Diagnosis of autism spectrum disorder: reconciling the syndrome, its diverse origins, and variation in expression

John N Constantino, Tony Charman

Recent discoveries about the pathogenesis and symptom structure of autism spectrum disorders (ASD) are challenging traditional nosology and driving efforts to reconceptualise the diagnosis of autism, a goal made all the more pressing by new prospects for early identification, targeted intervention, and personalised-medicine approaches to specific autistic syndromes. Recognition that ASD represents the severe end of a continuous distribution of social-communication abilities in the general population has stimulated attempts to standardise the measurement of autistic traits [A: traits OK?] and to set appropriate clinical thresholds for diagnosis. Over the next decade [A: OK?], rapid advances in our understanding of symptom structure and the diversity of causes of ASD could be incorporated into the next evolution in the diagnosis of autism, with important implications for research, clinical practice, public health, and policy. As differential effects of personalised therapies are identified in relation to specific causes of autism, the benefits of an updated diagnostic nosology will translate into the delivery of more effective care for patients.

Introduction

Until little more than a decade ago, autism was considered to be rare and usually accompanied by intellectual disability; standardised methods to calibrate the nature and severity of symptoms were not available, and only rarely could the syndrome be traced to a biological cause. All of that has changed.1,2 [A: refs OK?] Although clinician diagnosis maintains its tentative hold as the current standard for case designation, the diagnostic process [A: correct?] is increasingly informed by 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, rapid advances in the science of autism have occurred in each of Robins and Guze’s classic proposed requirements for the valid classification of mental disorders, published in 1970 (clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study).1

The diagnostic implications of these discoveries, especially recent findings related to symptom structure and biological cause, are numerous and largely encompassed by four overarching themes. The first theme comprises recognised limitations of the expert clinician paradigm as a standard of diagnosis.1 The second, the quantitative trait characteristics of ASD, reflects evidence that the defining features of the syndrome are continuously (not categorically) distributed in the general population and often arise from additive genetic influences that are shared with other neuropsychiatric conditions.2,5 Pronounced heterogeneity in the pathways of causation of ASD phenocopies,4 even within families,7 constitute the third theme. And finally, the fourth theme covers pleiotropic effects, in which the same deleterious genetic variant can give rise to various neuropsychiatric syndromes (eg, epilepsy, schizophrenia, attention deficit hyperactivity disorder [ADHD], learning disability, and intellectual disability) or other non-ASD comorbidities (motor coordination deficits or behavioural impairments),8,9 depending in part on genetic background.10 Some or all of these issues present similar challenges in the diagnosis of other complex medical disorders (eg, hypertension, diabetes, and inflammatory bowel disease).

The aim of this Series paper is to assimilate specific issues that have a bearing on the diagnosis of ASD. We begin by considering the strengths and limitations of current standards for diagnosis (invoking the first of the above-mentioned themes), before clarifying how the resulting diagnostic thresholds relate to the structure of symptoms in nature (the second theme). We review what is now known about the diversity of causes of autistic syndromes (the third and fourth themes), and finally discuss how knowledge of causation and symptom structure might be incorporated into the next evolution in the diagnostic approach to ASD. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),10 published in 2013, represents an attempt to modify the diagnostic process in tandem with the pace of recent discovery. However, to meet the complex needs of people affected by ASD and other neurodevelopmental disorders, we need to continue to build upon and refine the existing taxonomic framework in a manner that flexibly and faithfully accommodates advances in scientific understanding.

Contemporary clinical diagnosis of ASD

Diagnostic criteria

We begin with the paradigm of clinician diagnosis, which is the historical bedrock of case designation. Several noteworthy scientific advances were recognised in the development of DSM-5,11 which marks the first major
revision of the manual since the fourth edition (DSM-IV)\textsuperscript{4} was published in 1994. The DSM-5 diagnostic criteria for ASD are presented in panel 1. We note that the diagnostic criteria for autism in the International Classification of Diseases, tenth revision (ICD-10)\textsuperscript{5} are keyed to DSM-IV, and the extent to which the eleventh revision (ICD-11; currently in development) will reflect the changes incorporated into DSM-5 has not yet been precisely resolved. The first substantial change in DSM-5 is the collapsing of symptom criteria for ASD from three domains to two: deficits in social communication and social interaction (criterion A), and restricted, repetitive patterns of behaviour, interests, or activities (criterion B). This important revision was made partly on the basis of evidence that the social and communicative impairments that are most specific to ASD (impairment in reciprocal social interaction and impairment in social or pragmatic aspects of communication) are closely inter-related and that their severity is highly correlated, not only within populations of clinically affected children,\textsuperscript{16} but also in the general population\textsuperscript{17} (with the caveat that results of factor analyses of ASD symptoms can be variable as a function of how they are ascertained).

The second substantial change in DSM-5 is the inclusion of new severity specifiers (table), which categorise the impact of symptoms on adaptive functioning. An often-overlooked aspect of the characterisation of severity in ASD is that the core symptom burden (criteria A and B; panel 1) and impairment in social, occupational, or other important domains to two: deficits in social communication and social interaction (criterion A), and restricted, repetitive patterns of behaviour, interests, or activities (criterion B). This important revision was made partly on the basis of evidence that the social and communicative impairments that are most specific to ASD (impairment in reciprocal social interaction and impairment in social or pragmatic aspects of communication) are closely inter-related and that their severity is highly correlated, not only within populations of clinically affected children,\textsuperscript{16} but also in the general population\textsuperscript{17} (with the caveat that results of factor analyses of ASD symptoms can be variable as a function of how they are ascertained).

The second substantial change in DSM-5 is the inclusion of new severity specifiers (table), which categorise the impact of symptoms on adaptive functioning. An often-overlooked aspect of the characterisation of severity in ASD is that the core symptom burden (criteria A and B; panel 1) and impairment in social, occupational, or other important

\textbf{Panel 1: DSM-5 diagnostic criteria for autism spectrum disorder 299.00 (F84.0)}

\begin{enumerate}
\item[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):
\begin{enumerate}
\item 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.
\item Deficits in non-verbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and non-verbal 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 non-verbal communication.
\item Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
\end{enumerate}

\item[B)] Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):
\begin{enumerate}
\item Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
\item Insistence on sameness, inflexible adherence to routines, or ritualised patterns or verbal non-verbal behaviour (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
\item Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
\item Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
\item[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).
\item[D)] Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
\item[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.
\end{enumerate}

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger’s disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:
\begin{itemize}
\item With or without accompanying intellectual impairment
\item With or without accompanying language impairment
\item Associated with a known medical or genetic condition or environmental factor
\item Associated with another neurodevelopmental, mental, or behavioural disorder
\item With catatonia (refer to the criteria for catatonia associated with another mental disorder)
\end{itemize}

Reproduced from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5),\textsuperscript{11} by permission of the American Psychiatric Association.

www.thelancet.com/neurology
areas of adaptive functioning (criterion D; panel 1 and table) are 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 was previously given a diagnosis of Asperger’s disorder on the basis of very substantial ASD symptomatology, but is now 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 symptoms counts. Improvements in adaptive functioning are achievable and crucial for patients with ASD, but are grossly under-appreciated when measuring outcomes exclusively as a function of core symptom burden, as still often occurs in clinical trials. The hybrid severity index published in DSM-5 (table) translates the effect of symptoms in each criterion domain (A and B) onto three broad categories of adaptive functioning, each of which is defined by descriptive scoring anchors that indicate the level of support that an affected individual requires.

The third major revision in DMS-5 [A: correct?] is that it is now deemed appropriate to simultaneously diagnose ASD with other psychiatric or developmental disorders (eg. ADHD) when there is ample evidence for comorbidity, in view of overwhelming evidence that many known inherited causes of ASD are genetically independent from the causes of other common neuropsychiatric disorders, and it is therefore entirely possible for an individual to be affected by more than one neuropsychiatric condition. The change will help to ensure that, regardless of causes, all the needs of an individual are recognised and addressed. [A: OK?]

### The diagnostic process

Implied, but not explicit in the diagnostic criteria themselves, are the elements of information gathering that are required to establish DSM-5 diagnostic criteria A–E (panel 1), which constitute what can be thought of as three pillars of the diagnostic process: (1) ascertainment of current symptomatology sufficient to meet criteria A, B, and D; (2) acquisition of a developmental history consistent with an ASD (criterion 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 behaviour 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, and tantrums and outbursts); and to endorse the presence or absence of the pathognomonic repetitive or stereotyped behaviours of ASD, including observations of rigid or repetitive patterns of behaviour.

Similarly, clinician confirmation relies on a diversity of prompts to elicit a child’s highest capacity for social

<table>
<thead>
<tr>
<th>Social communication</th>
<th>Restricted, repetitive behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 3 “Requiring very substantial support”</td>
<td>Severe deficits in verbal and non-verbal 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.</td>
</tr>
<tr>
<td>Level 2 “Requiring substantial support”</td>
<td>Marked deficits in verbal and non-verbal 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 who has markedly odd non-verbal communication.</td>
</tr>
<tr>
<td>Level 1 “Requiring support”</td>
<td>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 from 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.</td>
</tr>
</tbody>
</table>

Reproduced from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), by permission of the American Psychiatric Association.

*Table: Severity specifiers for the characterisation of variation in adaptive functioning in autism spectrum disorder*
communication, and to introduce enough sensory arousal to elicit stereotyped 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 in which the child is asked about his or her life at home and at school, friendships, and daily interactions with peers. Having made direct observations of the child and gathered adequate information to satisfy criteria A, B, and D, the clinician must determine that the clinical-level impairment in adaptive functioning is largely attributable to ASD and not to an alternative psychiatric or developmental disorder (the most common entities in differential diagnosis are intellectual disability, language disorder, ADHD, anxiety disorders, and psychotic disorders). For more detailed information on assessment algorithms, we refer the reader to previously published sources.22,23

Panels 2 and 3 provide brief illustrative case examples of ASD diagnosis.

What becomes immediately evident in the diagnostic process, especially for milder ASD syndromes, is that fulfillment of DSM-5 criteria A, B, and D is, by definition, exquisitely sensitive to the notion of clinical threshold. There is an apparent tension between expert clinician judgment about where these thresholds should lie and the fundamental nature of the features described by criteria A, B, and D (their respective distributions, interrelations, and biological causes) that raises continuously evolving questions about how the clinical thresholds for these criteria 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 be diagnosed? Should absolute symptom burden or level of impairment of adaptive functioning dominate parameterisation of the clinical threshold? In traditional ASD research, emphasis has unequivocally been on the former. If subclinical ASD symptomatology exacerbates another primary diagnosis (eg, ADHD or borderline intellectual functioning) in a manner that substantially contributes to impairment in adaptive functioning, should a diagnosis of ASD be made?

The evolving definition of disorder and shifting diagnostic boundaries

Perhaps more so than for many neuropsychiatric 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 Kanner4 and Hans Asperger.24 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”; four 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.

Panel 2: Case study 1—autism spectrum disorder diagnosed in infancy

SS, a boy whose maternal uncle had 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 behaviours, including examining the shadows cast by his fingers for extended periods of time. Despite these concerns, he seemed to recognise the meaning of the word “no”, 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 examination, SS exhibited poor eye contact and was preoccupied with objects, including a ball in the room, which he began to roll forward and chase repeatedly; he did not respond to the examiner’s prompts to include him in the game [A: OK?]. He was non-verbal. His parents were counselled on methods to engage him in turn-taking reciprocal play, and they were instructed to return in 3 months to review his progress. At age 18 months he remained essentially non-verbal, exhibited stereotyped behaviours 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, after years of specialised early-childhood and early-elementary education, featuring early intensive behavioural 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 about the presence of comorbid intellectual disability. He was fairly non-cooperative with intellectual testing and the results were not released [A: to whom?] 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 specialised education programmes, 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.
The diagnostic category of “autistic disorder” was first introduced into the psychiatric classification system in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). The description, heavily influenced by Rutter, broadly matched that of the more severe cases described by Kanner, characterised by delay in language milestones and poor communication skills, intellectual disability (previously referred to as 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 onwards, subsequent changes to the classification systems both broadened the concept of the clinical presentations that should be included in what we now call “autism spectrum disorder”—and, along with this, the number of individuals to whom the diagnosis applied—and introduced several new diagnostic labels that, in hindsight perhaps mistakenly, were taken by the clinical subtypes described in DSM-IV—autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger’s disorder—did not have scientific validity in terms of distinct neurobiological or genetic aetiologies, or truly independent cognitive associates that differed between the diagnostic subtypes (aside from those inherent in the different specific diagnostic criteria), in particular with regard to language and intellectual ability. The reversion to a single-disorder category of “autism spectrum disorder” in DSM-5.

The long interval between the next revision of the manual in 2013 (DSM-5) gave more time for clinical and basic scientific research to inform the decisions made by the Neurodevelopmental Disorders Work Group than had been allowed during the several 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” in DSM-5.

The first factor was the recognition that ASD syndromes are aetiologically as well as clinically heterogeneous, as we discuss in more detail below. The second 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 in terms of distinct neurobiological or genetic aetiologies, or truly independent cognitive associates that differed between the diagnostic subtypes (aside from those inherent in the different specific diagnostic criteria), in particular with regard to language and intellectual ability. This might be too high a bar to set for clinical diagnostic criteria, in view of the long-recognised fact that clinical utility and (natural) validity are not the same thing. However, it
became increasingly apparent that the diagnostic subtypes lacked clinical validity. Only a few years after the publication of DSM-IV introduced Asperger’s disorder into the classification system, Miller and Ozonoff\(^5\) reviewed the original case descriptions in Asperger’s 1944 paper\(^6\) and concluded that all cases would have met DSM-IV criteria for autistic disorder. The third factor that is likely to have strongly influenced the DSM-5 reversion to a single ASD category was a seminal study showing that, even among expert research groups, the use of the sub-classifications was unreliable and bore no relation to the symptom scores measured on standardised diagnostic instruments [A: correct?].

The final important change in DSM-5 is the introduction of clinical specifiers to be noted alongside the diagnosis of ASD, including the timing and nature of onset (eg, with regression) [A: correct?] and the presence or absence of the following features: language impairment; intellectual impairment; known medical or genetic conditions; precipitating environmental factors; other specific neuro-developmental, mental, or behavioural disorders; or catatonia. The degree to which the simplified nosology and structure of DSM-5 is a better description of nature than previous conceptions of autism—and the clinical research utility of the specifiers—will be known only when a body of empirical work using the system has accumulated [A: sentence correct?].

One concern is that DSM-5 has introduced a diagnostic constriction, with epidemiological evidence suggesting that up to 20% of individuals who met criteria for one of the pervasive developmental disorders under DSM-IV do not meet DSM-5 criteria [A: for ASD?], in particular those without intellectual disability.\(^4\) DSM-5 has also introduced a new diagnostic category termed “social (pragmatic) communication disorder”, characterised by persistent difficulties in the use of verbal and non-verbal communication for social purposes, in the absence of restricted and repetitive interests and behaviours, although its clinical utility, evidence base, and relation to ASD are currently unknown.\(^8\) It remains to be seen how health services, insurers, and commissioners will respond to these radical changes to the diagnostic system, and also whether family members and individuals with ASD will welcome the changes. We also note that there are as yet unresolved questions about whether diagnoses such as social communication disorder (in which social communication deficits and restricted, repetitive behaviours are dissociated) and Asperger’s disorder (eliminated from DSM-5; in which social communication and structural language impairments were dissociated) represent biologically tractable subtypes of ASD,\(^9\) irrespective of whether 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 the presentation of autism—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 [A: in the development of DSM-5?] that the core features can be better understood as a spectrum of presentations. The seminal work of Wing,\(^3\) Nordin and Gillberg,\(^9\) Pickles and colleagues,\(^6\) and Piven and colleagues\(^6\) in recognising this spectrum\(^9\) and introducing the notion of a “broader autism phenotype”\(^4\) [A: refs OK for spectrum and BAP?] stimulated attempts to standardise the ascertainment of autistic symptoms for both affected and unaffected individuals in families with ASD.

DSM-5 has clarified the symptom criteria for ASD, operationalised the distinction between symptom burden and impairment, and alluded to the continuous nature of autistic traits in the general population [A: correct as edited?]. Nevertheless, the questions of where to draw the diagnostic line and how to incorporate the assignment of specific genetic causes to an increasing proportion of all cases of ASD present important challenges and opportunities in the diagnosis of autism. Our responses to these questions will have direct implications for those affected in terms of access to support services and personalised approaches to medical care [A: new paragraph OK?].

**Progress in the measurement of autistic traits**

**Standardised measures of symptom burden**

A range of screening and diagnostic instruments for ASD has been developed over the past two decades.\(^22\) However, a long list of potential methods to choose from is not necessarily a good thing for either the clinical or the research field, particularly in view of the fact that the properties of many of these instruments [A: OK?] have not been extensively studied or well established. However, several 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),\(^2\) the Developmental, Dimensional and Diagnostic Interview (3di),\(^4\) and observational measures such as the Autism Diagnostic Observation Schedule, second edition (ADOS-2).\(^2\)

Although 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 (ie, developmental history vs current symptom ascertainment vs clinician confirmation), the populations for whom they are standardised, and the degree to which they are sensitive measures of subclinical variation in ASD traits. They also vary in terms of the need for trained raters, the time needed to train raters or to complete assessments [A: OK?], and the cost and feasibility of application in clinical settings. Among the most notable limitations is the degree to which the accuracy of many
screening and diagnostic instruments has been validated in individuals with ASD with intellectual disability. There is also recognition that few of the methods have been validated in non-western cultures or in low-income or 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—even though such work has begun.46

Quantitative approaches to the measurement of autistic traits

When standardised methods for quantitative assessment of ASD symptoms and traits have been applied to the general population, the unequivocal finding from a host of studies, implementing numerous methods of measurement, is that the traits and features that characterise autism are continuously—not bimodally—distributed in nature.52,47 This observation implies that there is an arbitrary nature to diagnostic cutoffs in ASD, and points to the need for methods of the type that have been applied to other quantitative human traits—such as height, weight, intelligence, and blood pressure—to derive standardised, percentile-based guidelines for clinical diagnosis. Remarkably, the characteristic traits and symptoms of the autistic syndrome (deficits in reciprocal social behaviour, impairment in social communication, repetitive behaviour, and restriction in range of interests) are as highly inter-related 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,64 even though the overlap in biological causation of the respective symptom domains is not fully understood.65

At present, whether subprofiles 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 remains unclear.65 Furthermore, when standardised quantitative methods are implemented in the study of families affected by ASD, subclinical autistic symptoms and traits are observed among first-degree relatives with a frequency an order of magnitude higher than that observed in the general population.73,75 Recently, in very large genetic-epidemiological studies, it has been confirmed that the genetic susceptibilities to these subclinical syndromes exhibit near-complete overlap with genetic underpinnings of the clinical-level syndromes,53 strongly suggesting that the continuous distributions observed in nature relate to quantitative accumulation of causal susceptibility. A more detailed review of discrete subpopulations that partly contribute to the continuum observed in nature has been published previously.72 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 parameterising diagnostic thresholds in this manner.75

An in-depth, two-stage population study of autism prevalence indicated that 2.5% of the population are affected,76 approaching the proportion that defines clinical thresholds for other human quantitative traits (eg, height and short stature). A recent systematic review of studies of members of the general population that used the Autism Spectrum Quotient (AQ) [A: OK?], a self-report measure of autism traits, showed that both males and females have a close to normal distribution [A: of which traits?] but that there is a highly significant shift [A: difference?] between the sexes, with males scoring higher than females.77 Failure to incorporate sex-specific norms in the diagnostic process has contributed to significant differences in the rates of community diagnosis for girls versus boys who manifest precisely the same level of quantitative symptom burden.55,57,58 and there is evidence that female sex can very often moderate the phenotypic expression of inherited susceptibility to ASD.59,60

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 predictable relations between the variables (analogous to the height-vs-weight norms for males and females used in paediatric practice) to accurately ascertain the relative contribution of ASD symptomatology to a given neurodevelopmental syndrome.61 This is becoming especially relevant as we understand more fully the biological influence (effect of inheritance [A: correct?]) on each (separable) axis of human development, and we recognise that even rare monogenic syndromes commonly have adverse effects on multiple domains of development (eg, effects of 16p11.2 rearrangements on intelligence, social responsiveness, and weight78), each influenced by the mutation in a manner that represents a predictable shift against a (bi-parental) genetic and environmental background for that trait. In this way, rare syndromes can be more deeply understood, 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.

Causation and an impending revolution in ASD diagnosis

The past decade has witnessed an explosion in scientific discovery of the causes of autism. Although, so far, neither a laboratory test nor a neural signature that can reliably establish the presence of a non-syndromic ASD is available, a rapidly increasing proportion of all cases—
approaching the majority—can be attributed to the influence of deleterious genetic variants or combinations of variants, and it is expected that understanding of the genetics of autism will play a major part in revolutionising diagnosis. Twin and family studies involving tens of thousands of individuals in ASD-affected families have overwhelmingly established the important role of genetic factors in the causation of most autistic syndromes. Accumulated results of genetic studies have led to enormous progress in accounting for the inherited variance associated with autism. The first important finding of such studies has been that of 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 recessively inherited, most involving autosomal loci—contribute to ASD susceptibility in up to 40% of autistic syndromes. Second, these studies have revealed 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. Furthermore, in the presence of some highly penetrant disease-causing mutations (eg, 16p11.2 deletion syndrome), the expression of ASD symptoms—ascertained using standardised methods—can be highly variable, influenced in large measure by family genetic background. The third important research finding relates to 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 the risk for ASD (odds ratio between 1.0 and 1.2)—are responsible for most of the genetic risk for ASD on the basis of cumulative polygenic risk. Finally, 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 genotype-phenotype relations will contribute to a shift beyond descriptive syndromes towards a nosology informed by causation.

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 genetic variants with a moderate to high level of penetrance. In turn, the phenotypic expression of these genetic influences varies on the basis of the manner in which they interact with other key attributes of the individual, including genetic background, sex, the intrauterine environment, and early life experience (including, for example, infectious diseases, serious medical complications during the neonatal period, or as yet poorly understood effects of variation in the human microbiome). These interactions between various causative factors reinforce the need for a personalised-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, epilepsy, intellectual disability, anxiety, and the psychopathologies. Although none of these symptom clusters is specific to ASD, some mutations—eg, those associated with fragile X syndrome (FMR1), neurofibromatosis type 1 (NF1), 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, seem to be exacerbated by the presence of ASD, and are not themselves predictive of a specific ASD susceptibility.

In summary, advances in understanding the causes of autism—its genetic and population structure—suggest that diagnosis will ultimately benefit from further movement towards standardised quantitative characterisation of the defining features of ASD, conducted simultaneously with (and controlling for) multi-axial characterisation 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 and colleagues 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 susceptibility is driven more by background genetic factors upon which rare variants not shared between family members are responsible for crossing over the tipping point of clinical-level effect.

As the cost of genotyping continues to fall, as false discovery rates are minimised, as an increasing proportion of patients’ conditions are traced to specific genetic variants, and as the sample sizes of large genetic registries continue to grow, specification of the relative effect of causal and protective variants in individuals will increasingly become feasible. Even as this field is evolving, the calibration of clinical practice in a manner that raises awareness among clinicians of the effect and relevance of quantitative phenotypes, of multiplier effects of comorbid developmental liabilities, and of the opportunity to subgroup patients on the basis of
deleterious variants, stands to accelerate the discovery process. As differential effects of personalised therapies are identified in relation to specific genetic origins,72-74 the benefits of an updated diagnostic nosology—including positive effects on the pace of new discovery—will translate into the delivery of more tailored and sophisticated care for patients.

Advancing the frontier of early diagnosis

Another traditional diagnostic boundary that is being challenged [A: correct?] 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.75,76 Several converging lines of evidence support the view that early intervention can lead to more positive outcomes [A: OK?]: the presence of higher neural plasticity early in life; [A: ref?] evidence from prospective infant sibling studies that atypical neurodevelopment might be present even in the first year of life in those who subsequently develop symptoms of ASD;77 and preliminary evidence that some of these atypical developmental processes might be amenable to intervention from as young as 10 months of age.78,79

Over the past 20 years, an increasing number of studies has 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 of screening or familial risk. After initial studies by Lord,80 and Cox and colleagues,81 more recent studies have followed children from 2 years to 7 years82 and 9 years83,84 of age. In short, these studies show that diagnosis from as young as 2 years of age is relatively stable and that the judgment of experienced clinicians is more reliable than that of existing diagnostic instruments for this age group. Notwithstanding the evidence in support of clinical judgment, there can be particular difficulties when considering a diagnosis of ASD in very young children, ranging from overlap in presentation (and hence differential diagnosis) in the case of 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 (eg, 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.85

Increasingly sophisticated approaches have been adopted to examine trajectories of ASD symptoms over time. These studies have shown that, in most individuals, symptom profiles are relatively stable from age 2 years to adolescence, although about 20% of children who are ultimately diagnosed with ASD have marked regressions after apparently healthy developmental progress over the first two years of life. Moreover, around 10% of individuals show improving trajectories,86 dubbed “bloomers” by Fountain and colleagues.87 Confirming the broad independence between symptom severity and adaptive impairment, a recent study has shown that distinct trajectories groupings defined by these domains are largely non-overlapping during the preschool period.88 Similar analyses have been conducted with infants at familial risk of ASD on the basis of having an older sibling with a diagnosis. Using this at-risk design it is possible to track from as young as 6 months of age the trajectory of the roughly 20% of at-risk siblings who go on to have ASD at 36 months of age.89 Landa and colleagues90,91 and Ozonoff and colleagues92,93 have shown that although the different outcome groups look similar at 6 months of age, soon afterwards 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 (figure).

The task ahead is to understand the constitutional (eg, variability in genetics and brain structure and function) and environmental (eg, demographics and specific interventions) factors that influence such trajectories. Until recently, the evidence base for psychological interventions with young children with ASD was poor in terms of both quality and quantity. However, a new wave of well-designed randomised controlled trials is providing increasing support for interventions that use behavioural and developmental approaches.77,85,94 For example, Dawson and colleagues94 reported improvements in language and communication skills in preschool children with ASD after 2 years of intensive developmental behavioural therapy (the Early Start Denver Model) delivered by trained specialists and caregivers. [A: correct?] And Kasari and colleagues95 reported that dyadic joint engagement in preschool children with ASD improved after 3 months of twice-weekly caregiver-mediated intervention. [A: correct?] [A: additions OK?]

Efforts to advance earlier diagnosis have also revealed neurocognitive signatures of early ASD risk that might 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 used novel technologies—including eye tracking and EEG or event-related potential methods—to study infant neurocognitive predictors of later ASD diagnosis.77 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,96 reduced social orienting,97 and a reduced neural response to dynamic gaze shifts from 6 months of age.98 However, differences in non-social neurocognitive processes have also been associated
The trajectories are based on a prospective study of 25 infants later diagnosed with an autism spectrum disorder. Although no integrative theoretical account has achieved widespread acceptance, several models of emergent neurodevelopmental atypicality have been proposed. The clinical field awaits the outcome of translational work (which 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, whether the findings from studies of infants with high familial risk will generalise to the broader population of individuals with ASD remains unclear, as does the extent to which the findings are specific to ASD as opposed to other neurodevelopmental disorders (eg, ADHD and language delay), and caution is therefore required.

Even when reliable diagnostic biomarkers are ready for implementation, it will be important for clinicians to remain mindful of the limitations of prediction in individuals, and of the fact that diagnosis is not equivalent to prognosis. Although autism severity is remarkably stable over the course of life in a group-statistical sense, slow, steady recoveries occur in isolated cases, steady improvement in adaptive functioning is achievable for most patients, and hope is a crucial ingredient that allows families to continuously (throughout life) marshal the resources and support necessary to optimise 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 as having autism second, 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.

Factors associated with under-diagnosis

Over the past decade, it has become clear that several social and cultural factors are associated with the likelihood of receiving a community clinical diagnosis of ASD. Even when showing the same level of ASD symptoms, girls are less likely to be diagnosed than are boys, and those who do receive a diagnosis have more intellectual and behavioural impairment than do boys with a diagnosis. The extent to which this disparity can be attributed to the thresholds on current screening and diagnostic instruments (or clinical judgment) working differently for males and females (and thus needing sex-specific recalibration) remains unclear, as does the question of whether girls are typically protected against the expression of inherited ASD susceptibility in a manner that contributes to the universally observed male-to-female ratio of 3·5:1 among those with a diagnosis of ASD. Whatever specific genetic, developmental, or environmental factors play a part in this sex difference in prevalence, 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 higher prevalence in boys is fully apparent. A distinct public-health consequence of non-recognition of autistic syndromes in females relates to the risk of transmission of ASD to their own offspring. Except for families transmitting known deleterious variants, very little is known about how to estimate intergenerational transmission risk for women affected by undiagnosed (subclinical) autistic syndromes that run phenotypically, in male relatives. Another factor that leads to under-diagnosis is social disadvantage (parental education, income, and socioeconomic status) and minority ethnic status. 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. Among populations of children whose parents and caregivers are unaware of the early symptom manifestations of autism, or who do not have access to primary paediatric care, or whose primary-care providers are inexperienced in screening for the characteristic symptoms of ASD, diagnosis can be delayed and early.
Panel 4: Reconceptualising the diagnosis of autism spectrum disorder

The next generation of advances in the classification of autism spectrum disorder (ASD), based on rapid advances in the science of autism and better understanding of other neuropsychiatric and neurodevelopmental conditions, could be associated with several improvements in the diagnosis of ASD, with implications for research, clinical practice, public health, and policy. Key refinements that we hope to see are listed below.

- A refined diagnosis should reflect the fact that ASD represents the severe end of a continuous distribution of social-communication abilities in the general population.
- Symptom ascertainment should be standardised for sex and mental age.
- The interactions and expected relations between autistic symptomatology and other (quantitative) influences on child development should be specified (as expectations for weight are based on height and standardised in the concept of body mass index).
- The influences of subclinical autistic symptoms and other dimensions of social-behaviour liability that jointly result in clinical-level impairment in adaptive functioning should be subsumed into a coherent nosology without necessarily invoking the double diagnosis of comorbidity.
- When identified, specific causal influences (eg, monogenic syndromes), their unique profiles of behavioural disability and symptom burden, their associated symptoms (eg, epilepsy, intellectual disability, attention deficit hyperactivity disorder), and their interactions with background (polygenic) inherited liabilities should be recognised in the diagnostic system.
- Pleiotropic effects of known causes of ASD should be categorised in a manner that recognises their potential to influence other psychiatric syndromes.
- Motor coordination impairment should be incorporated into sets of criteria that are sufficient to make the diagnosis.
- Protocols and algorithms for feasible ascertainment of developmental history, current symptom burden, and clinical confirmation should place reliable, expedient diagnosis within reach for most children in public health-care settings.
- Impairments in adaptive functioning attributable to the characteristic symptoms of ASD should be more precisely specified, standardised, and implemented as standards for eligibility for access to services.

Conclusions and future directions

Key considerations for a reconceptualisation of diagnosis in autism, informed by the scientific advances described above, are summarised in panel 4. 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 that has shaped our understanding of what autism is has been very rapid over the past decade. When combined, accumulating information about what causes ASD in any individual, and how this relates to the variability in family risk and transmission, and increasing understanding of how the clinical syndrome and its causes relate to variation in ASD traits within the broader population, put us at a tipping point in terms of the approach to diagnosis.

Rapid advances in our understanding of the quantitative nature of autistic traits, the heterogeneity of genetic factors that contribute to ASD susceptibility, and the phenomenon of pleiotropy—coupled with increasingly evident limitations of the clinician diagnosis—are moving the specialty beyond the traditional model to one that is increasingly guided by biological measurement. Progress in many areas of study, including developmental biology, genetics, epidemiology, and neuroimaging will ultimately help to hone the diagnostic process and assist in the identification of subsets of ASD patients who are likely to benefit from specific therapies, including existing therapeutic options and treatment approaches that have yet to be discovered.

Search strategy and selection criteria

We searched PubMed for papers published between Jan 1, 2000, and Jan 31, 2015, using the search terms “autism”, “diagnosis”, “family studies”, and “genetics”. We also searched our own files and the reference lists of selected papers. We selected only papers published in English. The final reference list was generated on the basis of relevance to the topics covered in this Series paper, the aim of which is to synthesise recent scientific advances that have a direct bearing on the challenges of and potential refinements to the diagnosis in autism.
Contributors
JNC and TC contributed equally to the development of this Series paper.

Declaration of interests
JNC receives royalties from Western Psychological Services for the commercial distribution of the Social Responsiveness Scale-2, a quantitative measure of autistic traits. TC declares no competing interests.

Acknowledgments
The work of [JNC] is supported by US National Institutes of Health (NIH) grant HD068479 and a Eunice Kennedy Shriver National Institute of Child Health and Human Development award (U54 HD087011) [A: correct?] to the Intellectual and Developmental Disabilities Research Center at Washington University, St Louis, MO, USA. The content of this Series paper is solely the responsibility of the authors and does not necessarily represent the official views of NIH. TC receives support from the European Union’s [A: correct?] Innovative Medicines Initiative Joint Undertaking under grant agreement number 115300, including a financial contribution from the European Union’s Seventh Framework Programme (FP7/2007–2013) and a European Federation of Pharmaceutical Industries and Associations (EFPIA) companies’ in-kind contribution. [A: correct as edited?]

References


