Autism

Meng-Chuan Lai, Michael V Lombardo, Simon Baron-Cohen

Autism is a set of heterogeneous neurodevelopmental conditions, characterised by early-onset difficulties in social communication and unusually restricted, repetitive behaviour and interests. The worldwide population prevalence is about 1%. Autism affects more male than female individuals, and comorbidity is common (>70% have concurrent conditions). Individuals with autism have atypical cognitive profiles, such as impaired social cognition and social perception, executive dysfunction, and atypical perceptual and information processing. These profiles are underpinned by atypical neural development at the systems level. Genetics has a key role in the aetiology of autism, in conjunction with developmentally early environmental factors. Large-effect rare mutations and small-effect common variants contribute to risk. Assessment needs to be multidisciplinary and developmental, and early detection is essential for early intervention. Early comprehensive and targeted behavioural interventions can improve social communication and reduce anxiety and aggression. Drugs can reduce comorbid symptoms, but do not directly improve social communication. Creation of a supportive environment that accepts and respects that the individual is different is crucial.

Definition

In 1943, child psychiatrist Leo Kanner described eight boys and three girls,1 including 5-year-old Donald who was “happiest when left alone, almost never cried to go with his mother, did not seem to notice his father’s home-comings, and was indifferent to visiting relatives…wandered about smiling, making stereotyped movements with his fingers…spun with great pleasure anything he could seize upon to spin….Words to him had a specifically literal, inflexible meaning….When taken into a room, he completely disregarded the people and instantly went for objects”. In 1944, paediatrician Hans Asperger described four boys,2 including 6-year-old Fritz who “learnt to talk very early...quickly learnt to express himself in sentences and soon talked ‘like an adult’...never able to become integrated into a group of playing children...did not know the meaning of respect and was utterly indifferent to the authority of adults...lacked distance and talked without shyness even to strangers...it was impossible to teach him the polite form of address....Another strange phenomenon...was the occurrence of certain stereotypic movements and habits”.

These seminal reports1,2 vividly portray what is now called autism or the autism spectrum. The spectrum is wide, encompassing classic Kanner’s syndrome (originally entitled autistic disturbances of affective contact) and Asperger’s syndrome (originally called autistic psychopathy in childhood). Understanding of autism has evolved substantially in the past 70 years, with an exponential growth in research since the mid-1990s (figure). Autism is now thought of as a set of neurodevelopmental conditions, some of which can be attributed to distinct aetiological factors, such as Mendelian single-gene mutations. However, most are probably the result of complex interactions between genetic and non-genetic risk factors. The many types are collectively defined by specific behaviours, centring on atypical development in social communication and unusually restricted or repetitive behaviour and interests.

The mid-20th century view of autism as a form of childhood psychosis is no longer held. The first operational definition appeared in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), and was strongly influenced by Michael Rutter’s conceptualisation of impaired social development and communicative development, insistence on sameness, and onset before 30 months of age.3 The subsequent revisions in the fourth edition (DSM-IV) and the 10th revision of the International Classification of Diseases (ICD-10), in which autism was referred to as pervasive developmental disorder, emphasised the early onset of a triad of features: impairments in social interaction; impairments in communication; and restricted, repetitive, and stereotyped behaviour, interests, and activities.

The latest revision of DSM—DSM-5, published in May, 2013—adopted the umbrella term autism spectrum disorder without a definition of subtypes, and reorganised the triad into a dyad: difficulties in social communication and social interaction; and restricted and repetitive behaviour, interests, or activities (table 1). Atypical language development (historically linked to an autism diagnosis) was removed from the criteria, and is now classified as a co-occurring condition, even though large variation in language is characteristic of autism.4 The new criteria give improved descriptions and organisation of key features, emphasise the dimensional nature of autism, provide one diagnostic label with individualised specifiers, and allow for an assessment of the individual’s need for support (helping provision of clinical services).5

Search strategy and selection criteria

We searched PubMed, PsycINFO, the Cochrane Library, and Google Scholar for reports published between Jan 1, 2000, and June 20, 2013. We used the search terms “autism”, “autism spectrum disorder”, “pervasive developmental disorder”, and “Asperger syndrome”. We searched for other relevant earlier reports in the reference lists of reports identified through the database search. We mainly report summary findings from systematic reviews, meta-analyses, authoritative book chapters, and research articles published since 2008. We cite major updated reviews to provide further reading.
How prevalence estimates will be affected by the new criteria and how autism spectrum disorder will relate to the newly created social (pragmatic) communication disorder (defined by substantial difficulties with social uses of both verbal and non-verbal communication, but otherwise not meeting criteria for autism spectrum disorder) remain to be assessed.

Autism could potentially be subgrouped at clinical (eg, by developmental pattern or trajectory and comorbidity), cognitive, and aetiological levels (eg, by genetic and environmental correlates). Although the term autism spectrum disorder is frequently used, the term autism spectrum condition also signals a biomedical diagnosis for which individuals need support and recognises areas in which affected individuals are different from those without autism, but without the negative overtones of the disorder label.

**Epidemiology**

**Prevalence**

The prevalence of autism has been steadily increasing since the first epidemiological study, which showed that 4.1 of every 10 000 individuals in the UK had autism. The increase is probably partly a result of changes in diagnostic concepts and criteria. However, the prevalence has continued to rise in the past two decades, particularly in individuals without intellectual disability, despite consistent use of DSM-IV criteria. An increase in risk factors cannot be ruled out. However, the rise is probably also due to improved awareness and recognition, changes in diagnosis, and younger age of diagnosis.

Nowadays, the median worldwide prevalence of autism is 0.62–0.70%, although estimates of 1–2% have been made in the latest large-scale surveys. A similar prevalence has been reported for adults alone. About 45% of individuals with autism have intellectual disability, and 32% have regression (ie, loss of previously acquired skills; mean age of onset 1–78 years).

Early studies showed that autism affects 4–5 times more males than females, although the difference decreased in individuals with intellectual disability. However, large-scale population-based studies have shown that 2–3 times more males are affected, probably irrespective of intellectual disability. Females with autism might have been under-recognised. Empirical data suggest high-functioning females are diagnosed later than males are, and indicate a diagnostic bias towards males. Females need more concurrent behavioural or cognitive problems than males do to be clinically diagnosed. The diagnostic bias might be a result of behavioural criteria for autism or gender stereotypes, and might reflect better compensation or so-called camouflage in females.

Nevertheless, a male predominance is a consistent epidemiological finding that has aetiological implications. It could imply female-specific protective effects, such that females would have to have a greater aetiological (genetic or environmental) load than would males to reach the diagnostic threshold. These protective effects would mean that relatives of female probands would have an increased risk of autism or more autistic characteristics than would relatives of male probands. Alternatively, male-specific risks could heighten susceptibility. The existence of sex-linked aetiological load and susceptibility emphasises the importance of stratification by sex, and of comparisons between males and females to disentangle the aetiological role of sex-linked factors at genetic, endocrine, epigenetic, and environmental levels.

### Features

<table>
<thead>
<tr>
<th>Core features in DSM-5 criteria*</th>
<th>Associated features not in DSM-5 criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent deficits in social communication and social interaction across multiple contexts</td>
<td>Atypical language development and abilities</td>
</tr>
<tr>
<td>Restricted, repetitive patterns of behaviour, interests, or activities</td>
<td>Motor abnormalities</td>
</tr>
<tr>
<td>Deficits in social–emotional reciprocity</td>
<td>Age 6 years: frequently deviant and delayed in comprehension; two-thirds have difficulty with expressive phonology and grammar</td>
</tr>
<tr>
<td>Deficits in verbal and non-verbal communicative behaviours used for social interaction</td>
<td>Age 6 years: deviant pragmatics, semantics, and morphology, with relatively intact articulation and syntax (ie, early difficulties are resolved)</td>
</tr>
<tr>
<td>Deficits in developing, maintaining, and understanding relationships</td>
<td>Motor delay, hypotonia, catatonia; deficits in coordination, movement preparation and planning, praxis, gait, and balance</td>
</tr>
<tr>
<td>Stereotyped or repetitive motor movements, use of objects, or speech insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or non-verbal behaviour</td>
<td>Excellent attention to detail</td>
</tr>
<tr>
<td>Highly restricted, fixed interests that are abnormal in intensity or focus</td>
<td>–</td>
</tr>
<tr>
<td>Hyper-reactivity or hyperreactivity to sensory input or unusual interest in sensory aspects of the environment</td>
<td>–</td>
</tr>
</tbody>
</table>

*“Information reproduced from DSM-5; by permission of the American Psychiatric Association.”

### Table 1: Behavioural characteristics of autism

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent deficits in social communication and social interaction across multiple contexts</td>
<td>Deficits in social–emotional reciprocity, Deficits in verbal and non-verbal communicative behaviours used for social interaction, Deficits in developing, maintaining, and understanding relationships</td>
</tr>
<tr>
<td>Restricted, repetitive patterns of behaviour, interests, or activities</td>
<td>Stereotyped or repetitive motor movements, use of objects, or speech insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or non-verbal behaviour, Highly restricted, fixed interests that are abnormal in intensity or focus, Hyper-reactivity or hyperreactivity to sensory input or unusual interest in sensory aspects of the environment</td>
</tr>
</tbody>
</table>

For version with full references, see appendix. DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
### Developmental

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability</td>
<td>45%</td>
<td>Prevalence estimate is affected by the diagnostic boundary and the definition of intelligence (eg, whether verbal ability is used as a criterion)</td>
</tr>
<tr>
<td>Language disorders</td>
<td>Variable</td>
<td>In DSM-IV, language delay was a defining feature of autism (autistic disorder), but it is no longer included in DSM-5</td>
</tr>
<tr>
<td>Attention-deficit hyperactivity</td>
<td>28-44%</td>
<td>An autism-specific language profile (separate from language disorders) exists, but with substantial inter-individual variability</td>
</tr>
<tr>
<td>Tic disorders</td>
<td>14-38%</td>
<td>In DSM-IV, not diagnosed when occurring in individuals with autism, but no longer so in DSM-5</td>
</tr>
<tr>
<td>Motor abnormality</td>
<td>≤79%</td>
<td>Clinical guidance available</td>
</tr>
</tbody>
</table>

### General medical

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>8-30%</td>
<td>Increased frequency in individuals with intellectual disability or genetic syndromes</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>9-70%</td>
<td>Common symptoms include chronic constipation, abdominal pain, chronic diarrhoea, and gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>≤38%</td>
<td>Altered immune function, which interacts with neurodevelopment, could be a crucial biological pathway underpinning autism</td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>≤5%</td>
<td>Collectively called syndromic autism</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>50-80%</td>
<td>Insomnia is the most common</td>
</tr>
</tbody>
</table>

### Psychiatric

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>42-56%</td>
<td>Common across all age groups</td>
</tr>
<tr>
<td>Depression</td>
<td>22-70%</td>
<td>Common in adults, less common in children</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>7-24%</td>
<td>Shares the repetitive behaviour domain with autism that could cut across nosological categories</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>12-17%</td>
<td>Mainly in adults Most commonly recurrent hallucination High frequency of autism-like features (even a diagnosis of autism spectrum disorder or pervasive developmental disorder) preceding adult-onset (52%) and childhood-onset schizophrenia (30-50%)</td>
</tr>
<tr>
<td>Substance use disorders</td>
<td>≤16%</td>
<td>Potentially because individual is using substances as self-medication to relieve anxiety</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>16-28%</td>
<td>Oppositional behaviours could be a manifestation of anxiety, resistance to change, stubborn belief in the correctness of own point of view, difficulty seeing another's point of view, poor awareness of the effect of own behaviour on others, or no interest in social compliance</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>4-5%</td>
<td>Could be a misdiagnosis of autism, particularly in females, because both involve rigid behaviour, inflexible cognition, self-focus, and focus on details</td>
</tr>
</tbody>
</table>

### Personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid personality disorder</td>
<td>0-19%</td>
<td>Could be secondary to difficulty understanding others’ intentions and negative interpersonal experiences</td>
</tr>
<tr>
<td>Schizoid personality disorder</td>
<td>21-26%</td>
<td>Partly overlapping diagnostic criteria Same to Wing’s loners subgroup</td>
</tr>
<tr>
<td>Schizotypal personality disorder</td>
<td>2-13%</td>
<td>Some overlapping criteria, especially those shared with schizoid personality disorder</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>0-9%</td>
<td>Could have similarity in behaviours (eg, difficulties in interpersonal relationships, misattributing hostile intentions, problems with affect regulation), which requires careful differential diagnosis</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>19-32%</td>
<td>Partly overlapping diagnostic criteria</td>
</tr>
<tr>
<td>Avoidant personality disorder</td>
<td>12-25%</td>
<td>Could be secondary to repeated failure in social experiences</td>
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(Continues on next page)
Proportion of individuals with autism affected | Comments
---|---
(Continued from previous page)

### Behavioural

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive behaviours</td>
<td>≤68%</td>
</tr>
<tr>
<td>Self-injurious behaviours</td>
<td>≤50%</td>
</tr>
<tr>
<td>Pica</td>
<td>≤36%</td>
</tr>
<tr>
<td>Suicidal ideation or attempt</td>
<td>11–14%</td>
</tr>
</tbody>
</table>

For version with full references, see appendix. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition. DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition. *Particularly in high-functioning adults.

### Risk and protective factors

Epidemiological studies have identified various risk factors, but none has proven to be necessary or sufficient alone for autism to develop. Understanding of gene–environment interplay in autism is still at an early stage. Advanced paternal or maternal reproductive age, or both, is a consistent risk; the underlying biology is unclear, but could be related to germline mutation, particularly when paternal in origin. Alternatively, individuals who have children late in life might do so because they have the broader autism phenotype—ie, mild traits characteristic of autism—which is known to be associated with having a child with autism, although this idea needs further research. Additionally, prevalence of autism has been reported to be two times higher in cities where many jobs are in the information-technology sector than elsewhere; parents of children with autism might be more likely to be technically talented than are other parents.

Gestational factors that could affect neurodevelopment, such as complications during pregnancy and exposure to chemicals, have been suggested to increase risk of autism. A broad, non-specific class of conditions reflecting general compromises to perinatal and neonatal health is also associated with increased risk. Conversely, folic acid supplements before conception and during early pregnancy seem to be protective. There is no evidence that the MMR (measles, mumps, and rubella) vaccine, thiomersal-containing vaccines, or repeated vaccination cause autism.

### Co-occurring conditions

More than 70% of individuals with autism have concurrent medical, developmental, or psychiatric conditions (table 2)—a higher proportion than that for psychiatric outpatients and patients in tertiary hospitals. Childhood co-occurring conditions tend to persist into adolescence. Some co-occurring conditions, such as epilepsy and depression, can first develop in adolescence or adulthood. Generally, the more co-occurring conditions, the greater the individual’s disability. The high frequency of comorbidity could be a result of shared pathophysiology, secondary effects of growing up with autism, shared symptom domains and associated mechanisms, or overlapping diagnostic criteria.

### Prognosis and outcome

A meta-analysis showed that individuals with autism have a mortality risk that is 2–8 times higher (95% CI 1·8–4·2) than that of unaffected people of the same age and sex. This difference is mostly related to co-occurring medical conditions. Studies done before the widespread application of early intervention programmes showed that 58–78% of adults with autism have poor or very poor outcomes in terms of independent living, educational attainment, employment, and peer relationships. Higher childhood intelligence, communicative phrase speech before age 6 years, and fewer childhood social impairments predict a better outcome. Yet, even for individuals without intellectual disability, adult social outcome is often unsatisfactory in terms of quality of life and achievement of occupational potential, although it is associated with cognitive gain and improved adaptive functioning during development. Childhood follow-up studies have shown varying developmental trajectories in children with autism and in their siblings. The best possible outcome—ie, reversal of diagnosis, negligible autistic symptoms, and normal social communication—has also been reported.

Transition to adulthood, which often involves loss of school support and child and adolescent mental health services, is a challenge. The end of secondary education is often accompanied by slowed improvement, probably due to reduced occupational stimulation and insufficient adult services. More than half of young people in the USA who have left secondary education in the past 2 years are not participating in any paid work or education. The mean proportion of adults with autism in employment (regular, supported, or sheltered) or
full-time education is 46%. Furthermore, little is known about how ageing affects people with autism.

**Early signs and screening**

Early identification allows early intervention. Previously, children with autism were often identified when older than 3–4 years, but toddlers are now frequently diagnosed because atypical development is recognised early. Early indicators are deficits or delays in the emergence of joint attention (ie, shared focus on an object) and pretend play, atypical implicit perspective taking, deficits in reciprocal affective behaviour, decreased response to own name, decreased imitation, delayed verbal and non-verbal communication, motor delay, unusually repetitive behaviours, atypical visuomotor exploration, inflexibility in disengaging visual attention, and extreme variation in temperament. These indicators contribute to screening and diagnostic instruments for toddlers. However, identification of high-functioning individuals is still often later than it should be, particularly for females.

Variability in age, cognitive ability, and sex leads to differential presentation and the need for appropriate screening instruments (table 3). Care should be taken during selection of screening instruments (and the cutoff for further action), because the target sample and purpose of screening vary. Routine early screening at ages 18 and 24 months has been recommended. The advantages and disadvantages of action after a positive result should be carefully considered, as should the identification and management of individuals who have false-positive results.

Studies of siblings of probands from an early age could potentially identify early behavioural and neural predictors of emerging autism. Signs of autism are not reliably present at birth, but emerge through a process of diminishing, delayed, or atypical development of social-communication behaviours, starting between the ages of 6 and 12 months. Examples of potential predictors of a subsequent autism diagnosis are poor attention to social scenes or human faces at age 6 months, little infant–parent interaction (reduced dyadic mutuality, including shared attention, infant acceptance of parental involvement, playing together, interactive flow, and shared body orientation; infant positive affect; and attentiveness to parent) at age 12 months, and reduced flexibility in control of visual attention or orientation (disengagement) at ages 7 months and 14 months. Brain response when infants view faces with dynamic eye gaze at age 6–10 months (measured by event-related potential) predicts an autism diagnosis at 36 months. Developmental trajectory of white-matter-tract organisation from age 6 to 24 months predicts diagnosis at 24 months. Even some high-risk siblings who do not qualify for an autism diagnosis by age 3 years still have residual signs of delayed development and more autistic signs than do low-risk siblings, suggesting that developmental surveillance and early intervention is also important for these individuals.

**Clinical assessment**

Diagnostic assessment should be multidisciplinary and use a developmental framework of an interview with the parent or caregiver, interaction with the individual, collection of information about behaviour in community settings (eg, school reports and job performance), cognitive assessments, and a medical examination. Co-occurring conditions should be carefully screened.

The interview of the parent or caregiver should cover the gestational, birth, developmental, and health history, and family medical and psychiatric history. It should have specific foci: the development of social, emotional, language and communication, cognitive, motor, and self-help skills; the sensory profile; and unusual behaviours and interests. Behavioural presentation across different contexts should be investigated. Ideally, a standardised, structured interview should be incorporated into the assessment process (table 3). Adaptive skills should be checked with standardised instruments (eg, Vineland adaptive behaviour scales). In children, parent–child interaction and parent coping strategies should be specifically investigated, because they are relevant for the planning of interventions.

Interviews with the individual should be interactive and engaging to enable assessment of social-communication characteristics in both structured and unstructured contexts. Again, information should ideally be gathered with standardised instruments (table 3). For adolescents and adults capable of reporting their inner state, self-report questionnaires are helpful (table 3), but their validity should be weighed against the individual’s level of insight. How individuals cope in a peer environment should also be assessed.

School reports and job performance records are valuable data indicating an individual’s strengths and difficulties in real-life settings. They also help with individualisation of educational and occupational planning. Cognitive assessments of intelligence and language are essential; standardised, age-appropriate, and development-appropriate instruments should be used to measure both verbal and non-verbal ability.

Neuropsychological assessments are helpful for individualised diagnosis and service planning.

A medical examination is important in view of the high frequency of comorbidity. Physical and neurological examinations (eg, head circumference, minor physical anomalies and skin lesions, and motor function) and genetic analyses (eg, G-banded karyotype analysis, FMR1 testing, and particularly chromosomal microarray analysis) should be done. Other laboratory tests—eg, electroencephalography when awake and asleep if seizures are suspected, neuroimaging when intracranial lesions are suspected, and metabolic profiling when neurometabolic disorders are suspected—can be done as necessary.

**Cognition and neuroscience**

In the mid-20th century, autism was thought to originate from the emotional coldness of the child’s mother, even
though this hypothesis had no empirical support. By contrast, concurrent neurobiological hypotheses\textsuperscript{96} and Kanner’s proposal of an “innate inability to form the usual, biologically provided affective contact with people”\textsuperscript{1} have received scientific support. Cognition and neurobiology are related, and their development is characterised by a complex interplay between innate and environmental factors. Cognition provides a guide to simplify the various domains of concern (table 4), although they are by nature interlinked.

Since impaired theory of mind was specifically reported in children with autism in 1985,\textsuperscript{98} difficulties with mentalising—ie, understanding of mental states in both self and others—are believed to be core to social-communication deficits (table 4). Studies\textsuperscript{99,100} have confirmed that development is atypical not only for the behavioural expressions of mentalising, but also for their developmental precursors in triadic social interaction (eg, joint attention and pretend play) and dyadic social perception (eg, eye contact, emotion perception, action–perception mirroring, social orienting, biological motion processing, and face processing).

<table>
<thead>
<tr>
<th>Screening: young children</th>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checklist for autism in toddlers (CHAT)</td>
<td>18 months</td>
<td>14-item questionnaire: nine completed by parent or caregiver and five by primary health-care provider; takes 5–10 min</td>
</tr>
<tr>
<td>Early screening of autistic traits (ESAT)</td>
<td>14 months</td>
<td>14-item questionnaire: completed by health practitioners at well-baby visit after interviewing parent or caregiver; takes 5–10 min</td>
</tr>
<tr>
<td>Modified checklist for autism in toddlers (M-CHAT)</td>
<td>16–30 months</td>
<td>23-item questionnaire: completed by parent or caregiver; takes 5–10 min</td>
</tr>
<tr>
<td>Infant toddler checklist (ITC)</td>
<td>6–24 months</td>
<td>24-item questionnaire: completed by parent or caregiver; takes 5–10 min</td>
</tr>
<tr>
<td>Quantitative checklist for autism in toddlers (Q-CHAT)</td>
<td>18–24 months</td>
<td>25-item questionnaire: completed by parent or caregiver; takes 5–10 min; ten-item short version available</td>
</tr>
<tr>
<td>Screening tool for autism in children aged 2 years (STAT)</td>
<td>24–36 months</td>
<td>12 items and activities: assessed by clinician or researcher after interacting with the child; takes 20 min; intensive training necessary; level-two screening measure</td>
</tr>
<tr>
<td><strong>Screening: older children and adolescents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social communication questionnaire (SCQ)</td>
<td>&gt;4 years (and mental age &gt;2 years)</td>
<td>40-item questionnaire: completed by parent or caregiver; takes 10–15 min</td>
</tr>
<tr>
<td>Social responsiveness scale, first or second edition (SRS, SRS-2)</td>
<td>&gt;2.5 years</td>
<td>65-item questionnaire: completed by parent, caregiver, teacher, relative, or friends (self-report form available for adult in SRS-2); takes 15–20 min</td>
</tr>
<tr>
<td>Childhood autism screening test (CAST)</td>
<td>4–11 years</td>
<td>37-item questionnaire: completed by parent or caregiver; takes 10–15 min</td>
</tr>
<tr>
<td>Autism spectrum screening questionnaire (ASSQ)*</td>
<td>&gt;7–16 years</td>
<td>27-item questionnaire: completed by parent, caregiver, or teacher; takes 10 min</td>
</tr>
<tr>
<td>Autism spectrum quotient (AQ), child and adolescent versions*</td>
<td>Child: 4–11 years; adolescent: 10–16 years</td>
<td>50-item questionnaire: completed by parent or caregiver; takes 10–15 min; ten-item short versions available</td>
</tr>
<tr>
<td><strong>Screening: adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism spectrum quotient (AQ), adult version*</td>
<td>&gt;16 years (with average or above-average intelligence)</td>
<td>50-item questionnaire: self-report; takes 10–15 min; ten-item short version available</td>
</tr>
<tr>
<td>The Ritvo autism Asperger diagnostic scale–revised (RAADS-R)</td>
<td>&gt;18 years (with average or above-average intelligence)</td>
<td>80-item questionnaire: self-report, done with a clinician; takes 60 min</td>
</tr>
<tr>
<td><strong>Diagnostic: structured interview</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The autism diagnostic interview-revised (ADI-R)</td>
<td>Mental age &gt;2 years</td>
<td>93-item interview of parent or caregiver; takes 1.5–3 h; intensive training necessary</td>
</tr>
<tr>
<td>The diagnostic interview for social and communication disorders (DISCO)</td>
<td>All chronological and mental ages</td>
<td>362-item interview of parent or caregiver; takes 2–4 h; intensive training necessary</td>
</tr>
<tr>
<td>The developmental, dimensional, and diagnostic interview (3Di)</td>
<td>&gt;2 years</td>
<td>266-item computer-assisted interview of parent or caregiver; takes 2 h; 53-item short form available, which takes 45 min; intensive training necessary</td>
</tr>
<tr>
<td><strong>Diagnostic: observational measure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The autism diagnostic observation schedule, first or second edition (ADOS, ADOS-2)</td>
<td>&gt;12 months</td>
<td>Clinical observation via interaction: select one from five available modules according to expressive language level and chronological age; takes 40–60 min; intensive training necessary</td>
</tr>
<tr>
<td>Childhood autism rating scale, first or second edition (CARS, CARS-2)</td>
<td>&gt;2 years</td>
<td>15-item rating scale: completed by clinician or researcher; takes 20–30 min; accompanied by a questionnaire done by parent or caregiver; moderate training necessary</td>
</tr>
</tbody>
</table>

For version with full references and for sources, see appendix. *Particularly sensitive for high-functioning individuals.

Table 3: Screening and diagnostic instruments
Although many (high-functioning) individuals with autism achieve some degree of explicit or controlled mentalising, the implicit, automatic, and intuitive components are still impaired, even in adulthood. Early-onset mentalising difficulties seem to be specific to autism, but late-onset deficits are reported in disorders such as schizophrenia. Mentally is closely entwined with executive control and language, so that the dichotomous view of social versus non-social cognition is potentially misleading in autism.

Historically, the domain of mentalising has been largely centred on others, but self-referential cognition and its neural substrates are also atypical in autism. Therefore, deficits in the social domain are not only about difficulties in the processing of information about other people, but also about processing of self-referential information, the relationship that self has in a social context, and the potential for using self as a proxy to understand the social world.

A consistent network of brain regions—including the medial prefrontal cortex, superior temporal sulcus, temporoparietal junction, amygdala, and fusiform gyrus—are hypoactive in autism across tasks in which social perception and cognition are used. Dysfunction in the so-called mirror system (ie, brain regions that are active both when an individual performs an action and observes another person performing the same action) has been inconsistently implicated in imitation or observation of action or emotion in autism. However, brain structures do not act separately. Although studies of autism showing atypical development of the so-called social brain are promising, equal attention should be paid to how these brain structures interact with the rest of the neural system.

Executive dysfunction could underlie both the unusually repetitive stereotyped behaviours and social-communication deficits in autism (table 4). However, the consistency of reports has been challenged, and impaired performance could be underpinned by difficulties with mentalising. Imaging studies have shown that frontal, parietal, and striatal circuitry are the main systems implicated in executive dysfunction in autism. Executive dysfunction is not specific to autism; it is commonly reported in other neuropsychiatric conditions (although with different patterns). One view is that strong executive function early in life could protect at-risk individuals from autism or other neurodevelopmental conditions by compensating for deficits in other brain systems.

Individuals with autism often have a preference for, and superiority in, processing of local rather than global sensory-perceptual features (table 4). Individuals without autism often show the opposite profile. This difference could explain the excellent attention to detail, enhanced sensory-perceptual processing and discrimination, and idiosyncratic sensory responsivity (ie, hyper-reactivity or hyporeactivity to sensory input or unusual interest in sensory features of the environment) in autism. It could also contribute to the exceptional abilities disproportionally recorded in individuals with autism. Additionally, top-down information processing in individuals with autism is often characterised by reduced recognition of the global context, and a strong preference to derive rule-based systems. The neural bases are spatially distributed and task dependent, but converge on enhanced recruitment of primary sensory cortices, reduced recruitment of association and frontal cortices involved in top-down control, and enhanced synchronisation of parietal-occipital circuits.

### Neurobiology

Neurobiological investigation has identified patterns of brain perfusion and neural biochemical characteristics, which are described elsewhere. Additionally, systems-level connectivity features and plausible neuroanatomical, cellular, and molecular underpinnings of autism have been identified. Evidence from electrophysiology and functional neuroimaging (resting-state and task-based connectivity), structural neuroimaging (white-matter
volume and microstructural properties, molecular genetics (cell adhesion molecules and synaptic proteins, and excitatory–inhibitory imbalance), and information processing have given rise to the idea that autism is characterised by atypical neural connectivity, rather than by a discrete set of atypical brain regions. Ideas about the precise way in which connectivity is atypical vary, from decreased fronto-posterior and enhanced parietal-occipital connectivity, reduced long-range and increased short-range connectivity, to temporal binding deficits. Although none fully explains all the data (findings depend on the definition of connectivity, the developmental stage of the individual, the spatial and temporal scales, task vs no-task conditions, how motion artifacts are handled, and specific neural systems of concern), they support the heuristic value of the tenet that neural networks in autism are atypical in various ways.

One frequently reported neuroanatomical feature of autism is a trajectory of generalised early brain overgrowth when aged 6–24 months. Other than increases in total brain volume, the amygdala is enlarged in young children with autism, although this enlargement is no longer present by adolescence. Early brain overgrowth tends to be reported more in boys who have developmental regression than in other subgroups, and might be a result of generalised physical overgrowth or biased norms of head circumference in past studies. Additionally, meta-analyses suggest some consistent neuroanatomical differences across the lifespan in both grey-matter (eg, amygdala, hippocampus, and pre-cuneus) and white-matter structures (eg, arcuate and uncinate fasciculi). A reduction in the volume of the corpus callosum is also a fairly consistent finding. Many findings are age dependent, indicating the importance of developmental change.

Post-mortem studies have shown a reduction in neuron number in the amygdala, fusiform gyrus, and cerebellum, and signs of persistent neuroinflammation. However, most donated brain tissue is from older children, adolescents, and adults, so might not show early atypical development. One exception is a study of young children that showed significant increases (rather than decreases) in neuron number in the prefrontal cortex.

Genes typically differentially expressed across frontal and temporal cortices are less differentially expressed in autism; gene networks implicated in neuronal mechanisms are underexpressed in autism and enriched with autism susceptibility genes, whereas gene networks involved in immune processes are overexpressed. Neocortical dysgenesis marked by atypical patterning of cortical minicolumns (reduction in size, increased neuronal density, and increase in cell dispersion) is also of interest and is potentially associated with atypical synaptogenesis and an imbalanced excitatory-to-inhibitory ratio, both of which are important for neural connectivity.

Interaction between the immune and the nervous systems is substantial throughout life, challenging the dogma of the so-called immune privilege of the CNS. Frequency of immunological anomalies is increased in individuals with autism and their families. In autism, altered immune processes affect a wide array of neurodevelopmental processes (eg, neurogenesis, proliferation, apoptosis, synaptogenesis, and synaptic pruning), with persistent active neuroinflammation, increased concentrations of pro-inflammatory cytokines in serum and cerebrospinal fluid, and altered cellular immune functions. Maternal IgG antibodies that target the fetal brain or other gestational immune dysregulation could be pathogenic in some cases. Neuroimmune mechanisms could have key roles in some aspects of the pathophysiology of autism, but the exact biology awaits clarification.

In autism, alterations in both serotonin and γ-aminobutyric-acid (GABA) systems have been reported quite consistently, such as hyperserotonenaemia and an altered developmental trajectory of brain serotonin synthesis capacity, and reduction in the expression of GABA synthetic enzymes and receptors. Because of their relation with affiliative and social behaviours, the oxytocin and vasopressin systems’ roles in social impairments in autism are an active focus of investigation, including treatment trials. The role of androgens (and oestrogens) in modulation of risks and protections, particularly prenatally, in the emergence of autism is also being tested in view of the accumulating evidence of a link between fetal testosterone and autistic traits. Prenatal hormones could be associated with the extreme-male-brain cognitive profile of reduced mentalising and enhanced systemising in autism development.

**Genetics**

Twin studies have suggested that autism has high heritability (more than 80%). This heritability occurs in the context of environmental risks and gene–environment interplay, because the monozygotic concordance rates are never 100%. Epigenetic mechanisms and specific gene–environment interplay are important but understudied. From an evolutionary viewpoint, autistic traits could have been subject to positive selection pressure, because of the potential benefits of a solitary single-minded obsessive focus on innovative understanding of a system. Such individuals might have successfully traded products or their building and fixing skills, thus acquiring resources and increasing their reproductive fitness, which could have contributed to the maintenance of autism alleles in the gene pool.

The genetic architecture of autism has proved to be complex and heterogeneous, as shown by studies of cytogenetics, linkage, association, whole-genome linkage or association, and whole-genome or exome sequencing. Many genetic variants linked to autism have a high degree of pleiotropy (ie, one gene affects more than one phenotype). A high degree of locus heterogeneity has also been reported, with speculations that up to 1000 genes are implicated. Both rare
mutations with large effect sizes and common variations with smaller effect sizes have a role.124–127

Rare mutations (ie, minor allele frequency <5% in the general population) are frequently identified in autism and can occur in the form of Mendelian genetic syndromes (so-called syndromic autism, occurring in about 5% of all individuals with autism), chromosomal abnormalities (about 5%), rare copy number variations (5–10%),125–127 and de novo and transmitted point mutations (single nucleotide variants) identified by exome sequencing.118,124 De novo mutations (copy number variations in the form of microdeletion or microduplication, and single nucleotide variants in the form of nonsense, splice-site, and frameshift mutations) that occurred in the germline (especially paternal) have a large effect size and could be causal,77–81 particularly in simplex cases (ie, when only one individual in the family has autism). Equally, copy number variations with moderate effect sizes and variable expressivity and penetrance could have some role.128 However, each identified copy number variation only occurs in at most about 1% of individuals with autism, again suggesting substantial genetic heterogeneity.112 Some of these rare mutations are clinically identifiable; therefore, screening is recommended as part of routine clinical examination.143,147

In terms of common variants (eg, single nucleotide polymorphisms with allele frequency >5% in the general population), genome-wide association studies have identified some important single nucleotide polymorphisms, but none has a large enough effect to be deemed causal.124 However, up to 40% of simplex families and 60% of multiplex families (in which more than one individual has autism) could have several single nucleotide polymorphisms that, when combined, have an additive effect on risk.124 Thus, common variability within single nucleotide polymorphisms could contribute to the emergence of autism, the associated features in families (the broader autism phenotype),42 the increased incidence of autism in offspring of parents with increased autistic traits,148 and autistic traits in the general population.155 Contributions from rare and common genetic variants are not mutually exclusive.114

As the genetics of autism unfolds, information is continually updated. The rapid progress of genetics, along with animal model systems and systems biology methods will enable the identification of diverse aetiologies and common molecular and cellular pathways crucial for neurodevelopment in autism. Such clarification could affect how the autisms are classified, diagnosed, and treated in the future.

**Intervention**

**Overview**

Intervention and support should be individualised and, if appropriate, multidimensional and multidisciplinary. The goals are to maximise an individual’s functional independence and quality of life through development and learning, improvements in social skills and communication, reductions in disability and comorbidity, promotion of independence, and provision of support to families. Additionally, individuals should be helped to fulfill their potential in areas of strength. Although autism is rooted in biology, most effective interventions so far are behavioural and educational; drugs have had only a minor role so far.

**Behavioural approaches**

Various behavioural approaches exist,156–158 and are classified here into five complementary categories (table 5). Comprehensive approaches target a broad range of skills (cognitive, language, sensorimotor, and adaptive behaviours) via long-term intensive programmes, and are grouped into applied behaviour analysis and structured teaching (table 5).158 The models based on applied behaviour analysis originate from the Lovaas method160 and are collectively referred to as early intensive behavioural intervention. The Early Start Denver Model is a further development, in which a developmental framework and relationship aspects are emphasised (table 5). Early intensive behavioural intervention seems to enable the development of intelligence, communication, and adaptive function, and, to a lesser extent, language, daily living skills, and socialisation.92 A shift from atypical to typical neurophysiology has been reported after 2 years of intervention with the Early Start Denver Model.92 However, too few randomised controlled trials have been done.103,158,159 The second comprehensive approach, structured teaching, originates from the TEACCH (Treatment and Education of Autistic and related Communication-handicapped Children) model (table 5). It is widely used across a broad age range, but little evidence is available from randomised controlled trials.158

Targeted approaches focus on specific cognitive behavioural domains. For non-verbal individuals, the Picture Exchange Communication System (table 5) could be helpful, at least in the short term.124 Some evidence of effectiveness is available for models promoting emotion recognition, theory of mind, imitation, and functional communication (table 5), but the generalisability to other domains of development is unclear.114 Joint attention or engagement training seems to be effective,91 and could be generalisable to natural contexts154 and language development.91 A curriculum targeting socially synchronous engagement for toddlers also seems to be effective.156 Social skill training for older children, adolescents, and adults is also promising (table 5). Programmes establishing independence are often used but still need systematic assessment (table 5). Vocational intervention is important, especially for transition into adulthood, but more randomised controlled trials are needed to assess their effectiveness (table 5). Targeted behavioural intervention can also be beneficial by reducing anxiety and aggression (table 5).

Parent-mediated intervention has the advantage of bringing treatment into home and community settings.
to enable transfer of skills to real-life settings, and increasing parents’ and caregivers’ self-confidence (table 5).37,156 Programmes can be comprehensive (eg, parent delivery of the Early Start Denver Model) or targeted (eg, at joint attention or communication; table 5). The benefit of parent-mediated intervention alone is unclear, and results are inconsistent (table 5). Nevertheless, parental and family involvement is important in therapist-mediated programmes.79,158

Sensory integration therapy—frequently used in occupational therapy—is sometimes offered as one component of a comprehensive programme to address sensory-based problems. However, its effectiveness is inconclusive37 and it should not be considered as a routine intervention for autism.25,158

The US Health Resources and Services Administration158 and the UK National Institute for Health and Care Excellence97 have provided clinical guidelines for behavioural interventions. They stress that comprehensive intervention should immediately follow diagnosis, and should be individualised (on the basis of developmental level, needs, and assets) and engage the family.

### Behavioural approaches

<table>
<thead>
<tr>
<th>Target group</th>
<th>Evidence for effectiveness</th>
<th>Intervention framework and goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive: ABA-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early intensive behavioural intervention</td>
<td>Young children (usually aged &lt;5 years)</td>
<td>Low or moderate</td>
</tr>
<tr>
<td>Early intensive behavioural intervention integrated with developmental and relationship-based approaches (eg, ESDM and floortime [developmental individual-difference, relationship-based model])</td>
<td>Young children (usually aged &lt;5 years)</td>
<td>Moderate or insufficient for ESDM; not established for floortime</td>
</tr>
<tr>
<td><strong>Comprehensive: structured teaching</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment and Education of Autistic and related Communication-handicapped Children (TEACCH)</td>
<td>Children, adolescents, and adults</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Targeted skill-based intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picture Exchange Communication System</td>
<td>Non-verbal individuals</td>
<td>Moderate</td>
</tr>
<tr>
<td>Training in joint attention, pretend play, socially synchronous behaviour, imitation, emotion recognition, theory of mind, and functional communication</td>
<td>Children</td>
<td>Not established, but potentially effective</td>
</tr>
<tr>
<td>Teaching social skills (eg, emotion recognition, turn-taking) with areas of interests (eg, in machines and systems)</td>
<td>Children, adolescents, and adults</td>
<td>Not established, but potentially effective</td>
</tr>
<tr>
<td>Social skill training</td>
<td>Children aged 6–10 years, adolescents, and adults</td>
<td>Low or moderate</td>
</tr>
<tr>
<td>Training in living skills and autonomy</td>
<td>Children, adolescents, and adults</td>
<td>Not established</td>
</tr>
<tr>
<td>Vocational intervention</td>
<td>Adolescents and adults</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Targeted behavioural intervention for anxiety and aggression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive behavioural therapy, ABA</td>
<td>Children, adolescents, and adults</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Parent-mediated early intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training for joint attention, parent-child interaction, and communication; or models like pivotal response training, parent delivery of the ESDM, and More Than Words</td>
<td>Young children</td>
<td>Insufficient or low</td>
</tr>
</tbody>
</table>

(Continues on next page)
might reduce repetitive behaviours, although findings are inconsistent (table 5). The effect of stimulants on co-occurring symptoms of attention-deficit hyperactivity disorder requires more study but is promising and has been recommended (table 5). Initial evidence suggests that atomoxetine also reduces co-occurring symptoms of attention-deficit hyperactivity disorder.

Some complementary and alternative medicines might be tolerated (eg, melatonin, vitamins, a gluten-casein-free diet, omega-3 fatty acids), but their effectiveness is not established. No treatment benefit of secretin has been recorded. Chelation therapies, hyperbaric oxygen therapy, intravenous immunoglobulin, and antifungal agents all have serious safety concerns without evidenced benefits, and should not be used.

Conclusions
Understanding of autism has changed substantially in the 70 years since it was first described. With the recent exponential increase in research and the inclusion of scientists from a wide range of disciplines, understanding will continue to evolve at an accelerated rate. The specialty has achieved much: it has reached a consensus about behavioural definition; accepted the increased prevalence; improved understanding about early presentation; established systematic clinical assessments and evidence-based interventions; clarified specific cognitive processes; and used a multidomain, systems-level approach to understand neurobiology. It is discovering rare and common, mutated and transmitted genetic variants, and potential epigenetic and environmental factors.

Nevertheless, future work is needed in many areas. First, to understand aetiologies and development, clarification of the substantial heterogeneity by subgrouping is essential. Second, progress needs to be made in understanding of early developmental mechanisms on which early

<table>
<thead>
<tr>
<th>Target group</th>
<th>Evidence for effectiveness*</th>
<th>Intervention framework and goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, adolescents, and adults</td>
<td>Risperidone; aripiprazole</td>
<td>To reduce challenging behaviours and repetitive behaviours; potential adverse effects include weight gain, sedation, extrapyramidal symptoms, and hyperprolactinaemia (risperidone)</td>
</tr>
<tr>
<td>Insufficient for effect and adverse effect</td>
<td>Citalopram; escitalopram; fluoxetine; and others</td>
<td>To reduce repetitive behaviours; potential adverse effects include activation symptoms (agitation) and gastrointestinal discomfort</td>
</tr>
<tr>
<td>Insufficient for effect and adverse effect</td>
<td>Methylphenidate</td>
<td>To reduce attention-deficit hyperactivity disorder symptoms; potential adverse effects include insomnia, decreased appetite, weight loss, headache, and irritability</td>
</tr>
</tbody>
</table>

Additionally, they emphasise that social-communication training (with a focus on social skills) should be offered, and non-verbal individuals should have opportunities to use the Picture Exchange Communication System (or alternative communication interventions if that is unsuccessful). The guidelines stress that functional analysis should be integrated into design of interventions for challenging behaviours. Supported employment should be offered for adults who have difficulty obtaining or maintaining jobs. Support for families is crucial. Importantly, more randomised controlled trials are needed for all intervention models to improve evidence for choosing an intervention for each individual and family. Finally, creation of autism-friendly environments is essential. Future research needs to focus on monitoring of outcomes, understanding of specific needs for preverbal and non-verbal individuals as well as adolescents and adults, and identification of key components in effective strategies. Generalisation of skills is still a major challenge.

**Drugs**

No biomedical agent has been shown to reliably improve social communication; experimental trials of drugs targeting various systems (eg, oxytocin, and cholinergic and glutamatergic agents) are in progress. Antipsychotic drugs have been shown to effectively reduce challenging and repetitive behaviours in children with autism, and insufficient evidence of usefulness in adolescents and adults is available (table 5). The risk of adverse effects is grounds for concern. Serotonin reuptake inhibitors might reduce repetitive behaviours, although findings are inconsistent (table 5). The effect of stimulants on co-occurring symptoms of attention-deficit hyperactivity disorder requires more study but is promising and has been recommended (table 5). Initial evidence suggests that atomoxetine also reduces co-occurring symptoms of attention-deficit hyperactivity disorder.

Table 5: Interventions by major model or agent

For version with full references, see appendix. ABA=applied behaviour analysis. ESDM=Early Start Denver Model. *Suggested by available systematic reviews and meta-analyses, with criteria directly following or similar to the Grading of Recommendations Assessment Development and Evaluation Working Group recommendation; different ratings for the same model or agent are from different reports.
recognition and interventions rely. Third, effective individualised educational and biomedical interventions for the whole lifespan need to be established. Fourth, key environmental factors that interact with the complex genetic architecture of autism need to be identified. Fifth, how autism affects individuals in different cultural contexts needs to be understood. Finally, environments should be made more autism friendly.

Contributors
M-CL did the initial literature search, summarised findings, and prepared the first draft of the report. MVL prepared figures. All authors contributed to the writing of the report.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgements
All authors are supported by the European Autism Interventions—A Multicentre Study for Developing New Medications (which receives support from the Innovative Medicines Initiative Joint Undertaking [grant agreement 115300], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme [FP7/2007-2013], European Federation of Pharmaceutical Industries and Associations companies, and Autism Speaks). M-CL is supported by Wolfson College (University of Cambridge, UK). MVL is supported by the British Academy and Jesus College (University of Cambridge, UK). SB-C is supported by the Wellcome Trust, the UK Medical Research Council, the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care for Cambridgeshire and Peterborough NHS Foundation Trust, the Autism Research Trust, the European Union ASC-Inclusion Project, and Target Autism Genome. We thank Wei-Tsuen Soong and Digby Tantam for valuable discussions.

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