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Diagnosis of Autism Spectrum Disorder: Reconciling the syndrome, its diverse origins, and variation-in-expression

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Abstract

Recent discoveries on the pathogenesis and symptom structure of autism spectrum disorders (ASD) are challenging traditional nosology, and invoke consideration of a reconceptualization of diagnosis, made all the more pressing by new prospects for early identification, targeted intervention and personalized medicine approaches to specific autistic syndromes. Here we review key strengths and limitations of current standards for diagnosis, clarifying the relationship between current diagnostic thresholds and

what is now known about the structure of symptoms in nature, assimilate recent advances in understanding about the diversity of *causes* of autistic syndromes, and finally propose ways for knowledge of causation and symptom structure to be incorporated into the next evolution in the approach to diagnosis of autism.

I. Introduction: The Shifting Landscape of Contemporary Clinical Diagnosis

Until about a decade ago, autism was rare, usually accompanied by intellectual disability, lacked standardized methods for calibrating the ascertainment of symptoms, and only rarely could be traced to a biological cause. All of that has changed. And although *clinician diagnosis* maintains its tentative hold as the current standard for case designation, that standard is increasingly informed by a steady progression of scientific discoveries that have challenged traditional perspectives on the appropriate threshold for assigning a clinical diagnosis and on how diagnosis should relate to the specific cause of an autism spectrum disorder (ASD) in an individual patient. In essence, in each of Robins and Guze's classic 1970[1] proposed requirements for valid classification of mental disorders (clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study) rapid advances in the science of autism have occurred.

The diagnostic implications of these recent discoveries, especially related to symptom structure and biological cause are numerous, and largely encompassed by four overarching themes (1) *Limitations of the Expert Clinician Paradigm* as a standard of diagnosis[2]*, (2) The Quantitative Trait Characteristics of ASD:* i.e. that the defining features of the syndrome are continuously (not categorically) distributed in the general population, and that they often arise from additive genetic influences that are shared with other neuropsychiatric conditions,[3-5] *(3) Pronounced Heterogeneity* in the pathways of causation to ASD phenocopies[6] even within families,[7] *and (4) Pleiotropic Effects,* that the same deleterious genetic variant can give rise to various neuropsychiatric syndromes (e.g. epilepsy, schizophrenia, ADHD, learning disability, intellectual disability) or other non-ASD comorbidities (motor coordination or behavioral impairments)[8,9] depending in part on genetic background.[10] Some or all of these issues present similar challenges in other complex medical diseases (e.g. hypertension, diabetes, inflammatory bowel disease).

The goal of this article is to assimilate the specifics for ASD: beginning with the strengths and limitations of current standards for diagnosis (invoking Theme 1 above), clarifying how the resulting diagnostic thresholds relate to the structure of symptoms in nature (Theme 2), next reviewing what is now known about the diversity of *causes* of autistic syndromes (Themes 3 and 4), and finally how knowledge of causation and symptom structure might be incorporated into the next evolution in the diagnostic approach to ASD. DSM-5 has represented a partial attempt to modify the diagnostic process in tandem with the pace of recent discovery, but it remains an important goal to continue to build upon and refine the existing taxonomic framework in a manner that flexibly and faithfully accommodates advances in scientific understanding.

Panel A. DSM-5 Diagnostic Criteria for Autism Spectrum Disorder 299.00 (F84.0)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper· or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Specify if:

With or without accompanying intellectual impairment

With or without accompanying language impairment

Associated with a known medical or genetic condition or environmental factor

With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119·120, for definition)

II. Foundational Elements of Contemporary Clinical Diagnosis of ASD

We begin with the paradigm for clinical diagnosis, which is the historical bedrock of case designation. Panels A and B list, respectively, diagnostic criteria for ASD according to the Diagnostic and Statistical Manual 5 (DSM-5)[11] and its published parameters for specifying *severity*. The information in these panels reflect the incorporation of several noteworthy scientific advances over DSM-IV (we note that ICD-10 criteria for autism are keyed to DSM-IV, and as of this writing it is not yet resolved precisely to what extent ICD-11 will reflect the changes incorporated into DSM-5). First is that the symptom criteria were collapsed from 3 domains to 2, in part on the basis of evidence that the social and communicative impairments that are most specific to autism spectrum disorders (impairment in reciprocal social interaction and impairment in social / pragmatic aspects of communication) are closely inter-related, and their severity highly correlated, not only within populations of clinically-affected children,[12] but in the general population[3], with the caveat that results of factor analyses of ASD symptoms can be variable as a function of how they are ascertained. Second, new severity specifiers (Panel B) categorize the

impact of symptoms on adaptive functioning. An often-overlooked aspect of the characterization of severity in ASD is that i) core symptom burden (DSM-5 Criteria A and B) and ii) impairment in adaptive functioning (DSM-5 Criterion D) are each quantifiable, and only partially correlated; there are many clinical situations in which core ASD symptom burden is pronounced but impairment relatively mild, and vice versa. Consider, for example, a well-adjusted individual who formerly carried a diagnosis of Asperger Disorder on the basis of very substantial ASD symptomatology but is successfully employed in a technical field, or an individual with milder ASD-specific symptoms accompanied by general cognitive impairment such that the combination results in profound impairment in adaptive functioning. Thus symptom burden and impairment in adaptive functioning constitute orthogonal axes of diagnosis, both of which are important to measure, and it can be well-argued that most of the proven benefits of currently-available interventions for autism are in the realm of adaptive functioning, not core symptom counts (see [13-15]). Improvements in adaptive functioning are achievable and critical for patients with ASD, but grossly under-appreciated when measuring outcomes exclusively as a function of core symptom burden, as still often occurs in clinical trials. Panel B represents the hybrid severity index published in DSM-5 that translates the impact of symptoms in each criterion domain (A and B) onto three broad categories of adaptive functioning, each of which are defined by descriptive scoring anchors depicting the *level of support* an affected individual requires. Third, it is now deemed appropriate to simultaneously diagnose ASD with other psychiatric or developmental disorders when there is ample evidence for comorbidity, given overwhelming evidence that many known inherited causes of ASD are genetically independent from the causes of other common psychiatric conditions,[16] and therefore it is entirely possible for an individual to be affected by more than one neuropsychiatric condition.

Panel B. Severity Specifiers: Characterizing variation in adaptive functioning in ASD

Severity level	Social communication	Restricted, repetitive behaviors
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and how has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to· and·fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

The diagnostic process

Implied, but not explicit in the diagnostic criteria themselves, are the elements of information-gathering that are required to establish diagnostic criteria A·E, and therefore constitute what can be thought of as 3 pillars of the diagnostic process: 1) ascertainment of current symptomatology sufficient to meet the A, B, and D criteria, 2) the acquisition of a developmental history consistent with ASD (C, provided by a primary caregiver of the child whenever possible), and 3) clinician confirmation.

Since the severity of current symptomatology can vary as a function of environmental context and demands, appraisal of symptoms requires *caregivers and teachers* to provide accounts of an affected individual's behavior in the social environment of home, school, and community, to report on their social interests and peer relationships (which cannot be ascertained on exam); to provide information on their day-to-day social communication, including use of verbal and non-verbal language and communication; imagination and play; sensory responses; self-help skills; mood; tantrums and outbursts; and to endorse the presence or absence of the pathognomonic repetitive or stereotypic behaviors of ASD including observations of rigid or repetitive patterns of behavior.

Similarly, *clinician confirmation* relies on a diversity of prompts to elicit a child's highest capacity for social communication, and to introduce enough sensory arousal to elicit stereotypic responses if they are not immediately evident. Depending on the age of the child or young person this interaction can be a play based assessment with toys commonly used by children within the local community or a more conversational interaction, asking the child about their lives at home and school, their friendships and daily interactions with peers. Having made direct observations of the child and gathered adequate information to affirm A/B/D, the clinician must determine whether the clinical-level impairment in adaptive functioning is largely attributable to ASD, and not to an alternate psychiatric or developmental disorder (the most common entities in *differential diagnosis* are intellectual disability, language disorder, attention deficit hyperactivity disorder (ADHD), anxiety disorders and psychotic disorders). For more detailed information on assessment algorithms, we refer the reader to previously published sources.[17,18] Panels C and D provide brief illustrative case examples of ASD diagnosis.

Panel C. A case of ASD diagnosed in infancy.

SS, a boy whose maternal uncle carried a diagnosis of idiopathic intellectual disability, was first evaluated at age 15 months. His parents were concerned that he would not engage in either symbolic or pretend play. He was not capable of (protodeclarative) pointing to share intention and rarely responded to his name being called. He seemed preoccupied with things that spin and had a history of peculiar behaviors including examining the shadows cast by his fingers for extended periods of time. Despite these concerns, he seemed to recognize what the word "no" means, would make eye contact when directly engaged, and enjoyed proximity to his parents. There was no history of head trauma or seizures and his hearing was completely intact.

On clinical exam, SS exhibited marginal eye contact and was preoccupied with objects, including with a ball in the room which he began rolling forward, chasing, rolling forward, chasing, etc., and did not respond to the examiner's prompts to join him in the game. He was non-verbal. His parents were counselled on methods to engage him in turn-taking reciprocal play, and instructed to return in 3 months to review his progress. At age 18 months he remained essentially non-verbal, exhibited stereotypic behaviors and a persistent lack of social reciprocity, and was given a clinical diagnosis of DSM-IV Pervasive Developmental Disorder (DSM-5 Autism Spectrum Disorder).

By age 7, following years of specialized early childhood and early elementary education, featuring early intensive behavioral intervention, speech and language therapy, augmentative communication, occupational therapy, and special education with an assigned 1:1 paraprofessional, his receptive language had continued to improve although his spontaneous verbal communication remained limited to short phrases and sentences, raising concern for the presence of comorbid intellectual disability. He was fairly non-cooperative with intellectual testing and the results were not released because it was felt by the assessors that the scores underestimated his true ability. An EEG obtained because of intense visual fixation patterns and concern for possible absence epilepsy was non-epileptiform, but abnormal in that the activity during wakefulness lacked a posterior dominant rhythm. He remained in intensive specialized education programs, was well-adapted at home with his family (entirely verbally redirectible, non-aggressive, and responsive to his parents' requests), and although content with isolation, enjoyed the company of his family and classmates at school.

Panel D. A case of ASD diagnosed in childhood.

DP was an 8 year old boy who was described by his mother as "different" from the time he was very young. He showed an unusual interest in books about geology and was exceptionally good at puzzles. He was inclined to repeat dialogues he had heard on television and passages from books in order to get ideas across. He had poor motor skills and at times endangered himself by mindlessly walking onto busy streets.

During his preschool years, DP rarely socialized with other children, and seemed more disinterested than anxious when in their company. In elementary school he was one of the first children in his class to read independently, was very proficient in math, but was stigmatized by his behavior. He answered rhetorical questions of his teachers aloud without being called upon and blurted out inappropriate comments to peers, which he often found humorous. He was disliked by his classmates, regarded as odd by them, and often teased, although he seemed largely oblivious to this.

On clinical examination he exhibited considerable difficulties in maintaining the flow of a conversation with the examiner, talked around the subject rather than providing direct responses, and repeatedly resorted to changing the conversation to discuss different types of rocks and geologic formations that he perseverated about. His eye contact was reasonably good when directly engaged in conversation, but he otherwise appeared aloof and somewhat detached. He spoke in a monotone voice, largely devoid of prosodic intonation. He had little insight into the way in which he was negatively regarded by his classmates and referred to them as his "friends" despite his mother's assertion that they never ask to play with him or include him in after-school gatherings.

A structured diagnostic interview regarding his developmental history revealed a level of symptoms that fell below the threshold for meeting diagnostic criteria for an autism spectrum disorder, however the burden of symptoms and level of impairment evident from the accounts of his parents and teachers, which were confirmed by clinical observation and deemed unlikely attributable to an alternate psychiatric diagnosis (e.g. ADHD, intellectual disability, anxiety disorder, or language disorder) resulted in a clinical diagnosis of autism spectrum disorder.

What becomes immediately evident in the diagnostic process, especially for milder ASD syndromes, is that fulfillment of the A, B, and D criteria of DSM-5 are, by definition, exquisitely sensitive to the notion of "clinical threshold." There is an apparent tension between expert clinician judgment about where this threshold should lie and the fundamental nature of A, B, and D (their respective distributions, inter-relationships, and biological causes) that raises continuously-evolving questions about how the clinical thresholds for A, B, and D should be established for the purpose of diagnosis. Should they represent percentile cutoffs of the normal distribution (as dominates the diagnosis of intellectual disability)? Should a patient with an established causal mutation for ASD whose symptoms fall just below the current clinical threshold not be diagnosed? Should absolute symptom burden or level of impairment of adaptive functioning dominate parameterization of the clinical threshold? In traditional ASD research, emphasis has unequivocally been on the former. If sub clinical ASD symptomatology exacerbates another primary diagnosis (e.g. ADHD or borderline intellectual functioning) in a manner that substantially contributes to impairment in adaptive functioning, should a diagnosis of ASD be invoked?

III. Evolution of the 'definition of disorder': Diagnostic boundaries and their effects on prevalence.

Perhaps more so than many psychiatric disorders, the evolution of our conception of what autism is, and how its diagnostic boundaries should be established, has been far from linear since the initial classic

descriptions over 70 years ago by Leo Kanner[19] and Hans Asperger (1944).[20] In many ways these pioneer clinicians got so much right. In small case series descriptions (11 children in Kanner's description of 'autistic disturbances of affective contact'; 4 children in Asperger's description of 'autistic psychopathy') they described characteristic features of ASD that are instantly recognisable and still resonate with clinicians and parents today.

The diagnostic category of 'autistic disorder' was first introduced into the psychiatric classification system in Diagnostic and Statistical Manual of Mental Disorders-III. The description, heavily influenced by Rutter,[21] broadly matched that of the more severe cases described by Kanner,[19] characterised by delay in language milestones and poor communication skills, intellectual disability (previously called 'mental retardation'), social aloofness, motor stereotypes and intense, narrow and odd preoccupations. This initial description still survives in the clinical vernacular today when clinicians refer to children as presenting with 'classic' or 'Kanner' autism. From this point on, subsequent changes in the classification systems both broadened the concept of what clinical presentations should be included in what we now call ASD – along with this the number of individuals to whom the diagnosis applied – and introduced a number of new diagnostic labels that, in hindsight perhaps mistakenly, were taken by both the clinical and scientific communities to stand for meaningful subtypes of ASD. First, DSM-III-R[22] introduced the term 'pervasive disorder not otherwise specified' (PDD-NOS) essentially a subthreshold definition of more mildly affected cases. Then, in DSM-IV[23] 'Asperger's Disorder' was introduced as a sub-category of the pervasive developmental disorders that recognised that individuals with average or above average intellectual disability and intact structural language skills could also show the clinical manifestations of ASD.

The longer interval before the next revision of DSM in 2013 (DSM-5)[11] gave more time for clinical and basic scientific research to inform the decisions that were made by the workgroup than had been the case in the relative blitz of revisions between 1980 and the mid-1990s. At least three factors were influential in the reversion to a single disorder category of 'autism spectrum disorder' (ASD) in DSM-5.

The first was the recognition that ASDs were aetiologically as well as clinically heterogeneous,[24] as will be discussed in further detail below. The second factor was an accumulation of research evidence that the clinical subtypes described in DSM-IV (autistic disorder, PDD·NOS, Asperger's disorder) did not have scientific validity either in terms of different neurobiological or genetic aetiology or of truly independent cognitive associates that differed between the diagnostic subtypes, aside from those inherent in the different specific diagnostic criteria, in particular regarding language and intellectual ability.[25,26] This may be too high a bar to set for clinical diagnostic criteria given the long recognised fact that clinical utility and (natural) validity are not the same thing.[27] However, it became increasingly apparent that the diagnostic subtypes lacked clinical validity. Only a few years after the publication of DSM-IV that introduced Asperger's Disorder into the classification system, Miller and Ozonoff[28] reviewed the original case descriptions in the 1944 Hans Asperger paper and concluded that all cases would have met DSM-IV criteria for Autistic Disorder. A recent seminal study that is likely to have strongly influenced the DSM-5 reversion to a single ASD category was that even amongst expert research groups the use of the sub-classifications was unreliable and bore no relation to the symptom scores measured on standardised diagnostic instruments.[2]

The final change in DSM-5 was the introduction of 'clinical specifiers' to be noted alongside the diagnosis, including the presence/absence of language impairment, intellectual impairment, known medical, genetic condition or environmental factor, another neurodevelopmental, mental, or behavioural disorder, catatonia and onset (e.g. with regression). The degree to which the simplified nosology and structure of DSM-5 – and the clinical and research utility of the specifiers – is a better description of nature will only be known when a body of empirical work using the system has accumulated. One concern is that DSM-5 has introduced a diagnostic constriction with epidemiological evidence that up to 20% of individuals who met criteria for one of the pervasive developmental disorders under DSM-IV not meeting DSM-5 criteria, in particular those without intellectual disability (Maenner et al., 2014, JAMA Psychiatry, 71, 292-300). DSM-5 also introduced a new diagnostic category Social (Pragmatic) Communication Disorder characterized by persistent difficulties using verbal and nonverbal communication for social purposes, in the absence of restricted and repetitive interests and behaviors (and in the absence of ASD), although its clinical utility, evidence-base and relation to ASD are currently unknown (Norbury, 2014, JCPP, 55, 204-216). It remains to be seen how services, insurers and commissioners respond to these radical changes to the diagnostic system and also whether family members and individuals with ASD welcome the changes. We note also that there are as yet unresolved questions about whether diagnoses like Social Communication Disorder (in which SC and RRB deficits are dissociated) or Asperger Disorder (eliminated from DSM-5, in which SC and structural language impairments are dissociated) represent biologically-tractable subtypes of Autism Spectrum Disorders (Lai et al, Brain 2013), whether or not they fall into phenotypic or genetic continua with the remainder of the spectrum.

Finally, and at first sight somewhat contradictorily, alongside the recognition that there is wide heterogeneity and variability in presentations – across individuals who meet diagnostic criteria for ASD, among their close relatives, and to some degree within individuals over the life course – there was a recognition that the core features were better understood as a *spectrum* of presentations. The seminal work of Lorna Wing,[30] Gillberg,[31] Pickles et al.[32] and Piven and colleagues[33] in recognising this stimulated attempts to standardize the ascertainment of autistic symptoms for both affected and unaffected individuals in ASD-affected families.

Standardized measures

A wide number of screening and diagnostic instruments have been developed over the past two decades (for a review see: Charman & Gotham, 2013).[17] However, a long list of potential tools to choose from is not necessarily a good thing for either the clinical or research fields, in particular when the instrument properties of many of these tools have not been extensively-studied or well-established. However, a number of instruments have been widely validated and are increasingly used in research and clinical practice in many countries. They range from checklist questionnaires for screening and rapid ascertainment of symptom severity to structured diagnostic instruments including the *Autism Diagnostic Interview Revised* (*ADI·R)*,[34] the *Developmental, Dimensional, and Diagnostic Interview* (*3Di)*[35] and observational measures such as the *Autism Diagnostic Observation Schedule – 2nd Edition* (*ADOS·2*).[29] While there is, as expected, overlap in the concepts and the content of ASD rating scales and diagnostic instruments, they differ in the aspect of the diagnostic process to which they apply (i.e. developmental

history versus current symptom ascertainment versus clinician confirmation), the populations for whom they are standardized, the degree to which they are sensitive measures of sub-clinical variation in ASD traits, level of requirement for trained raters, length, cost, and feasibility in clinical settings. Amongst the most notable limitations is the degree to which the accuracy of many screening and diagnostic instruments have been validated with individuals with ASD with intellectual disability. There is also recognition that few of the tools have been validated in non-Western cultures and low- and middle-income countries (in part the same could be said about the diagnostic construct – although this was an issue that Lotter studied in the 1970s), although such work has begun.

IV. Quantitative approaches to the ascertainment of symptom burden

When standardized methods for quantitative assessment of ASD symptoms and traits have been applied to the *general population*, the unequivocal result from a host of studies, implementing numerous measurement instruments, is that the characteristic traits and features that characterize autism are continuously—not bimodally—distributed in nature. [3,5,35,36] This observation implies that there is an arbitrary nature to diagnostic cut-offs in ASD, and invokes methods that have been applied to other quantitative human traits—such as height, weight, intelligence, blood pressure—to derive standardized, percentile-based guidelines for clinical diagnosis. Remarkably, the characteristic traits and symptoms of the autistic syndrome (deficits in reciprocal social behavior, impairment in social communication, repetitive behavior, and restriction in range of interests) are as *highly inter-correlated in the general population* as they are (by definition) in individuals with clinical ASD syndromes. Such homologous factor structures substantiate the use of unitary scores (akin to IQ for intelligence) as valid indices of symptom burden in both clinical and non-clinical populations,[37] even though the overlap in biological causation of the respective symptom domains is not fully understood.[38] As of this writing it remains unclear whether sub-profiles of the autistic syndrome, featuring more or less involvement of one or another of the respective symptom domains, will reliably map to independent sets of biological causes.[39]

Furthermore, when standardized quantitative methods are implemented in the study of families affected by ASD, sub clinical autistic symptoms and traits are observed among first degree relatives with a frequency an order of magnitude higher than observed in the general population.[40,41] Recently, in very large genetic-epidemiologic studies it has been confirmed that the genetic susceptibilities to these sub clinical syndromes exhibit near-complete overlap with genetic underpinnings of the clinical-level syndromes,[42] strongly suggesting that the continuous distributions observed in nature relate to quantitative accumulation of causal liability (see Constantino, 2011[3] for a more detailed review of discrete sub populations that partially contribute to the continuum observed in nature). Thus, although the diagnostic criteria for ASD do not yet consider percentile rank in the population distribution (as do diagnostic criteria for anorexia nervosa, hypertension, intellectual disability, and short stature), an increasingly-compelling case can be made for parameterizing diagnostic thresholds in this manner.[43] An in depth, two-stage population study of autism prevalence revealed identified 2.5% of the population affected,[44] encroaching the proportion that defines clinical thresholds for other human quantitative traits (e.g., height and short stature). A recent systematic review of studies using a self-report measure of autism traits (Autism Quotient; AQ) has demonstrated that both males and females show a close-to-normal distribution but a highly significant shift between the sexes with males scoring higher than

females (Ruzich et al., 2015, *Molecular Autism*, **6**:2). Failure to incorporate sex-specific norms in the diagnostic process has contributed to significant differences in rates of community diagnosis for girls versus boys manifesting precisely the same level of quantitative symptom burden, [3,45,46] and there is evidence that female sex can very often moderate the phenotypic expression of inherited liability to ASD. [87,89]

Moreover, in the same way that height influences weight, the neurodevelopmental characteristics of intelligence, attention, structural language capacity, emotion regulation and executive function can influence social communication, such that specification of the role of autistic symptomatology in an individual patient will ultimately require established *maps* of the expectable relations between the variables (analogous to the height versus weight norms for males and females used in pediatric practice) to accurately ascertain the relative contribution of ASD symptomatology to a given neurodevelopmental syndrome.[47] This is becoming especially relevant now that biological influence on each (separable) axis of human development is becoming better understood, and that it is common for even rare monogenic syndromes to exert adverse influences on *multiple* domains of development (e.g., effects of 16p11.2 on intelligence, social responsiveness, and weight[10]), each influenced by the mutation in a manner that represents a predictable shift-from-expected against a (bi parental) genetic and environmental background for that trait. In this way rare syndromes can be more deeply understood, i.e. not simply by the variable and idiosyncratic array of deficits with which they are associated, but by how they influence such traits in the setting of the specific genetic and environmental background of an individual.

V. Causation, and an Impending Revolution in ASD Diagnosis

The past decade has witnessed an explosion in scientific discovery of the causes of autism. Although to date there remains neither a laboratory test nor a neural signature that can reliably establish the presence of a non-syndromic ASD, a rapidly-increasing proportion of all cases—encroaching the majority—are resolvable to the influence of deleterious molecular genetic variants or combinations of variants, and it is expected that this will play a major role in revolutionizing diagnosis. Twin and family studies involving tens of thousands of individuals in ASD-affected families have overwhelmingly established the role of genetic factors in accounting for the majority of causal influence on autistic syndromes.[24,48,49] Accumulated results of molecular genetic studies published to date have made enormous progress in accounting for this inherited variance, and have revealed the following:

1) Causal heterogeneity: A diverse array of rare (less than 1% of all cases, usually less than 0.1% of all cases), highly-penetrant mutations – some de novo, some recessive inherited, the vast majority involving autosomal loci—account for up to 40 per cent of autistic syndromes (see [6,50]);
2) Pleiotropic effects of rare causal variants: Many of the rare variants that have been repeatedly associated with ASD have also been strongly implicated in the causation of other neuropsychiatric syndromes, including epilepsy, ADHD, schizophrenia, and intellectual disability.[8] Furthermore, in the presence of some highly-penetrant disease-causing mutations (e.g. 16p11.2 deletion syndrome), the expression of ASD symptoms—ascertained using standardized methods—can be highly variable, influenced in large measure by family genetic background.[10]

3) Quantitative genetic risk: common allelic variations, each presumably individually-preserved in the human population on the basis of adaptive value (in an evolutionary sense)—and none of which *singly* can account for more than a tiny elevation in risk for ASD (odds ratio between 1·0 and 1·2)—are responsible for the majority of genetic risk for ASD on the basis of cumulative polygenic risk.[4] Furthermore, specific sets of common and rare inherited allelic variations have been associated with a range of neuropsychiatric conditions (including both childhood-onset and adult-onset disorders), and further resolution of these relationships will contribute to moving beyond descriptive syndromes in psychiatry, and towards a nosology informed by causation.[8,50,51]

These findings have collectively suggested that the continuum of ASD traits observed in the population reflects the human distribution of polygenic risk, superimposed by clusters of cases attributable to a massively-overlapping array of rare, discrete molecular genetic variants of moderate· to high-level penetrance. In turn, the phenotypic expression of these genetic influences varies on the basis of the manner in which any discrete genetic cause interacts with other attributes of the genetic background,[10] the intrauterine environment, and early experience[43] of the individual (including, for example, infectious diseases, serious medical complications during the neonatal period, or as yet poorly understood effects of variation in the human microbiome). This reinforces an orientation to a *personalized medicine* approach to both diagnosis and treatment as is now implemented for many complex diseases, most notably in the field of oncology.

Resolution of many autistic syndromes with respect to the relative contribution of specific genetic variants also continues to illuminate understanding of the biology of autism "comorbidities" such as ADHD, motor coordination impairment,[53·55] epilepsy, intellectual disability, anxiety, and the psychopathologies. Although none of these symptom clusters are specific to ASD, some mutations (e.g. Fragile X Syndrome, Neurofibromatosis Type 1, Tuberous Sclerosis, and a host of newly-discovered variants) have been associated with predictable profiles of comorbidity (whenever ASD arises) and therefore blur the distinction between "core symptoms" and "associated symptoms," at least in the setting of these monogenic syndromes. In other pathways to ASD, associated symptoms are better predicted by family genetic *background*, appear exacerbated by the presence of ASD, and are not themselves predictive of a specific ASD susceptibility.[39]

In summary, advances in understanding the causes of autism—its genetic and population structure—suggest that diagnosis will ultimately benefit from further movement toward standardized quantitative characterization of the defining features of ASD, conducted simultaneously with (and controlling for) multi-axial characterization of those aspects of human development that influence the manifestation of autistic symptoms and impairments, and from the inclusion of genotype in taxonomic classification. For some putative causes of ASD, we are still at an early stage in the conversion from statistical association in large genetic studies to knowledge of the specific impact of a deleterious variant in an individual patient—recently Yuen et al.,[7] showed that among siblings concordantly-affected by ASD, when one carries what would be presumed to be a highly-deleterious variant, the other affected sibling may not share that variant, such that familial liability is driven more by background genetic factors upon which rare variants no-shared between family members are responsible for crossing over the "tipping point" of

clinical-level affectation. As the cost of genotyping continues to fall, as false discovery rates are minimized,[52] as increasing proportions of patients' conditions are traced to specific genetic variants, and the sample sizes of large genetic registries continue to grow, the relative impact of causal *and protective* variants in an individual patient will become increasingly specified. Even as this is evolving, calibrating clinical practice in a manner that raises awareness of the impact and relevance of quantitative phenotypes, of multiplier-effects of comorbid developmental liabilities, and of the opportunity to sub group patients on the basis of deleterious variants stands to accelerate the discovery process. As personalized therapies begin to demonstrate differential impact as a function of specific genetic origin (see [56·58]) the benefits of an updated diagnostic nosology will translate further into the delivery of more tailored and sophisticated care for patients, in addition to its own positive impact on the pace of new discovery.

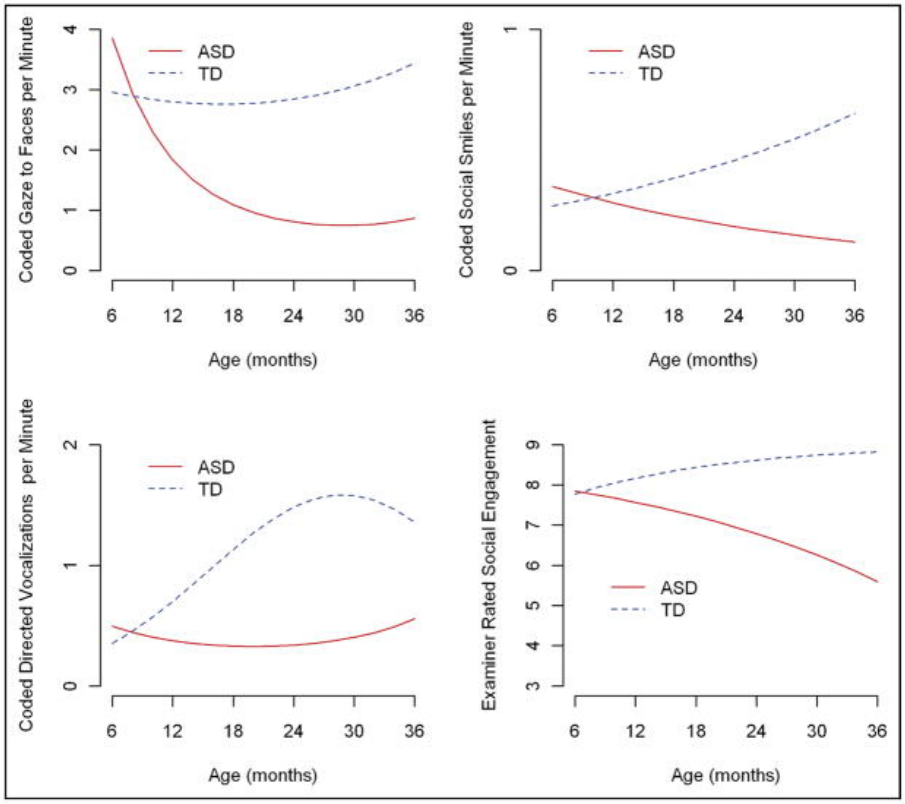
VI. Advancing the Frontier of Early Diagnosis

Another traditional diagnostic boundary that is being broached by advances in science is the timing of diagnosis. It has long been recognised that ASDs have an early onset, and a primary motivation for seeking to lower the age of diagnosis of ASD is to enable evidence-based interventions to be put in place.[59,60] Several converging lines of evidence support this view, including increased neural plasticity early in life, evidence from prospective infant sibling studies that atypical neurodevelopment may be present even in the first year of life[61] and preliminary evidence that some of these atypical developmental processes may be amenable to intervention from as young as 10 months of age.[62,63] Over the past 20 years an increasing number of studies have reported on outcomes of children with ASD diagnosed at a very young age either from clinical referrals of young children or from children identified as at risk on the basis screening or familial risk. After initial studies by Lord[64] and Cox et al.,[65] more recent studies have followed children from 2 years of age to 7[66] and 9 years of age[67, 68]. In short, these studies find that diagnosis from as young as 2 years of age is relatively stable and the judgement of experienced clinicians is more reliable than that of existing diagnostic instruments. Notwithstanding this, there can be particular difficulties when considering a diagnosis of ASD in very young children ranging from the overlap in presentation, and hence differential diagnosis, with children with intellectual disability or language delay, to the difficulty in judging the extent to which there is an impairment in adaptive and wider social functioning, for example when a young child is mostly cared for by parents or familiar caregivers and has little opportunity for broader social interaction with peers. In such circumstances the notion of a 'working diagnosis' with ongoing surveillance, monitoring and review over the course of sequential assessments can be valuable and help both clinicians and parents to better understand and recognise the pattern of development that will clarify the diagnosis one way or the other.[69]

Increasingly sophisticated approaches have been adopted to examine trajectories of ASD symptoms over time. These studies have demonstrated that in most individuals symptom profiles are relatively stable from age 2 years to adolescence, although some 20% of children who are ultimately diagnosed with ASD experience marked regressions following apparently healthy developmental progress over the first two years of life. Moreover, around 10% of individuals show improving trajectories,[12] dubbed

'bloomers' by Fountain et al.[70] Confirming the broad independence between symptom severity and adaptive impairment, a recent study has shown that distinct 'trajectories groupings' in these domain are largely non-overlapping during the preschool period.[71] Similar analyses have been conducted with infants at familial risk of ASD on the basis of having an older sibling with ASD. Using this at-risk design it is possible to track from as young as 6 months of age the trajectory of the ~20% of at-risk siblings who go on to have ASD at 36 months of age.[72] Landa and colleagues[73,74] and Ozonoff and colleagues[75,76] have shown that whilst the different outcome groups look similar at 6 months of age, soon after the first birthday the trajectories of those who go on to receive a diagnosis of ASD begin to diverge, with subtle developmental slowing across a range of domains including motor, language and social communication abilities (as shown in Figure 1). The task ahead is to understand the constitutional (e.g. variability in genetic and brain structure and function) and environmental (e.g. demographic, specific interventions) factors that influence such trajectories. Until recently, the evidence-base for psychological interventions with young children with ASD was poor both in terms of quality and quantity. However, a 'new-wave' of better-designed randomized controlled trials demonstrate increasing evidence for interventions that employ behavioral and developmental approaches.[13,77,78]

Figure 1. Reprinted from J Am Acad Child Adolesc Psychiatry. 2010 Mar; 49(3): 256–66



Efforts to advance earlier diagnosis have also revealed neurocognitive signatures of early ASD risk that may yield a first generation of diagnostic biomarkers that are shared by many or most autistic syndromes. Studies of infants at familial risk of ASD have utilized novel technologies, including eye tracking and electroencephalogram (EEG)/event related potential (ERP) methods, to study the infant neurocognitive predictors of later ASD diagnosis.[61] A number of neurocognitive biomarkers have been identified in the first year of life. These include differences in social response, such as a decline in eye fixation when viewing faces between 2 and 6 months,[79] reduced social orienting[80] and a reduced neural response to dynamic gaze shifts from 6 months of age.[81] However, differences in non-social neurocognitive processes have also been associated

with later ASD, including shorter fixation duration at 7 months of age[82] and a decline in attentional disengagement ability between 7 and 14 months.[83] Whilst no global theoretical account has achieved widespread acceptance a number of models of emergent neurodevelopmental atypicality have been proposed.[84,85] The clinical field awaits the outcome of the translational work that has now begun before such technologies can be used in a reliable way to augment behavioural assessment of individual infants and toddlers to aid early diagnosis in the future. However, caution is required as it remains unclear whether the findings from familial high-risk infants will generalize to the broader population of individuals with ASD, as well as the extent to which the findings are specific to ASD as opposed to other neurodevelopmental disorder such as ADHD and language delay (Johnson et al., 2015, JCPP, 56, 228-247).

Even when they are ready for implementation, it will be important for clinicians to remain consummately mindful of the limitations of prediction in individual patients, and that diagnosis is not equivalent to prognosis. Although autistic severity is remarkably stable over the course of life in a group-statistical sense,[12] slow, steady recoveries occur in isolated cases, steady improvement in adaptive functioning is achievable for most patients, and hope is a critical ingredient for families to continuously (throughout life) marshal the resources and supports necessary to optimize the adaptation and development of affected individuals. In this sense, over-prognostication carries with it the potential to do real harm, and predictions about any child's life prospects are best kept open, with an appropriate emphasis on what is possible, and honest recognition of the limits of what is known. It is important that children with ASD be viewed by clinicians, families, and themselves as *children* first and *having autism* second (not the other way around), and for affected individuals to be unequivocally respected for their own effort to overcome whatever threatens to limit their freedoms or relationships or expression of themselves, a striving that is shared by all people, with and without diagnosed disabilities.

VII. Factors associated with under-diagnosis

Over the past decade it has become clear that a number of social and cultural factors are associated with the likelihood of individuals receiving a community clinical diagnosis of ASD.[86] Even when displaying the same level of ASD symptoms, girls are less likely to be diagnosed than boys and those that receive a diagnosis show more intellectual and behavioural impairment.[45] It remains unclear the extent to which this is explained by the thresholds on current screening and diagnostic instruments (or clinical judgement) working differently for males and females (and thus require sex-specific recalibration) or whether girls are typically protected against the expression of inherited ASD susceptibility in a manner that would contribute to the universally-observed 3.5:1 M:F sex ratio in autism.[40,46,87·89] Whatever specific genetic, developmental or environmental factors play a role in this, it is clear that they are operating between the time of conception and the end of the second year of life when most ASD diagnoses are manifest and the sex ratio in prevalence is fully apparent. A distinct public health consequence of non-recognition of autistic syndromes in females relates to risk of transmission of ASD to their own offspring.[41,88] Except for families transmitting known deleterious variants, very little is known about how to estimate intergenerational transmission risk to women affected by undiagnosed (sub clinical) autistic syndromes running in their families and expressed more prominently

phenotypically in male relatives. Another factor that leads to under-diagnosis is social disadvantage (parental education, income, social economic status) and minority ethnic status.[90-92] Clinicians need to be alert to the possibility of under-identification and take special care as part of the diagnostic assessment process to consider the needs of potentially disadvantaged groups.

VIII. Concluding comments

Summarized in Panel E are key considerations for a reconceptualization of diagnosis in autism informed by the scientific advances described above.

Panel E. Re-conceptualizing diagnosis in ASD: A summary of implications for research, clinical practice, public health and policy.

A next generation of advances in nosology would be likely to improve ASD diagnosis to the extent that:

- A refined diagnosis reflects that ASD represents the severe end of a continuous distribution of social-communication abilities in the general population
- Symptom ascertainment is standardized for sex and mental age
- The interactions and expectable relationships between autistic symptomatology and other (quantitative) influences on child development are specified (as expectations for weight are based on height and standardized in the concept of body mass index)
- The influences of sub clinical autistic symptoms and other dimensions of social-behavior liability that jointly result in clinical-level impairment in adaptive functioning can be subsumed into a coherent nosology without necessarily invoking the double-diagnosis of comorbidity
- When identified, specific causal influences (e.g., monogenic syndromes), their unique profiles of behavioral disability and symptom burden, their associated symptoms (e.g., epilepsy, intellectual disability, ADHD) and their interactions with background (polygenic) inherited liabilities are recognized in the diagnostic system
- Pleiotropic effects of known causes of ASD are categorized in a manner that recognizes their potential to influence other psychiatric syndromes
- Motor coordination impairment is incorporated into sets of criteria that are sufficient to make the diagnosis
- Algorithms for feasible ascertainment of developmental history, current symptom burden, and clinical confirmation place reliable, expedient diagnosis within reach for the majority of children in public health settings
- Impairments in adaptive functioning attributable to the characteristic symptoms of ASD are more precisely specified, standardized, and implemented as standards for eligibility of service[93]

At times, the process of translation of scientific findings into clinical practice can feel frustratingly slow to clinicians and patients alike. However, the pace of discovery of our understanding of what autism is

has been very rapid indeed over the past decade. When combined, accumulating information from the etiological discoveries about what causes ASD in any individual, how this relates to the variability in family risk and transmission, and our increasing understanding of how the clinical syndrome and its causes relate to variation in ASD traits within the broader population, suggests that we are at a tipping point. While many viewed the revisions to the classification of ASD in DSM-5 to be revolutionary – and notwithstanding the perspective that many of them should lead to better clinical practice, benefiting patients – translational discoveries over the next decade might make DSM-6 both a very interesting read and also hail a 'true revolution' in scientifically-informed clinical practice.

Contributors

Drs. Constantino and Charman contributed equally to the development of this manuscript.

Declaration of Interests

Dr. Constantino receives royalties from Western Psychological Services for the commercial distribution of the *Social Responsiveness Scale·*2, a quantitative measure of autistic traits.

Search Strategy and Selection Criteria

The primary goal of this manuscript is to synthesize recent scientific advances that have direct bearing on challenges and potential refinements to diagnosis in autism. The final reference list was primarily derived from articles indexed in PubMed and was generated on the basis of relevance to the topics covered in this Review.

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