relevance, we have not provided good alternatives to drive our research on these conditions.

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Changing definition of ASD and dimensional approach

There is a long history of delineating the border that separates affected individuals from unaffected ones. In a sense, such effort to define the pathological conditions strictly has contributed to an advance in autism research. On the other hand, evidence indicates that the autistic condition lies on the spectrum from the extreme end to the milder end without a discrete cutoff at both behavioral and biological levels. The subthreshold condition that does not meet such a strictly defined diagnostic criteria has not long been paid attention to from clinicians and autism researchers when autism is considered as an entity. For example, there has been little focus on the possible early intervention for subthreshold children. Most early intervention studies chose children with ASD defined
strictly as research subjects. However, recent research suggests that subthreshold autistic traits persist throughout the life, and many maladapted adults who were subthreshold can be diagnosed as ASD using loosened DSM-5 criteria.

Similarly as in ASD comorbidity with multiple neuropsychiatric conditions occurs so frequently, subthreshold autistic symptoms are also often observed in other neuropsychiatric conditions such as ADHD, depression, bipolar disorder, and schizophrenia. Such behavioral overlap seems consistent with similarity at the level of brain structure, neural network, cognitive features, suggesting that autistic symptoms are not ASD-specific but also a cross-diagnostic element. Thus, future autism research should extend its scope using dimensional approach cross diagnostically beyond ASD vs. TD, which will not overlook a sub-group consisting of the heterogenous ASD and will contribute to both neuroscience and general clinical practice (not necessarily highly specialized clinical practice). To do so, dimensional approach should be validated cross diagnostically, like the RDoC approach proposed by NIMH tries to do.

Parenting a child with ASD revisited

This theme has been and still is likely to evoke unpredictable emotional reaction (and also irrational thought) in not only parents but also health professionals. The idea that wrong parenting causes autism has no scientific evidence, and no one would disagree with it. However, it is true that parent-child interactions are influenced by the presence of ASD in the child. As a result of it, there is a high risk for maltreatment towards a child with ASD or developing depression among mothers. Especially how the mother's role is recognized and valued in the society and what mothers themselves desire for their child regarding early development differs by cultural norm and stigma. For example, it is reported that Japanese mothers may emphasize emotional bonding and maturity whereas American mothers focus on verbal expressiveness and social skills. In addition, since autistic symptoms and mental health problems tend to aggregate within a family, there is a sub-group of vulnerable mothers. Future clinical or public health research related to autism should focus on vulnerable families based on evidence derived from community-based longitudinal studies for children with ASD and families, although most clinical studies examine short-term effectiveness for children who were chosen from the families participating in research.

Finally, I hope that in the future multi-cultural, multi-dimensional studies of ASD would reveal the mystery of the diversity related to the ASD syndrome and its development.

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One of the prominent hypotheses pertaining to the neurobiological origins of autism spectrum disorder (ASD) is the disrupted brain connectivity hypothesis (Just et al.,
2004; Kana, Libero, Moore, 2011). Despite the relative consistency of connectivity-related neuroimaging findings in ASD, one of the main issues hampering its reliability is its relatively poor specificity. For example, similar to ASD, disrupted connectivity has been found repeatedly in disorders like schizophrenia and attention deficit hyperactivity disorder (ADHD). An important avenue for future research in ASD is to generate studies, especially neuroimaging studies, along the lines of the NIH Research Domain Criteria (RDoC) initiative. Comparison of disorders like ASD, ADHD, and schizophrenia may provide more insight into the nature and extent of the disrupted connectivity hypothesis. A second potential gap involves investigating, estimating, and separating the effect of comorbid conditions with ASD and its impact on research findings. Comorbid conditions like ADHD with ASD has been a difficult problem for researchers. While researchers understand the significance of this problem at a conceptual level, practically they face an uphill task to identify cleaner/homogeneous sample. Studying the effect of comorbid conditions would be an important direction for future studies in ASD. Finally, intervention-related neuroimaging studies are badly needed in autism. The need for evidence-based intervention practices cannot be overemphasized. Neuroimaging studies that specifically target the effectiveness of existing cognitive and behavioral interventions in ASD and also testing the impact of novel interventions on the neurobiology of autism as well are needed.

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A government epidemiological survey of Neurodevelopmental Disorders (NDDs) including Autism in children aged 0-9 years in 2013 (total number of children=7280) in Bangladesh1 ascertained that the prevalence of all types of neurodevelopmental impairments (NDIs) was 185/1000, with the highest numbers of children with cognitive impairments (158/1000). Prevalence of NDDs was 70/1000. Within this category the prevalence of Autism Spectrum Disorder (ASD) was 1.55/1000; with significant disparity in the prevalence of ASD in rural (0.68/1000) versus urban middle and high income (30/1000) populations. A recent survey of ASDs showed similar trend, i.e., prevalence of ASD was 14/10,000 in rural populations versus 25/10,000 in urban populations2. This survey did not disaggregate relevance by family income. Case load of ASDs in clinical settings also show a similar disparity by family socioeconomic status. In the 15 Child Development Centers established within government tertiary hospitals serving the lowest income populations across the country3, there was a rising case load of ASDs in their General Developmental Assessment Clinic by family income, i.e, within low (6%), low middle (15%), middle (34%) and high income (44%) families3, page 24. These disparities in prevalence in epidemiological surveys and incidence in clinical settings by urban/rural residence and by wealth quintile pose questions regarding the antecedents or risk factors leading to ASDs in different populations within the same country, even with sociopolitical, geographical and cultural similarities, and where the professional skills, scales, tools, and procedures applied for the assessment and diagnosis of ASD
were the same. Epigenetic studies are needed to explore the underlying reasons for such differences, so that the country’s scarce resources can be allocated for the best interests of all children with autism and other NDDs.

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Over the last years, we have seen an impressive increase in the number of genetic diagnoses in autism. The introduction and maturation of next-generation sequencing technologies brought large-scale sequencing projects to the forefront of autism research. The progress is impressive both in the number of diagnoses made and in the number of novel genes discovered (Deciphering Developmental Disorders Study, 2017; Iossifov et al., 2014; De Rubeis et al., 2014; Stessman et al., 2017). The latest meta-analyses suggest that over a hundred genes have now been identified that, when disrupted, cause in autism (Coe et al., 2019; Satterstrom et al., 2018). While the increase in genetic knowledge is by all measures spectacular, several challenges lie ahead of us. First of all, the individual genetic causes, even the most frequently mutated genes including ADNP, CHD8 and SCN2A, none counts for more than a percentage of the total number of cases (Bernier et al., 2014; Helsmoortel et al., 2014; Weiss et al., 2003). The unprecedented genetic heterogeneity hampers the collection of larger cohorts of patients with the same underlying genetic ethiology, necessary for fine-tuning the full spectrum of clinical symptoms (Arnett et al., 2018; Van Dijck et al., 2019) and discourages initiatives for therapy because of the small patient population for any given disorder. A second challenge is the interpretation of the missense variants identified in the patients in the gene-identification studies (Coe et al., 2019; Deciphering Developmental Disorders Study, 2017; Satterstrom et al., 2018). Essentially all established diagnoses to date have either a gene inactivating variant or a missense variant belonging to the 0.1% most pathogenic sequence alterations, as judged by having a CADD score of > 30 (Kircher et al., 2014), while we are uncertain of the relevance of the great majority of the missense variants. Furthermore, it can be noted that the diagnoses are almost exclusively made in autistic patients on the severe end of the clinical spectrum, many of those co-morbid with ID. A huge challenge for the next
round of gene identification studies will be to pinpoint the genetic factors implicated in high-functioning patients with autism.

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There are many gaps in autism research. But relatively speaking, I believe the most
critical gaps are not in any particular type of research, i.e., whether the research is basic
science or clinical research; postmortem, animal, stem cell, or human research;
molecular genetic or brain imaging research; infant sibling or affected child, teen, or
adult research. I believe, like other areas of biomedical and psychological research, the
most critical gaps are in the quality of the research we do, the depth of the research,
and its clinical relevance (Chalmers et al., 2014; Ioannidis et al., 2014;

We still lack an integrative, in-depth understanding of the most basic questions in
autism research and the most basic problems and challenges faced by affected
individuals and their families. Truly high quality and integrative research seems
necessary to understand the extensive variation in autism, and elucidate the biomedical
and contextual risk and protective factors, mediating mechanisms and moderators
across the lifespan.

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The Research Challenge of Biobehavioral Variation and Autism Spectrum Disorder

The pronounced variation of biobehavioral phenotypes in humans reflects an
evolutionary strategy to optimize survival. This variation is no more apparent than in the
constellation of symptoms in autism spectrum disorder (ASD). Discerning the biological
origins of trait variation is complicated. However, a deeper understanding of phenotypic
heterogeneity may lead to more successful treatment outcomes. In an attempt to mitigate the research challenges inherent in such a varied population, one research approach only incorporates individuals with an identical gene mutation, or a diagnosis of the same syndrome associated with ASD. Yet even here, there can be substantial symptom heterogeneity. Conversely, testing constraints can result in studies that focus only on individuals with specific language or cognitive abilities, and yet conclusions are applied to the broader population. The issues are magnified because defining and capturing variability in complex behaviors such as social communication is challenging to measure systematically. Thus, current diagnostic and research tools tend to categorize children as demonstrating either “typical” or “atypical” behavioral profiles, without addressing variability within those categories. Clinical researchers have some appealing new opportunities with the availability of growing clinical and phenomic datasets, research capital for advanced information and statistical science. Moreover, advanced resolution of behavioral measures is improving the ability to discern phenotype patterns. Similar to human studies, research using animal models often seeks to minimize genetic and behavioral heterogeneity by focusing on the role of a particular causal gene mutation in a single inbred strain of mice. Though important discoveries have been made, translation of findings into genetically diverse human populations has been difficult. Here, opportunities exist based on strategies used by other biomedical fields to systematically interrogate phenotypic variation. Using modern tools such as genetic reference panels of vertebrate organisms, paired with higher-throughput molecular and behavioral assays, investigators can systematically examine the heritable origins of variation. Tackling heterogeneity experimentally in humans or model systems will deepen our understanding of typical and atypical development and facilitate innovation of new research-informed ASD interventions.

References
There is a need for more research on adults with autism, especially those who were not diagnosed until adulthood. These are primarily intellectually and verbally able individuals, many of whom have achieved major milestones of adulthood such as working, living independently, and having a partner.

Life course of individuals with autism. Which factors are related to better adult outcomes and which to poorer? Are there cohort-related differences, such that young adults today have different risk/protective factors than older adults? My work suggests that while supports and early intervention help youth with autism develop optimally, over-supporting (continuing supports past the time they are needed, limiting opportunities for growth because of fears about failure, etc.) by families delays progress into adulthood and reduces independence.

Psychopathology across the life span. Adults with autism have had many years to accrue psychopathology, for which they are at high risk. However treatments have lagged behind. It is difficult for psychiatrists to treat individuals with autism with medication because their response to medication is difficult to predict and often unstable. Research on factors related to atypical response to medication and leading to better guidelines for treatment is needed.

Distinguishing autism in intellectually able adults from conditions such as bipolar disorder, personality disorders, and schizophrenia remains a problem. There are many psychiatric inpatients with severe mental illness who also have undiagnosed autism, and who are at risk for incorrect diagnoses and treatment. Methods to identify and treat them more reliably are needed.

Sexual and identity development in autism. It is known that individuals with ASD are over-represented among the LGBTQ+ population. However, almost nothing is known about why this should be so. Developmental factors including delayed development of identity more generally, difficulty with feeling “different” from others, differing treatment of youth with ASD, and other factors should be examined.

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Overall, I think that adults, severely affected individuals, and non-speaking individuals have been neglected in research studies and their needs are great. I believe that new assessments and treatments can be developed that reduce their disability significantly. I also think that there is too little focus on treatment studies and that promising new treatments take about 10-15 years to be accepted for reimbursement which is the first step toward dissemination. This time lag reflects the need for two 5-year trials demonstrating efficacy in order to achieve acceptance. These trials are typically sequential thus prolonging the trial process. This needs to be shortened by starting new trials of promising treatments before the first trial is completed and starting dissemination trials before the second trial is completed. Many treatments with demonstrated effectiveness end up left on the shelf because there is no support for dissemination. This also means that successful treatments are present at the few sites that participated in the trials but not elsewhere. Meanwhile, many individuals continue to get no treatment or older, less effective treatments. This costs money and lives. A related problem is that clinical practice can be 20 years behind the known science and a more effective and faster way of disseminating research based advances needs to be found. We cannot rely on training programs in medical school and graduate school to update knowledge of autism. In our state there are 10-15 television channels reserved for public service or government broadcasts, most going unused. A channel could easily be used for disseminating new knowledge as determined by professional groups or NIH. With streaming, a similar service could be provided for updating professionals. I also think there are large holes in assessment instruments. Notable examples relate to adaptive function, social cognition, and pragmatic language comprehension. Clinicians and teachers need a relatively quick way to assess real life skills in these areas. Existing tests are insensitive and or long. Teachers have little training in recognizing behavior resulting from psychiatric disorders and miss the significance of what they see. I would say that research on employment and preparation for employment is lacking. Likewise, job programs and vocational programs may have a very poor understanding of the limitations of adults with autism resulting in continued attempts to match them with jobs that they are unable to do. I do think that the genetic
research has made enormous contributions to the understanding of the causes of autism with much more to be learned. It also contributes generally to genetics research.

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After decades of research activity, the neuroimaging community has yet to generate a clear picture of critical brain features in ASD. An underlying challenge is that the field needs to take heed of its own insights.

A prime example is our awareness of the heterogeneity of the disorder. The vast majority of neuroimaging studies in the field have tested for differences between ASD and typically developing (TD) groups. This conventional approach may be missing the point, if there is no unique pattern of atypical brain features that distinguishes ASD. And indeed, with growing awareness of the multitude of genetic risk factors, etiological pathways, and outcome phenotypes captured under the clinical umbrella of “ASD”, why should we expect the existence of a single atypical pattern? A more promising perspective for neuroimaging is to consider comparisons at the group level as a due diligence first-pass analysis, to then focus on the truly important question: What is the difference, not between ASD and TD groups, but between individuals with ASD? Various data-driven clustering techniques are available to pursue the question whether such differential patterns indicate subgroups (of individuals with shared brain features) within larger ASD cohorts.

Another insight concerns the imaging techniques themselves. For example, we know that fMRI does not directly measure neuronal activity or functional connectivity (but blood oxygenation related in complex ways to neuronal activity). We know that diffusion weighted imaging does not directly measure axonal tract microstructure (but movement of water molecules related to tissue organization in rather ambiguous ways). For adequate appreciation of findings from these and other techniques, it is crucial to take methods for what they are, rather than mistake the neuroscientific interpretation of findings for the findings themselves.

Finally, we know (since taking an undergraduate neurophysiology course or the like) that brain function and connectivity is exquisitely dynamic. However, the broad availability of MRI scanners – and the prodigious versatility of MRI in generating biologically relevant contrasts – has led the field to rely predominantly on brain assays that neglect dynamics. Of course, there have been decades of EEG research, with a more recently added small MEG literature, investigating dynamic brain function in ASD. However, MRI and electrophysiology remain largely segregated territories in ASD research and much effort in building bridges will be needed for a more comprehensive understanding of brain organization and neural processing in ASD.
The Importance of Research on the School-Aged Development of Children with ASD

For many very good reasons early preschool development and adult development are often emphasized in research on the natural course, and treatment of Autism Spectrum Disorder. However, the development of school-aged children with ASD has received relatively little systematic theoretical and empirical consideration in our science. It is not clear, though, how a detailed understanding of neurodevelopment and treatment of ASD is possible, nor how optimal adult development for all autistic people may be achieved, without a comprehensive understanding of the vital and extended period of school-aged development. For example, when considering intervention for ASD after age 5, it is important to recognize that instruction in school becomes the most common, longest-term, and equitable venue for intervention available to all affected children. Indeed, children with ASD spend so much time in school it may be difficult to provide opportunities for effective intensive intervention anywhere but in school. However, the research on learning, social communication and academic development in school-aged students has not been a point of emphasis in national funding or research planning.

Hence, effective interventions are not readily available for schools even though numerous studies indicate that the academic achievement and development of school-aged children with ASD remains poor, for verbally fluent as well as minimally verbal children. Not surprisingly, the post-secondary educational, vocational and social outcomes for high school students with ASD are well below expectations based on the range of IQ observed in these students. In order to improve the outcomes of affected youth and adults significantly, and to truly understand the developmental nature of ASD, we need to begin to prioritize the study of school-aged children. In particular, we will need innovative studies on learning in school-aged children with ASD, and teaching, to better leverage time in 1st through 12th grade in order to deliver more effective cognitive, social, academic and communication interventions with life-span impact.

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We need to make progress in numerous areas – both in the ‘basic’ and ‘clinical’ sciences.

Basic Sciences
Knowledge about underpinning mechanisms is severely constrained by lack of human brain tissue.
Relatively few efforts have been to ‘translate’ cellular and rodent models to man (and back). For example, it is unknown how well basic models recapitulate the human disorder.

There is a lack of translational research pipelines that take early stage basic science findings into man to rapidly test potential new (or repurposed) treatments. In other words basic and clinical sciences largely operate independently of each other.

Clinical science

We need to be able to ‘fractionate’ ASD into more biologically homogeneous subsamples.

There is a major focus on genes – but these efforts largely use an ‘all comers’ approach (i.e. with little or no attempt to address the heterogeneity of ASD). There needs to be more work on gene expression, gene-environmental interaction, and/or how the same genetic risk factor can have such divergent outcomes.

There is a major focus on ‘risk’ – yet relatively little on resilience. By understanding reliance better we are more likely to identify protective factors. Also our studies of ‘risk’ need to better incorporate the role of the environment – and especially during fetal development.

As a discipline we often focus mainly on ‘core’ symptoms. Yet it is the associated symptoms (e.g. epilepsy, sleep, anxiety/depression, intellectual disability) that often most impact on quality of life. Hence we could perhaps make more impact in the short term by increasing research on those associated symptoms that increase morbidity and reduce life expectancy.

We lack effective treatments. Also clinical trials - as currently designed - are hugely expensive, likely to fail (as they use an ‘all comers’ approach, have high placebo response rates, and lack objective outcome measures), and mainly target core symptoms. Hence we need to run cheaper, better targeted trials, that use objective outcome measures sensitive to change. In particular we need trials that target associated symptoms in addition to those which focus on the core disorder.

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As the human genome becomes ever more accessible, there is a belief by some that this will lead to breakthroughs for autism and that genetic testing and genetic engineering will reduce the number of new diagnoses. The fact that the genetics of autism are so complex and poorly understood, and that many of the genetic alterations are the result of de novo mutations and epigenetic processes, makes this highly unlikely. The gap in our understanding of the genetics of ASD, and the translation of the state of that knowledge into a digestible public message, is one of the major deficiencies in the realm of autism research. Families with children with ASD deserve to know the genetic contribution for their child and for future children they might have so they can make informed family planning choices. But they should also understand that
our understanding of the genetics of ASD do not allow us to predict the risk for an individual child. To pretend that we can do otherwise is unethical.

Another area in need of sound and replicated research is the area of transition to adolescence/ young adulthood. Every family struggles mightily with this transition and yet we do not have a solid body of evidence to inform practice in this arena. High functioning individuals with ASD are going to college and yet few colleges or universities have support systems in place for these students. Research that addresses the issues surrounding transition to independence is critically important to inform policies and practices. As the many children with a diagnosis of ASD age into adolescence and young adulthood, it is imperative that we understand what predicts the most successful transition to independence and to a fulfilling life. To ignore this issue will lock us into a responsive as opposed to a proactive approach.

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In Latin America, most countries are low and middle-income countries. In these countries, autism research infrastructure (number of researchers, full time research positions, research oriented organizations, etc.) and funding (both public and private) is very limited. ASD research is not only affected by lack of funding, but also by poverty, barriers in access to services (both diagnostic and treatment), stigma, limited legislation and poor public health infrastructure. To set an example of the lack of data in this region: to date, there are very few reliable estimates of ASD prevalence in Spanish-speaking countries.

In this context, gaps in autism research are very broad. Significant gaps can be seen in epidemiology (ASD prevalence and risk factor identification), tool validation (developmental surveillance, screening, diagnostic tools), treatment effectiveness (what is helpful, when, how much of it, for how long, and for whom) and its measurement, effectiveness of community-based and parent mediated interventions, medical comorbidities and biomedical interventions, ASD in adulthood, ASD in women, quality of life in ASD, inclusive education, amongst others.

Translational and implementation science are significantly relevant in low and middle income countries as they focus in connecting autism research and impact on health, and promoting the uptake of interventions that have proven effective into routine practice with the aim of improving quality of life of individuals with ASD and their families. It is very important to prioritize what families and individuals with ASD identify as important topics for research. Population oriented research usually gets a significant return on investment and this is specially important in funding constrained contexts such as Latin America.
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Given the emphasis in autism research for interdisciplinary science and for biobehavioral approaches to the disorder, there is a surprising gap in neuroscientific investigations of treatment effects in ASD. We now have a wealth of neuroscientific studies in ASD across the age span, from infancy into adulthood, and that field has made major methodological gains in studying brain structure and function in infants and young children as well as in persons with more severe disability. Given our understanding of the biology of learning and of action, it seems logical that the positive behavior changes and developmental accelerations that occur in the most effective early intervention approaches must result from changes in many levels of the brain’s learning chemistry and circuitry. While we have had to rely on animal models for past decades to develop hypotheses about neural processes underlying ASD symptoms, current brain imaging methods, both structural and functional, appear sophisticated enough to examine treatment-related changes in several aspects of central nervous system function. There remains a great deal of dismissal of the effects of early treatment among some ASD scientists, perhaps because behavior change data is considered to reflect “surface” changes rather than deep systemic changes in core neural processes. Demonstration of effects of behavioral treatment on neural development or function may elucidate neural mechanisms of change that could lead to more effective treatments, both behavioral and pharmacological. Evidence of changes at the neural level may also be needed to increase commitment of public health and finance systems to the provision of early high quality behavioral treatments. The bias towards funding effective interventions for biological as opposed to developmental disorders is easily seen when one compares the amount of money spent to treat a child when cancer onsets compared to the amount of money spent to treat a child when autism onsets. And yet ASD is also a biological disorder, and also one that responds to specific and focused treatments early in life. The plethora of neuroscientific investigations of brain differences of high functioning adults with ASD contrasts sharply with the dearth of studies examining how neural systems respond to intensive treatments early in life.

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Increasing early detection and access to specialized intervention in the real world

Within the past 15-20 years, our understanding of the early presentation of autism has increased dramatically, as has the number of evidence-based interventions suitable for use with very young children. We have learned that early, specialized intervention can
have positive effects that we never imagined possible when autism was first introduced in the DSM-III. We now have well-validated early screening tools, as well as a variety of naturalistic developmental, behavioral, interventions (NDBIs; Schreiberman et al., 2015) from which to choose. So why haven’t we been able to move the needle in terms of early autism detection and engagement in early intervention?

One of the most well-replicated findings in the autism literature is the average age at which parents of children with autism first become concerned about their behavior or development: 18 months. Yet the average age of an autism diagnosis still hovers around 4 years, or later for underserved populations. Granted, there are many obstacles to early diagnosis. It’s not easy to diagnose young children whose symptoms overlap with those of other disorders. The paucity of providers with specialized training in autism contributes to painfully long waiting lists for diagnostic evaluations. And, unfortunately, we operate within a medical model in which a formal diagnosis is often required for access to specialized interventions. The end result is that many children with autism are not identified or served appropriately until they reach school age.

We are unlikely to move the needle unless we are willing to expand our research approaches in at least two ways. The first involves extending our research into the community, and developing/evaluating feasible ways for front-line providers (i.e., those who have early and sustained contact with young children and families) to implement evidence-based screening and interventions. The second is moving away from a “diagnosis-treatment” healthcare delivery model when early autism symptoms are present, and toward a symptom-based preemptive model in which low intensity, yet specialized, interventions can be implemented by community providers (e.g., those working in Part C Early Intervention programs). While these approaches involve a bit of a paradigm shift, the field of implementation science offers some roadmaps for engaging with community providers, as well as models for “scaling up” successful strategies.

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Replication in Autism Research

Many have heard of the “replication problem” in psychological science— the failure of subsequent studies to confirm the original results. Further, we often do not know of non-replications as the publishing field is biased toward novel findings. Identifying the cause of non-replication, whether due to a false positive in the first study, a false negative in the subsequent study, or other factors, is of serious importance to the integrity of our field. Critically, within the field of autism research, non-replication is often attributed to sample heterogeneity—which reflects a diverse set of issues itself including the known phenotypic diversity of individuals with ASD, historic changes in clinical definitions of
ASD, and variability in age and sex within samples. It is practically difficult to match
groups of individuals across studies, but this limits our ability to seek larger truths about
the nature of autism without supporting evidence of replication.

How do we move beyond attributing replication issues to differences in group
characteristics? As sample heterogeneity is not likely to change in the future,
researchers need to adopt best practices of pre-registration of dependent variable
specifications and analytic plans, clear quality control metrics, transparency in the
transformation of raw data to dependent variables, and more investigation of the
psychometric properties of an experimental measure or dependent variable such as
validity and reliability. The knowledge of the reliability of the data will be a key
contribution to eliminating measurement as a contributing factor to non-replication. More
studies need to include psychometric properties prior to use of a measure in group
discrimination, subgroup stratification, or as an indicator of development or treatment
change.

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Despite an improvement over the past five years, there remains a substantial dearth of
rigorous clinical trials of existing and new interventions. The publication of a
randomised-controlled trial of a behavioural or pharmacological intervention that
involves pre-registration, a large sample size, the necessary treatment concealing, and
high-quality internal validity checks, is still a noticeable and infrequent event in the
autism research literature. These studies are, of course, highly complex, and require
considerable resources and planning to execute successfully. However, these
substantial challenges shrink into the background when juxtaposed with the potential
benefits. It is now universally acknowledged that ASD is heterogeneous in aetiological
origin, behavioural presentation, and expression across the life-course. Without a solid
evidence-base upon which we can provide families with accurate guidance in their
intervention decisions, we are flying blind amidst these fluctuating variables. The ethical
implications of this are immense, and this needs to be a key driver in our pursuit to
make the publication of these studies a more frequent event. There is no doubt that
cross-site (even, cross-nation) partnerships are critical to this endeavour. It is only
through targeted funding schemes, the work of professional societies, and critically, the
will of the scientific research diaspora, that this gap will start to be filled.