The *Lancet* Commission on the future of care and clinical research in autism

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Executive summary

Affecting about 78 million people worldwide, autism is a condition of global importance because of its prevalence and the degree to which it can affect individuals and families. Autism awareness has grown monumentally in the past 20 years, yet most striking is that much more could be done to improve life outcomes for the highly heterogeneous group of people with autism. Such change will depend on investments in science focused on practical clinical issues, and on social and service systems that acknowledge the potential for change and growth as well as the varied, complex needs of the autistic individuals and their families whose lives could be changed with such an effort.

The *Lancet* Commission on the future of care and clinical research in autism aims to answer the question of what can be done in the next 5 years to address the current needs of autistic individuals and families worldwide. Autism is a neurodevelopmental disorder that typically begins to manifest in early childhood and affects social communication and behaviours throughout the life span. Autism and other neurodevelopmental disorders have seen a tremendous influx of interest from the scientific community in the past 60 years. Substantial progress has been made in many areas of basic and applied science, but the limits of the knowledge and understanding of autism are also very clear. For clinical purposes, reviews and guidelines have proliferated, although the data on which many recommendations are based are typically from short-term interventions that address acquisition of specific skills that are hoped—but not yet known with confidence—to contribute to long-term gains across development. However, large gaps around key questions remain, such as what interventions and support strategies are effective for whom and when, and which interventions lead to changes beyond their proximal outcomes. Underlying these outstanding questions is a deep scarcity of information about what are the active elements or mechanisms, behavioural or neurobiological, for change. These issues are particularly important because autism affects from toddlers to elders and is almost always accompanied by other developmental, behavioural, and mental health difficulties or conditions that have major implications for lifelong outcomes.

On top of these issues is the fact that autism affects individuals and families worldwide, most of whom are receiving no support outside of their own resources. If evidence-based approaches to support the lives of autistic children, adolescents, and adults who are living now are to be developed (in contrast to the fervent hopes for neurobiological approaches in the future), knowing what works for whom, when, and at what intensity is imperative, and will allow the design of systems that are cost-effective, affordable, and scalable across the globe. Such approaches are not possible on the basis of the currently existing data, but might become possible in the future.

In response to this challenge, our Commission proposes a novel, modified stepped care and personalised health model of intervention and assessment for individuals with autism and their families. One important necessity (but not always considered in such models) is that treatment and support takes into account the preferences, needs, and costs (financial and otherwise) to individuals and families at each step. These individual differences across autistic children, adolescents, adults, and their families are nested within communities, cultures, and social systems that must also be considered.

Key messages

- At least 78 million people worldwide have autism; the majority do not receive support from, or have access to, adequate health-care, education, and social care services
- Children and adults with autism can have happy and healthy lives, but urgent action is required to promote these outcomes
- Autism is heterogeneous and requires personalised, evidence-based assessments and interventions, accessible and affordable to every person, that can improve the lives of individuals and their families
- People with autism have complex needs; meeting these needs requires government coordination between health-care, education, finance, and social sectors across the life span, and active inclusion and participation of autistic people and their families
- A stepped care and personalised health approach to delivering services and monitoring effectiveness across time provides a framework for efficient and equitable distribution of resources to improve outcomes
- More information about the economic and personal consequences of autism is urgently needed to inform the case for government and societal investment, action, and support worldwide
- People with autism and those with other neurodevelopmental conditions have many similar needs; developing appropriate systems of care for people with autism will also improve outcomes for individuals with other neurodevelopmental conditions
- Valuing autism and neurodiversity benefits society as a whole
- Research that will result in immediate improvements in the lives of people with autism and their families should be prioritised

Key messages: actionable recommendations

- Although autism affects at least 78 million people worldwide, formal documentation of their existence is limited to a subset of countries. Formal documentation through governmental health-care, education, and social care systems for people with autism would be a first step in determining the needs and addressing the potential inequalities faced by these individuals.
- Autism is a complex but common neurodevelopmental disorder that requires personalised assessments and intervention strategies. A stepped care and personalised health model to assess and direct interventions can increase the effectiveness of approaches. Governments and health-care systems must recognise the need for integration across systems to support the needs of autistic individuals and their families across development.
- Autism is a neurodevelopmental disorder that changes with and affects development; a single assessment or a single treatment is never sufficient. Follow-up assessments and personalised treatment plans that focus on individual strengths, difficulties, and changes in contexts and expectations across the life span are needed.
- Interventions for autism and for co-occurring conditions should begin as soon as signs are noticed and then monitored with more comprehensive assessment once begun. No one should wait for months or years to start treatment because they are unable to find an appropriate assessment. However, within a reasonable period of time (depending on age and context), assessments do need to be supported and undertaken to identify personalised needs.
- Focused research strategies at the government or institutional level should be prioritised with an emphasis on clinical practice that can increase the understanding of what interventions work, for whom, when, how, with what general outcomes, and at what cost. National and international infrastructures should be developed to help such projects to move beyond single investigator-led (albeit multisite) studies to more integrated attempts that take into account individual differences within autism. Infrastructures should also support studies that build on each other and provide evidence for broader community implementation and effectiveness, rather than simply showing that an intervention is better than a waiting list or treatment as usual.
- Governments and services should monitor access to provision to ensure that underserved groups, including those who are minimally verbal, girls and women, minority ethnic groups, from socially disadvantaged backgrounds, or with severe co-occurring conditions, have equitable access to appropriate services.

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Using data from a large-scale epidemiological sample (generously shared with us by the Norwegian Institute of Public Health), we provide initial examples of how and why such a stepped care and personalised health approach could be applied to address both the core features of autism and co-occurring conditions.

Individuals with autism and other neurodevelopmental disorders are a valued part of society and represent a prototype of neurodiversity. At the same time, many individuals with autism have profound needs and are vulnerable to harm, marginalisation, and exclusion, and societal attitudes to difference, inclusion, and equity will affect their life experiences and outcomes. Autistic individuals and their families can show extraordinary strengths and persistence, patience, and perception that can change their development as well. Respect for this diversity and heterogeneity, as well as for the power of development and the possibility of change, is vital. Now is the time for optimism, with a focus on ways to make changes happen. It is a time for realism and for recognising the varied needs of autistic people, including those with severe intellectual disabilities and language impairments, and those with significant strengths in the same or other areas. It is also a time to acknowledge the scarcity of resources in low-income and middle-income countries and in some high-income countries, and to ensure that different underserved groups, such as those who are minimally verbal, women, minority ethnic individuals, and those with severe co-occurring conditions, are included. Societies in every part of the world have a duty of care to all people with autism and those who care for them, and investment in research and services needs to be targeted wisely to help them to reach better life outcomes and propel the change that makes this possible.

Because it is defined by the intersection of social communication and sensory, restricted, and repetitive behaviours and interests, autism is a relatively specific disorder. Yet, it is also one of many neurodevelopmental disorders, with which it can share many aspects. We believe that, at times, considering autism as a specific condition is important, and that at other times, recognition of the overlap with other neurodevelopmental disorders is more appropriate. In the context of individual, familial, cultural, and regional diversity, we propose that stepped, personalised models of intervention and services (based on focused research that tests them and their implementation) can change the lives of autistic individuals and those with other neurodevelopmental disorders throughout the world.

Introduction

This Commission brought together stakeholders in autism from six continents and a range of perspectives, including clinicians and other health-care providers, researchers, advocates, self-advocates, and parents to address the future of health care in autism. One decision made early on was to focus on recommendations that could be put into effect within the next 5 years, with the potential to have immediate and long-term effects on quality of life for autistic individuals and their families. Although numerous well tried interventions and treatments for autism exist, not enough is known about which treatments or services should be offered when, to whom, for how long, with what expected outcomes, and for what cost. These questions are outside the scope of most contemporary basic science or even translational research, which is currently often prioritised over more practical knowledge, leaving autistic individuals, families, and providers without evidence-based guidance.

The promise of basic science to positively affect clinical practice for autism and neurodevelopmental disorders remains distant for most people with autism. We support the ongoing need for basic scientific research, but clinical

practice cannot wait for the search for biomarkers and a clearer understanding of the genetics and neurobiology of autism that might lead to the development of biological first-line treatments, initially for highly specific subpopulations. We do not, in any way, wish to reject efforts in these areas, but we rather want to stress the need to complement them with different systematic strategies and goals that will yield immediate results. Similarly, in these unique times, the COVID-19 pandemic has presented a pressing need to directly address human behaviour and practical service provision (eg, social distancing and ensuring adequate protective equipment and hospital capacities), even as rapid advances in basic science have made a crucial contribution to reducing the impact of the virus. Even more so in autism, waiting for basic science to address the heterogeneity of potential causes and treatments of this complex condition without tackling the current real-life needs of individuals and families globally is not an option. We argue, in this Commission, that targeted research can change lives now by improving mental and physical health and strengthening support systems. Clinical science should not be considered second-class compared with fundamental biological research, which is simply unable to answer many of the questions that arise in considerations of human mental health and development.[1] Although autism is a neurobiological condition, the clinical challenges it raises for society and for a very heterogeneous group of individuals are predominantly not ones that are likely to be solved by biomedical solutions for most people in the near future. The focus of this Commission is on how to fill this gap between clinical challenges and solutions.

In addition, reflecting that social justice is a recurrent theme in the conceptualisation of ways forward, we advocate that the same quality of care should be expected for everyone, everywhere. Therefore, we discuss pertinent information from progress to date, even if it has occurred only in high-income countries (HICs), recognising the need to continue rigorous science and innovative clinical practice in HICs and in low-income and middle-income countries (LMICs). The responsibility of health-care and other service providers is to discern the most efficient, effective, and economical ways to support change anywhere and everywhere for autistic people and their families, and to help to put such methods into practice across diverse communities, cultures, and countries. For this reason, rather than following a traditional approach to descriptions of clinical practice that begin with screening, assessment, and diagnosis and then move on to interventions, we first emphasise the importance of valuing diversity and three other themes that are fundamental to a better understanding of the lives and needs of all autistic people: heterogeneity, potential for change, and systems of care. We then begin the discussion of clinical practice with a focus on interventions and support strategies (and gaps therein) that can make a real-life difference to those who live with autism today. The principle is that diagnoses and assessments should lead to information that contributes to decisions about interventions and services—issues that are subsequently discussed.

Recognising and valuing diversity

Autism is a complex neurodevelopmental condition. This complexity partly explains why services and research to date have been inadequate to achieve the positive outcomes that are possible for many individuals. The complexity of autism reflects several conceptually distinct aspects that are helpful to understanding the needs of each autistic individual. The term heterogeneity describes ways in which autism manifests differently between people who have the condition and within individuals across the life span. Potential for change, the recognition of which is not as widespread as it should be, is inherent in our use of the overarching term neurodevelopmental condition. Finally, individuals live within local and broader systems of care that include health, education, and social care services that they will or could access; and within familial, local, cultural, and global environments that differ widely in countries and continents worldwide. We believe that autism allows difference and neurodiversity to be appreciated and valued for the benefits they bring to society as a whole. We describe first how each of these three themes, alongside cultural and global differences and neurodiversity, are important for an understanding of any autistic individual and of the differences between individuals who have this diagnosis.

Autism—or autism spectrum disorder, the formal term used in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and WHO's International Classification of Diseases, 11th revision (ICD-11)—is a common, highly heritable, and heterogeneous neurodevelopmental disorder that can co-occur with other conditions.[2] Since the publication of Leo Kanner's first case series,[3] autism is diagnosed on the basis of observation and reported behaviour. The worldwide prevalence is estimated to be 1–2%, meaning that at least 78 million people in the world have autism.[4,5] We use the term autism because it is shorter and more acceptable to many autistic people than autism spectrum disorder.[6] This Commission also includes both identity-first language (ie, autistic person) and person-first language (ie, person with autism) to reflect the variability in the language preferences of the autism community. Although quality of life can improve, the impairments in social behaviour, understanding, and communication that characterise autism and that are accompanied by restricted, repetitive interests or unusual reactions to various environmental sensations have been repeatedly shown to result in lifelong difficulties that limit independence and community participation.[7] These difficulties often not only affect the individual with autism but also place extraordinary

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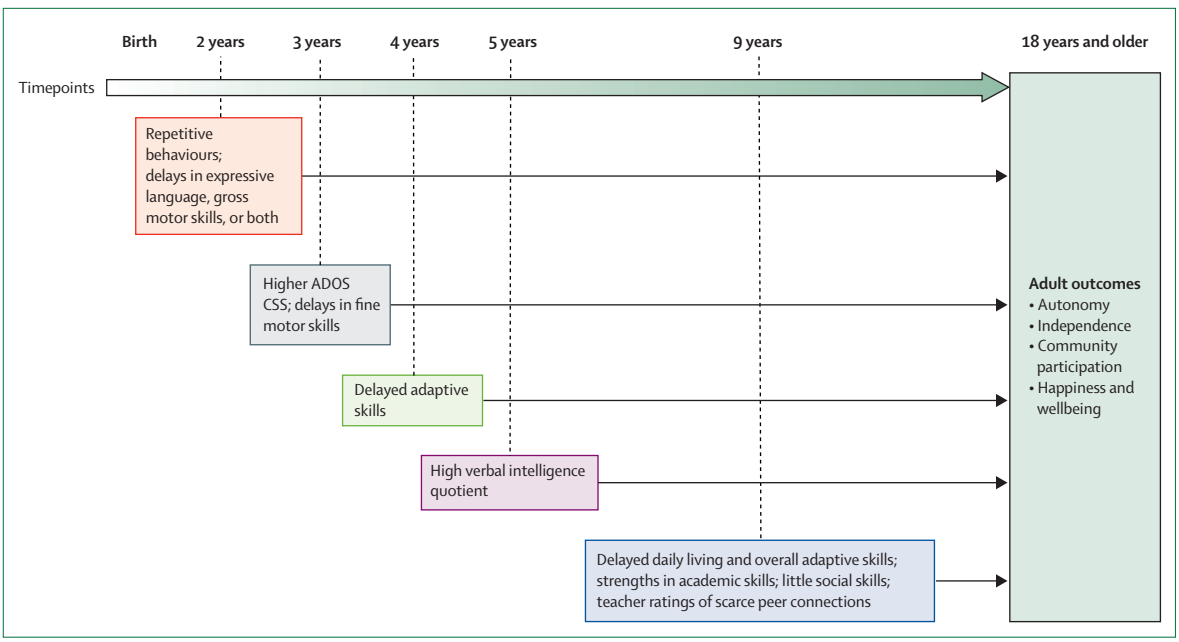

Figure 1: **Milestones listed at the age at which they become predictive of adult functioning**[7]
ADOS CSS=Autism Diagnostic Observation Schedule Calibrated Comparison Score.

demands on families.[8] Children as young as 2 years old can be diagnosed with autism, but many children and adults are not diagnosed until later in life, partly because signs and symptoms might not be clear, and partly because of insufficient recognition and understanding of autism and poor access to appropriate services. Some individuals with autism have average or above average intelligence and language abilities, are university-educated, in professional jobs, in a marriage or partnership, and have children. Others have a severe intellectual disability, little or no functional communication skills, few social relationships outside their immediate family, and require constant lifetime care.

About 50 years ago, research showed that autism is a neurobiological condition often, but not always, associated with intellectual disability and epilepsy.[9] Autism is caused by a combination of many different rare and common genetic variants, some of which can be associated with other neurodevelopmental or psychiatric disorders, and most of the population with autism to date does not yet have profiles with known genetic findings.[10] Although research into the neurobiology of autism is amassing intriguing findings, no reliable diagnostic biomarkers or psychopharmacological treatments for core features of autism exist yet. However, autism includes many diverse behavioural aspects, emerging during different points of development, that predict eventual independence and quality of life. Figure 1 shows when, in development, different factors became predictive of adult outcomes defined by objective measures of work and activities, independent living, and social relationships in one longitudinal study with participants aged 2–26 years.[7,11] These factors and the interventions and social systems that can support them are also covered in this Commission.

Cross-cutting themes

Heterogeneity

The presentation of autism changes over time, requiring different interventions across the life span; from the point of first concern to later adulthood. Heterogeneity refers to the longstanding observation that individual differences in the aetiology, clinical presentation, and care needs of autism vary over time. Not recognising heterogeneity in autism can adversely affect public awareness, assessment and diagnosis, clinical management, access to services, public policy, and equity.

Heterogeneity in diagnostic classification systems

Over time, psychiatric diagnostic systems have tried to capture this heterogeneity. The term pervasive developmental disorder was introduced in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders and in the 9th revision of the International Classification of Diseases, followed by the designation of autism spectrum disorder in DSM-5 and in ICD-11.[12,13] The word pervasive highlights that autism affects more than one developmental domain, and the term developmental recognises that autism is a lifelong condition appearing in early childhood, although its manifestations change across the life span. The idea of spectrum acknowledges the breadth of individuals who qualify for the diagnosis, embracing both dimensional (from less to more severe) and kaleidoscopic (the

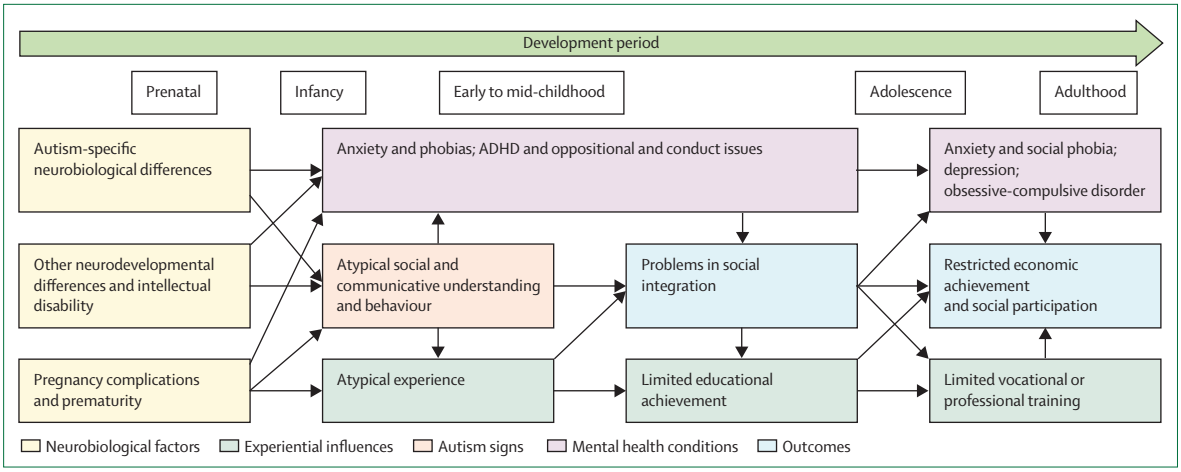

Figure 2: **Neurobiological and experiential influences on signs of autism, mental health, and life outcomes across development**
ADHD=attention-deficit hyperactivity disorder.

so-called colour spectrum) variation in diverse profiles of strengths and needs across individuals.

Autism as one of many neurodevelopmental disorders

Autism belongs to a broader category of neurodevelopmental disorders, a group of overlapping conditions characterised by an early onset of difficulties in developmental domains, which result in functional impairments.[12,13] Neurodevelopmental difficulties range from domain-specific to pervasive, and across motor, language, learning, adaptive, and social communication skills, and regulation of attention, activity, impulses, and emotions. Diagnostic subgroups such as autism, attention-deficit hyperactivity disorder, and intellectual disability are distinguished from each other on the basis of the profile of strengths and difficulties across these neurodevelopmental dimensions, although much neurobiological and phenotypic overlap is evident.[14] An individual's functioning can vary widely within and across these dimensions, and profiles of strengths and weaknesses can change with age, contextual demands, and interventions. Autistic individuals require different (and sometimes adapted) interventions that overlap with those for individuals with other neurodevelopmental disorders (eg, communication-oriented parent-mediated interventions for toddlers with autism and language delay; stimulant medication for a child with autism and attention-deficit hyperactivity disorder; or modified cognitive behaviour therapy for an adolescent with autism and anxiety).

Co-occurring conditions

All neurodevelopmental disorders, including autism, can and often do co-occur with physiological conditions (eg, epilepsy and gastrointestinal disorders),[15] mental health disorders (eg, anxiety, depression, and attention-deficit hyperactivity disorder),[16] and a range of challenging behaviours (eg, self-injury, aggression, and sleep difficulties). The presence of co-occurring conditions contributes to the enormous heterogeneity in individual presentation and can substantially affect daily functioning, which in turn leads to different needs for support and services. However, many lives can be greatly improved by appropriate, individualised interventions and treatment. Some of these co-occurring conditions, such as language delay or seizures, are more common in individuals with autism and an intellectual disability.[17] Other problems, such as aggression, oppositionality, anxiety, and emotional dysregulation, present across diagnostic entities.[18]

Heterogeneity is also evident in the number, severity, and nature of co-occurring conditions. For example, language delay can fall within a wide range, from mild to severe. Limitations in receptive or expressive language unquestionably add to the social communication impairments in children. Delays in language are often parents' greatest initial concerns and later continue to affect many adults with autism, showing associations with impaired daily living skills and with disruptive behaviours across the life span.[19] For other autistic individuals, structural and functional language skills are intact, but difficulties with pragmatics (ie, the social use of language) become apparent as they age, and can interfere with communication with peers.[20] Similarly, as shown in figure 2, people with autism vary in whether and to what degree they have other neurodevelopmental disorders, such as attention-deficit hyperactivity disorder or an intellectual disability, as well as mental health conditions such as anxiety. As discussed later, these differences interact, and their effect can be compounded across the development period, causing even more disruption over time.

Cultural heterogeneity

Heterogeneity is also reflected in the diversity within family units, within cultures, and across countries.

Panel 1: **Person portraits illustrating the variability in presentation, strengths, and needs of autistic people**

Adir

Adir is an 18-year-old, non-verbal man with profound autism, intellectual disability, and epilepsy who lives in a small town in the Midlands, UK, in a close-knit family that immigrated from Yemen. He was diagnosed with autism at the age of 4 years and his parents enrolled him in a preschool that specialised in supporting those with severe needs, with the hope that he could eventually join a mainstream class. At preschool, Adir received behavioural interventions, speech and language therapy, and participated in a social skills group. He took medication to manage his seizures. Later, he was given medication because his behaviour could become challenging when he was upset or agitated. By age 16 years, he was over 180 cm tall, weighed 125 kg, and his behaviour was challenging for others to manage. He was not fully toilet-trained and had frequent incidents, especially when frustrated. Adir's family could not find affordable care that met his needs, so his mother quit her job to look after him. During outbursts, he became physically aggressive towards himself and others, creating a safety risk for him and his caregivers. Several efforts at supported employment proved unsuitable and resulted in aggressive outbursts and him being dismissed. Much against their original plans to care for him at home, his parents are currently considering residential placement, where he will receive constant care.

Franco

Neither Franco's parents—White, conservative, working-class people living in a small town in Kansas, mid-west USA—nor his paediatrician observed any obvious early signs of autism, and Franco reached most of his developmental milestones on time. However, his parents reported that he was a very fussy baby and did not want to be cuddled or held. Around the age of 18 months, he began wandering off and interacting with his parents less frequently, and stopped looking at their faces and forming new words. At the time, his parents had just had a baby girl and the paediatrician attributed his altered behaviour to this change at home. Franco spent most days walking in circles, trying to get outdoors, and sorting his toys by size and colour. He insisted on eating only foods that were white and would start biting his own arm and pinching his caregiver if anyone tried to put new foods on his plate. Eventually his parents had him assessed and he received a formal autism diagnosis at the age of 3 years. For the next 2 years, he received general early intervention services at home 2–3 times a week. By age 5 years, he was making enough progress to be enrolled in a mainstream kindergarten with a full-time aide. At school, he enjoyed music and was well mannered, but spent most of his time by himself, playing with toys alone or in parallel with other children. Franco had little awareness of danger and would wander off away from the family home. His parents added child-proof locks to all their gates and fences, but with age he became more adept at climbing them. However, he was starting to show reciprocal smiles and his teachers and parents were pleased with his progress. He had a very strong and repetitive interest in being pushed on the swings at school and loved having his aide push him constantly at breaks. In fact, this was the one activity he clearly enjoyed and after school he would constantly go to the door asking his mother to take him to the school playground, where he said the good swings were. One afternoon, at the age of 7 years, he wandered away from his home and nearly drowned in a nearby pond, but was rescued by a neighbour. His parents purchased an electronic tagging device and asked his school to ensure an aide is with him at all times when he is out of class, but the school does not have the capacity for this monitoring to continue indefinitely.

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Families, which differ in composition, beliefs, and priorities, are the primary source of support for most autistic children and adults. Moreover, cultures—even within the same region—differ not only in languages, beliefs, and priorities, but also in their access to and use of resources.[21] Research and clinical practice should pay careful attention to these differences and to how scalable and sustainable models of care can be implemented for autistic individuals worldwide. Examples of autistic individuals in different families in different cultures are illustrated in panel 1.

Autism and neurodiversity

Neurodiversity refers to the natural variability within human brains and minds.[22] Recognition of human diversity helps us to better understand autistic individuals in ways that have far-reaching effects. These effects cut across issues as broad as human rights, equity and social justice, respect for difference, and the need to take individual and family preferences into account. Valuing neurodiversity has the potential to create stronger and wiser communities and positive social values.

The concept of neurodiversity is also the basis of an international civil rights movement that arose primarily as a response to the marginalisation of autistic people. The neurodiversity movement considers autism as a neurological difference rather than a disorder and is sometimes associated with opposition to efforts to find a cause or cure.[23] This movement also includes those with other neurodevelopmental conditions, such as attention-deficit hyperactivity disorder, bipolar disorder, dyslexia, and epilepsy, as well as those with differences in gender identity.[22–24] Individuals prefer to self-identify as a member of the neurodiverse community rather than with psychiatric and medical diagnoses that highlight impairment and disorder.[23] Some emphasise that the term neurodiversity includes all forms of neuro-developmental diversity, including those with the highest needs.[22] Others within and outside the neurodiversity community stress that the reality of disability for some people and some families should not be underestimated.[25] Concerns about how access to services would be affected if autism were regarded as natural variation (that does not need intervention) also exist.

Not all autistic people and stakeholders identify with the neurodiversity movement.[26] Controversy exists about how those with the highest support needs, including those with substantial intellectual disabilities and limited functional communication and who are unable to advocate for themselves (ie, those with what is called profound autism, described in further detail in panel 2), are represented by a non-medical model. Many autistic people struggle with their difficulties and feel excluded from society; some might seek a cure whereas others embrace autism as part of their identity, thankful for some aspects of who they are despite the challenges that come with difference; most are somewhere in the middle.[26] The ambition for full participation of autistic individuals in debates on issues ranging from service provision to setting research priorities is to ensure all views are represented, including those of individuals who cannot speak for themselves and who might require that a parent

or another close contact speak for them. A sometimes overlooked aspect in ongoing debates about neurodiversity in the autism community is that experiences, views, and attitudes vary across stakeholder groups. In fact, holding a plurality of views at one time is possible. Another consideration for the Commission is that the current debates on medical versus social models of disability can be quite different across social, cultural, and global communities.

From the neurodiversity perspective, diversity enriches and is a strength of societies, but requires adjustments from all sides. Even for autistic people who do not need much support, daily life situations can be exhausting, not only because of the excess of sensory stimuli but also because of a constant struggle to decipher social cues, to communicate, and to deal with unexpected changes. Accommodations in the environment can make some disabilities become differences and even advantages (eg, the Roim Rachok Programme[30]). Although individual factors contribute, and acceptance and accommodations do not always eliminate impairments, a substantial proportion of the risk of poor outcomes is likely to be socially produced.[25] All developmental disorders induce society to reflect on the degree to which those with the highest levels of need are supported, on including people who are different, and on making an effort to build communities and institutions that function well for all citizens.

Potential for change

Autism was initially believed to be an intractable neurodevelopmental disorder with few effective treatment options, but a more optimistic view is emerging. Systematic reviews and meta-analyses of intervention studies for young children with autism published over the past 10 years have identified evidence-based psychosocial interventions that, when done in high-quality, university-led trials in HICs, resulted in change that could mitigate the influence of autism on development for some people.[31,32] Furthermore, longitudinal research suggests that some individuals can compensate for difficulties associated with autism in ways that lead to very positive outcomes.[33] Although not all people will change to the same degree, people with profound autism can have lives with social contacts, meaningful activity, and independence in some skills.[7] Consequently, the question is no longer whether change and improvement are possible for people with autism, but rather what factors enable people with autism to live positive, fulfilling lives, what are the key elements of effective interventions, and what are the micro-environmental and macro-environmental barriers to change for autistic individuals.

Evidence for early intervention

In many cases, autism and other neurodevelopmental conditions are apparent in the first 3 years of life. Accordingly, much intervention research has focused on reducing the impact of autism on early development. Developmental and behavioural intervention trials with young children are methodologically challenging[34] and a strong evidence base requires an accumulation of data from multiple trials. Nevertheless, replicable results across studies indicate that early intervention can have positive effects on social communication, language, cognition, and adaptive behaviour in young children with autism.[31,32]

Historically, early intervention started with instructor-led, high-intensity applied behaviour analysis and discrete trial training that relied on external rewards to motivate learning and cognition[35] and reduce problematic behaviours. This approach, as originally implemented, has little support from well designed randomised controlled trials. However, it has been modified over the past few decades to be more naturalistic and developmentally appropriate, often with

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Sofía

Sofía lives in Argentina with her husband and son. She has a PhD in renaissance art history. She is fluent in three languages, reads prolifically, and has an intelligence quotient of over 125. During college and graduate school, she spent most of her time at the library or at home, reading. Sofía had a few friends that were part of study groups she participated in. She failed her oral examinations once, before passing on the second try. Before she was diagnosed with autism, she saw her problems as mostly consisting of restlessness, problems concentrating, and severe sensory issues that caused her physical pain. She also had problems on tasks that required her to think abstractly, but she was able to quickly recite different trends in art, artists, styles, paintings, and the evolution of painting styles across time periods. Since receiving her PhD, she has had difficulty obtaining and keeping a job because required meetings with her colleagues caused her extreme anxiety. She was dismissed from three jobs and was frustrated because she did not understand why. Finally, at the age of 30, when her 18-month-old son's behaviours became overwhelming, both mother and child were diagnosed with autism by her child's behavioural paediatrician. Sofía now works from home part-time, as an editor of an art journal. Her employer allows her to work flexible hours and she mostly interacts with her colleagues via the internet.

Samir

Samir is a 10-year-old boy living in a rural Indian village. His parents had a difficult relationship and his father, a farmer, was his main caregiver. Samir had always been a child who did not understand rules and his father worried about him since he was young. When Samir was placed in the village school, the teachers raised concerns about him not learning anything and wanting to be on his own. However, his father felt he would grow out of this behaviour and was reassured by relatives that boys often talk late. A few months later, when Samir did not develop like other children, his father took him to a traditional doctor, who gave him complementary medicines and a charm to tie on Samir's wrist, which had little effect except their cost to the family. Finally, on a schoolteacher's advice, Samir was taken to a child development centre, where he was given a diagnosis of autism at the age of 6 years. He was advised to return for speech and language therapy. However, the two bus rides each way were not sustainable, particularly because of the loss of daily wages and the absence of any visible change in Samir after 2 weeks of attending the sessions. His father negotiated with his village school that Samir would attend for part of the day with his peers. He has realised that his son might not finish school, but is working towards Samir being independent with his self-care and able to help with the cattle when he grows up.

Panel 2: Profound autism

With the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the 11th revision of the International Classification of Diseases (ICD-11), autism was considered a single spectrum disorder defined on the basis of two core domains: impaired social communication and repetitive, restricted, and sensory behaviours. These criteria, which can be met through history or observation, must be accompanied by a current functional impairment. The tremendous heterogeneity of autism is acknowledged in both diagnostic systems through specifiers that include intellectual and language levels, the presence of co-occurring mental health conditions that can vary in severity, and genetic, neurological, and other medical conditions (figure 2). However, the DSM-5 clinical specifiers and the detailed subcategories in ICD-11 (with and without a disorder of intellectual development and functional language impairment) are not easily or consistently used in practice or in research.

Until the 1990s, most children and adults diagnosed with autism also had intellectual disabilities. However, reflecting the broadening conceptualisations of autism as a spectrum disorder, prevalence studies in high-income countries within the past 5 years have shown that most children diagnosed with autism do not have a co-occurring intellectual disability.[5] Despite genetic studies that have the greatest implications for more severely affected individuals, many other areas of research have focused on less severely affected autistic people. The media have also focused much of their attention on the growing proportion of autistic people without an intellectual disability. Children and adults with autism and severe and profound intellectual disability have vastly different educational and long-term care needs that cannot be properly planned for if these individuals are not identified. However, when children receive early diagnoses of autism (for example, at the age of 2 years), those who will have substantial delays (resulting in intellectual disabilities) are not clearly distinguishable from those who will develop fluent speech and potentially function more independently.[27] Therefore, although some of these children will later be diagnosed with an intellectual disability, not all are distinguished within administrative systems and many families continue to identify them as having autism. Nevertheless, they are minimally verbal or non-verbal; most often, they are not able to advocate for themselves and rely on family members to communicate their needs to policy makers, the media, medical professionals, and the scientific community. They and their families are at risk of being marginalised by a focus on more able individuals. Many of these individuals need constant monitoring, even as adults, because of safety concerns including being at a higher risk of abuse and maltreatment due to their need for help with daily living skills and personal care.

For these reasons, our Commission proposes that the designation of profound autism be adopted as an administrative term to apply to children and adults with autism who have, or are likely to have as adults, the following functional needs: requiring 24 h access to an adult who can care for them if concerns arise, being unable to be left completely alone in a residence, and not being able to take care of basic daily adaptive needs. In most cases, these needs will be associated with a substantial intellectual disability (eg, an intelligence quotient below 50), very limited language (eg, limited ability to communicate to a stranger using comprehensible sentences), or both. To represent the intensity of needs in a standard manner, profound autism is thus defined not by autistic features but by intellectual or language disability. The word profound was selected because it is less commonly used colloquially than severe, and the term low-functioning is disliked by many. Profound autism can be associated with complex co-occurring difficulties, including self-injury, aggression, and epilepsy, but is not defined by these factors. Profound autism is not included in the recent revisions of the diagnostic systems (and we are proposing it as an administrative term, not as a formal nosological diagnostic entity); rather, it extends, amplifies, and wraps into a more useable term the additional specifiers included in both systems—namely, the presence of intellectual and language impairment in addition to a diagnosis of autism in the Diagnostic and Statistical Manual of Mental Disorders, and "autism spectrum disorder with disorder of intellectual development and with absence of functional language" (code 6A02.5) in the International Classification of Diseases. Someone who has some of these characteristics but is functioning well in a supportive setting might choose not to use this term, but we offer it for the benefit of autistic people, families, and clinicians and for the purposes of advocacy and description. We hope that its introduction will spur both the clinical and research global communities to prioritise the needs of this vulnerable and underserved group of autistic individuals.

The term profound autism is not appropriate for young children. It might begin to be useful, with the consent and participation of families, from early school age (eg, from the age of 8 years) for children with autism and severe to profound intellectual disability or minimal language, given the evidence that these factors are not likely to change. The term might be most helpful in adolescence and adulthood. It is not intended to describe other severe difficulties related to autism that might apply to individuals with extraordinary life circumstances, trauma, family conflict, scarcity of resources, or those with co-occurring mental health problems. We acknowledge that the word profound can have different connotations and other terms might be more appropriate in other languages. For example, in Spanish, the words *severo* or *grave* might be more appropriate because of different meanings of *profundo* (ie, deep).

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As part of this Commission, we analysed data from three samples: first, 8-year-olds in the Norwegian Mother, Father and Child Cohort (MoBa) study,[28] a population-based pregnancy cohort study led by the Norwegian Institute of Public Health; second, 12-year-olds to 23-year-olds in the Special Needs and Autism Project, or SNAP,[29] a British population-based study that identified children with autism and special educational needs; and third, the Early Diagnosis Study, or EDX, a US-based longitudinal study (figure 1) that followed up children referred at the age of 2 years up to the age of 30 years.[7] We used the criteria of either verbal, non-verbal, or full-scale intelligence quotient at or below 50, or minimally verbal status as defined by Module 1 of the Autism Diagnostic Observation Schedule. For data from the MoBa study, we used the criterion of mothers replying negatively to the question of whether their child was able to talk using short phrases or sentences. The proportion meeting the profound autism criteria was 18% (95% CI 12–24%) in MoBa; 23% (13–28%) in SNAP; and 48% (37–58%) in EDX. The proportion of female individuals was higher among those meeting profound autism criteria than in those not meeting the criteria, although confidence ranges overlapped (MoBa: 45% [95% CI 28–63%] *vs* 17% [12–24%]; SNAP: 19% [5–42%] *vs* 13% [6–21%]; and EDX: 23% [10–36%] *vs* 4% [0–11%]).

At the age of 25 years, none of the individuals in the EDX sample meeting profound autism criteria were living independently or had full-time paid employment (although some had supported employment).[7] Of the 39 (48%) of 82 adults who met these criteria at the age of 25 years, 34 (86%) of 39 met the criteria for profound autism at the age of 5 years and 36 (92%) at the age of 9 years. Only two individuals moved out of the profound autism category between the ages of 9 years and 18 years, as a result of improvements in language level and intelligence quotient to above 50. These data are specific to this cohort, defined by their early identification at a young age. Therefore, although they are not representative of current prevalence rates, the findings support the stability and validity of the concept of profound autism. In the SNAP sample, of the 18 adolescents identified with profound autism at the age of 12 years and who were reassessed at the age of 23 years, 15 (83%) continued to meet the criteria, of which nine (weighted 79%) lived in specialist residential accommodation and six (weighted 18%) lived with their family with high levels of support; again supporting the stability and validity of the concept in terms of high care and support needs.

The three samples reported here used different methods of sampling and recruitment. In addition, there were differences in the methods used to assess intellectual disability, language capabilities, and signs of autism (ranging from direct in-person evaluations to questionnaires, patient registries, and electronic health records), and in length of follow-up. They range from an early clinic-referred sample from nearly 30 years ago (EDX) to two population designs that involved screening and follow-up of current cases of children with identified special needs (SNAP) and a nationwide cohort with screening and diagnostic assessment in combination with linkage to registry diagnoses and review of electronic health records (MoBa). These new data on profound autism lay the groundwork for an important area of future clinical research and practice.

lower-intensity delivery and greater emphasis on the child as an active partner in communication.[36] In addition, other studies have focused on teaching parents to support the child in the development of early communication and social interaction.[37,38] There is emerging evidence that such programmes might be effective in LMICs, such as India and Pakistan.[39] On the basis of a transactional model whereby behavioural signs signify the presence of autism and substantially affect subsequent development, early impaired social communication behaviours such as joint attention, symbolic play, or imitation are often targeted by interventions.[40] Thus, an intervention can teach particular skills that have immediate value (eg, how to ask for help or how to say no) and support pivotal skills (eg, joint attention and imitation) that contribute to change in processes that have cascading developmental effects on language and cognition.[41]

Why and when is change possible

The possibility of change follows from the hypothesis that, because of the plasticity of neurodevelopment, enrichment and modification of the environment and experience through interventions can have an important influence on behavioural and neurodevelopmental processes over time (figure 3).[41] Furthermore, research has shown that different aspects of development emerge and might perhaps be more easily modified at different times (figure 1).[11] Learning by enrichment of experience or modification of the environment to better address individual needs can have profound effects on typical and atypical neurodevelopment beyond childhood.[42,43] These effects might be especially relevant for higher cognitive and executive functions associated with frontal cortical development,[44] which have a role in an individual's capacity to compensate for some of the difficulties associated with autism.[45] Evidence corroborates the positive effect of interventions on enhancing cognitive and emotional self-regulation and improving compensatory skills in children with autism;[46] other evidence shows reduction of social difficulties in school-aged children (generally meaning children aged 6–18 years) and young adults.[47] Thus, throughout development, interventions can result both in reduction of manifestations and in enhancement of compensatory processes and quality of life in people with autism, from mid-childhood to adulthood. As for other chronic and

enduring health conditions, one-off, time-limited interventions will not be sufficient to enable long-term change for most people with autism. Instead, a developmentally sequenced series of staged and personalised interventions will be required for each individual, according to their developmental stage, profile of strengths and needs, and co-occurring conditions.[48]

Awareness that change is possible is crucial to the development, study, and incorporation of effective approaches into health care and education programmes to support autistic people and their families across the life span. These interventions include appropriate, enhanced-education programmes in schools and higher education settings, and community and clinic-based programmes that support peer interactions, leisure and social activities, and adaptive skills, and that treat co-occurring conditions such as anxiety or depression.[43] Beyond the development and documentation of the efficacy and effectiveness of these programmes, issues related to how, when, and who implements them must also be directly addressed to determine cost-effectiveness and feasibility, both financially and in terms of burden on the individual, family, and community.[49]

Systems of care

The autistic person's identity as a service user

We define system of care loosely so as to include the set of health, education, social care, employment, financial, and safety net services, including informal networks or relationships, that families and autistic people potentially have access to in a given community. This definition includes both general systems of health and education and systems, programmes, or benefits targeted at people with disabilities or special needs. Changing systems of care can improve outcomes for many more autistic people than solely focusing on individuals.

A defining feature of the lifetime of some people with autism living in HICs is engagement with service systems providing health and therapeutic interventions, material support, health insurance, education and training, community support, and direct care. Some individuals and families have intense involvement with services at one time and much less, or none, later; others have never interacted with services much, or at all. Receiving an autism diagnosis can be a doorway into a social role as a potential lifelong service user, augmented by help and support from family members, neighbours, and the community. Entry into, and use of, services from this perspective becomes more than a set of discrete events that happen to an individual. Service use for many people with autism and their family members can become a key element that has a broad influence on the course, social identity, and meaning of their lives. However, in contrast to the experience of families with the most support in HICs, most people with autism in LMICs and many in HICs live in communities with little to no dedicated infrastructure for people with developmental disabilities or special health care needs,

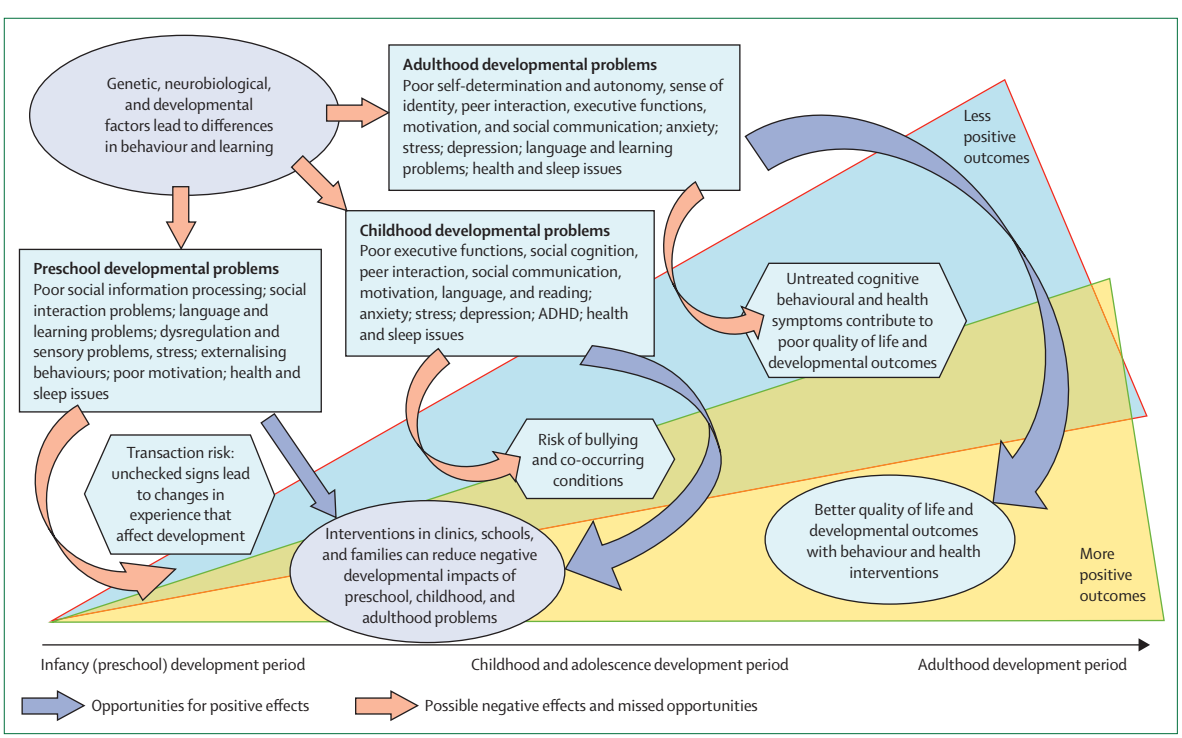

Figure 3: **Influences on the path of typical development**
ADHD=attention-deficit hyperactivity disorder.

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resulting in families being left to manage on their own.[50,51] Many families in both LMICs and HICs assume primary caregiver roles and create their own informal systems of care involving nuclear and extended family and community groups, such as neighbours or church members.[51] Figure 4 shows the potential effect of differing levels of service, formal recognition of autism, active support, and community adaptation on the outcomes and functioning of the heterogeneous population of autistic individuals.

As discussed throughout this Commission, the needs of individual autistic people and their families are heterogeneous and evolve over the life course. No single system of care delivers services across all domains or life stages. Many systems, such as special education and paediatric care, end at a particular age. Other forms of social care might not be established in many regions and cultural contexts.[51] Care is sought from multiple sectors and providers, with integration, coordination, and transition of care being major lifelong challenges for both families and providers.

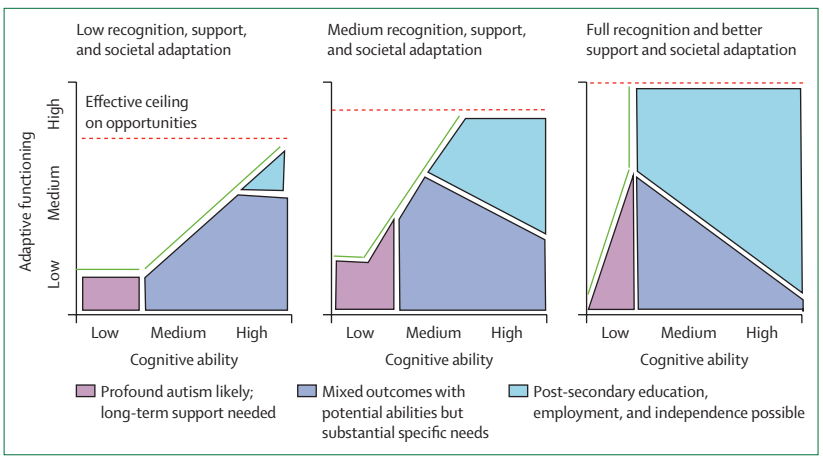


Figure 4: **Societal response and services can optimise outcomes for all people with autism**
The green line indicates the hypothetical degree to which the environment supports the adaptive potential of autistic people with different cognitive abilities.

Fit between individual needs and service organisation

Most community services are delivered through systems originally designed to meet the needs of other populations. For instance, in HICs, many systems of services for people with autism and other neurodevelopmental disorders began in the mid-20th century as systems of care for people with intellectual disabilities. These legacy systems often use intelligence quotients thresholds to establish eligibility, which can exclude autistic individuals without marked developmental delays. Community mental health systems might not be sufficiently equipped to assist people with both mental health issues and autism, which again leaves people with autism (with and without intellectual disabilities) deprived of support from existing systems of care.[52] Even in contexts with strong legislative frameworks, where it is against the law for mental health services to discriminate against people with autism (eg, in the UK), people can still find challenges in accessing adequate support;[53] hence the need for patient navigation programmes—a well known concept in other areas of medicine, including primary care, under which explicit support options exist for patients requiring guidance in moving through health-care (and social service) systems.[54]

System-level solutions

System-level challenges require system-level solutions, in addition to individualised care. This Commission recommends a blended approach to systems improvement that integrates evidence-based treatment practices into care systems along with improvement science (which identifies, implements, evaluates, and disseminates strategies to drive incremental, data-driven improvements in system performance).[55] Improvement science methods, including implementation, are widely used in school,[56] community,[57] and health-care administration,[58] but have not yet had much effect on care systems for people with developmental disabilities. The triple aim of such methods is to simultaneously yield improvements in patient-perceived quality, population health, and care costs per capita.[59] For example, if criteria for entering into early intervention were changed from requiring an established diagnosis to possible or probable autism (while undergoing further assessment), earlier targeted intervention could begin for a greater number of children with autism and other neurodevelopmental disorders. By contrast, in some countries, a diagnosis of autism might lead to exclusion from mental health services, which restricts eligibility for psychiatric and psychosocial services (panel 3).

The importance of transitions

Although primarily relevant in countries and contexts where adequate services exist, the theme of transition, defined as changes in contexts (eg, entering or leaving school) or service eligibility (eg, becoming a legal adult), is prominent in the life-course framework. Transitions can also be crucial starting points for the development of programmes in regions with few resources. Importantly to the concept of potential for change in skills across the life span, transitions intersect with the theme of service experiences in two major ways. Service transitions occur when the status of people changes from non-eligible to eligible, or when people are transferred from one system of care to another. Service experiences during pivotal developmental periods might exert an especially strong influence on subsequent life outcomes,[64] establishing a foundation for continued achievement and healthy development. Several models exist for handling the transition from paediatric to adult health care, but issues of availability and access to quality care within communities persist.[65] For example, poor knowledge regarding the health care of young autistic adults among

Panel 3: Policy and practice in diverse settings

Policy innovations can affect the performance of support systems and autistic individuals, both positively and negatively, often with a focus on access to care. For example, although no autism-specific policies exist in South Africa, there is a National Early Childhood Policy that can allow access to early intervention in the preschool years (generally meaning before the age of 6 years); yet the corresponding services are managed by a single government agency with age-limited jurisdiction.[60] In Argentina, a National Autism Law (2014) complements a National Disability Law (2019) that obliges all health agencies to provide better access to primary care and diagnosis, and also raises the need for a comprehensive and interdisciplinary approach, training of health professionals, and more research. Peru has a similar law and a National Plan for People with Autism. In India, autism was initially excluded from the Persons with Disabilities Act (1995), but was recognised in the National Trust Act (1999) after persistent campaigning by parents and is now represented in the Rights for Persons With Disabilities Act (2016). However, the struggle for certification continued until 2015, at which point autistic children only received certification based on their intelligence quotient. Only in 2016 was autism certified via nationally designed and validated tools, although implementation challenges continue as parents struggle to get certificates. In the USA, the passing of autism insurance mandate laws broadened access to autism-specific interventions and shifted some costs from families to insurers.[61] Regional changes in rules also resulted in improved access to early intervention in some states and reduced racial disparities in others.[62] In countries with universal health care systems, such as the UK, national guidance (eg, provided by the National Institute for Health Care and Excellence) and online resources assist in the development and implementation of quality standards and allow for comparison of service performance. National charities encourage families to refer to these guidelines and hold providers to account.

Having a universal health-care system does not always assure access to care. For example, in Canada, early intervention for autism is not covered under universal medical insurance and eligibility for public funding varies by province, deeply hindering the implementation of national guidelines. In Australia, the Helping Children with Autism initiative (2008) led to improvements in available early intervention for children aged up to 6 years. With the introduction of the National Disability Insurance Scheme (2016), intervention and functional support became available for people with disabilities, including autism, across the life span. However, of note, the roll-out of this ambitious scheme has been marked by flaws in implementation and controversy and inequities in access.[63]

primary care providers, especially in rural or low resource settings, threatens their long-term health outcomes.[65]

Remote technology is one potential solution to empower and strengthen community-based health care for individuals with autism across the life span. Adaptation of the Extension for Community Healthcare Outcomes model enabled knowledge transfer from centres of excellence to primary care providers about the care of transition-aged individuals with autism, although it did not change providers' behaviour.[66] The Extension for Community Healthcare Outcomes model has also been used to promote best primary care practices by connecting autism specialists with primary care providers in remote areas of the world.[67]

Major issues in clinical practice and research

Intervention

With increased funding for research and a 30 times increase in the number of papers published, an extraordinary amount of information about autism has accumulated in the past 50 years.[68] We chose to start this section on clinical practice by focusing on interventions and services known to effect change and on the kinds of change that might be expected. We propose that information about the effectiveness of various interventions has an important potential to guide the diagnostic assessment, which is not often done. In addition, knowledge about evidence-based interventions and their documented outcomes can help to identify targets for monitoring and review, which would improve the usefulness of assessments across the heterogeneity of autism and provide better information for individuals and systems about what interventions have the greatest potential to yield useful and cost-effective changes. We hope this discussion will result in readers considering more seriously how the results of assessments and diagnoses might be used to help individuals, and what the outcome of such a process should be—moving beyond the notion of an assessment as merely a diagnostic label.

In HICs, most children with autism are in school and many receive some form of preschool services.[69] Evidence supports interventions focused on specific needs, including the development of early social communication and language abilities,[31] social skills,[47] or co-occurring conditions, such as hyperactivity, disruptive behaviour, or anxiety,[70,71] with a growing, although still scarce, number of independent replications.[72] Nevertheless, almost no comparisons across approaches exist.[73,74] Outside HICs, many children and adults receive little support beyond the efforts of their families.[50,75] Even in HICs, once children begin attending school, most of the help they receive comes from schools, where approaches vary from skilled to minimal.[76] After secondary school, even in HICs, there is a services and treatment gap in which many families and autistic individuals find themselves on their own,[64] and this gap is the constant reality all the way across development for most autistic people in LMICs.

Compared with the 1970s and 1980s, more children with autism in HICs are now gaining academic skills and participating in higher education,[77] and a greater proportion of adults are living independent lives.[78] Nevertheless, those with the most positive outcomes remain a minority.[33] Because more people with average to above average cognitive ability receive diagnoses of autism in HICs now than 50 years ago, whether improvements in some outcomes are due to higher abilities in more recently diagnosed cohorts or to improved interventions and services is unknown. Moreover, although measuring trends over time is difficult, objective measures of quality of life for autistic adults have improved only minimally.[79] The importance of subjective factors, such as wellbeing and mental health, is becoming increasingly recognised and requires more research.[7] There is much evidence that mental health,

as well as physical health, can be challenging for a substantial proportion of autistic adults.[15,16] Therefore, an urgent need exists for effective interventions and services worldwide and across the autism spectrum.

A novel stepped care and personalised health model for interventions in autism

Our goal is to propose approaches to clinical practice, including clinically oriented research designs, that can have real, immediate, and long-lasting effects on the lives of children and adults with autism and their families. We outline a novel, adapted, precision health-integrated, stepped care model for intervention, which includes aspects of personalised medicine approaches and recognises the wide range of strengths, needs, preferences, and circumstances of autistic people and their families worldwide. Our stepped care and personalised health model takes the heterogeneity of autism into account by recognising that the profile of strengths and needs of each autistic individual and their family should determine the intervention and support priorities, but also that these can change over time—and in a stepped manner—with development and as interventions produce effects. We are aware that the terms stepped care and personalised health are used by different disciplines, in different contexts, and with specific meanings. We are deliberately expanding the use of these terms in a new way to discuss the integration of both treatment and assessment through measurement-based care and shared decision making that takes into account patient and family preferences and resources, at every step of the way. Many of the issues raised by this approach are also equally relevant to other neuro-developmental disorders, although the concept of autism beyond the dimensions by which it is defined continues to be needed.

Given the heterogeneity of autism and of families, cultures, and community resources, a diagnosis of autism does not directly lead to a single treatment plan, nor is there any single intervention that is effective or even needed for all individuals with autism. Personalised approaches are, therefore, essential. Nevertheless, some general principles can be applied in our modified stepped care and personalised health model (figure 5) to better organise the existing knowledge about interventions. This is not precision medicine based on biomarkers.[80] To date, no valid biomarkers have been found to be sufficiently predictive of the behaviours and circumstances that need to be changed to be useful, although in the future such biomarkers might be found. Our emphasis in this Commission is on changes to practice, systems, and research that can improve the lives of autistic people living now. In the time of the COVID-19 pandemic, the results of a focused commitment to the development of vaccines through the efforts of science are now evident; we call on governments, services, and funding agencies to have a similar focus on how to improve the lives of autistic individuals and their families through evidence-based interventions and support.

Stepped care models arose to prominence in an attempt to address physical health in LMICs.[81] Stepped care approaches outline a system of treatment delivery and monitoring in which the least resource-intensive service is offered first, and then gradually stepped up to more intensive or specialist-delivered treatments if necessary. These approaches have been aimed primarily at improving access and reducing cost, which are of vital importance given the treatment gap between people who currently receive adequate services and those who need them.[82] A key principle in stepped care is task sharing, in which services are provided whenever possible by the least expensive and most accessible provider, with supervision and training provided by more highly trained professionals.[83] Ironically, in the USA, obtaining funding for the highest, most expensive clinician (eg, a psychiatrist or neurologist) is often easier than for a less expensive provider (eg, a behavioural technician supervised by a psychologist or an occupational therapist). Emerging models of stepped care for mental health have been proposed, although experience with long-term conditions such as autism is scarce.[82,84] In addition, for autism, as with other lifelong conditions, many factors beyond monetary considerations draw attention to the so-called life costs to people, which informs our concept of personalised health. These factors include the role of families, personal preferences, and the possibility of using everyday experiences to support skill building and mental health outside of a health-care system.[84] The role of the family is almost always crucial; therefore, stepped care and personalised health models must consider the needs, abilities, and personal costs (not just financial) to the family and directly to the autistic person. We propose that moving beyond the important concept of participatory research[85] is crucial and participatory decision making should be incorporated into each step of clinical practice and systems.[86] This joint participation means including both autistic individuals and their families, who make most of the decisions during childhood and for many, albeit not all, adults. What might appear to be a less expensive intervention in monetary terms can have other costs. For example, a clinic-based cognitive behaviour therapy group run by non-experts can require lower health-care investment and be convenient for a health-care system, but be costly for autistic people who are challenged by sensory aspects of transportation or for families who have to travel to the group, which competes for time with other responsibilities.

Another challenge for stepped care and personalised health arises from the heterogeneity of autism. A stepped approach that is also personalised requires accounting for the widely varying needs, skills, and circumstances of the autistic child, adolescent, or adult and respective family.[48] A recent, thoughtful review of maximising potential in autistic people organises different

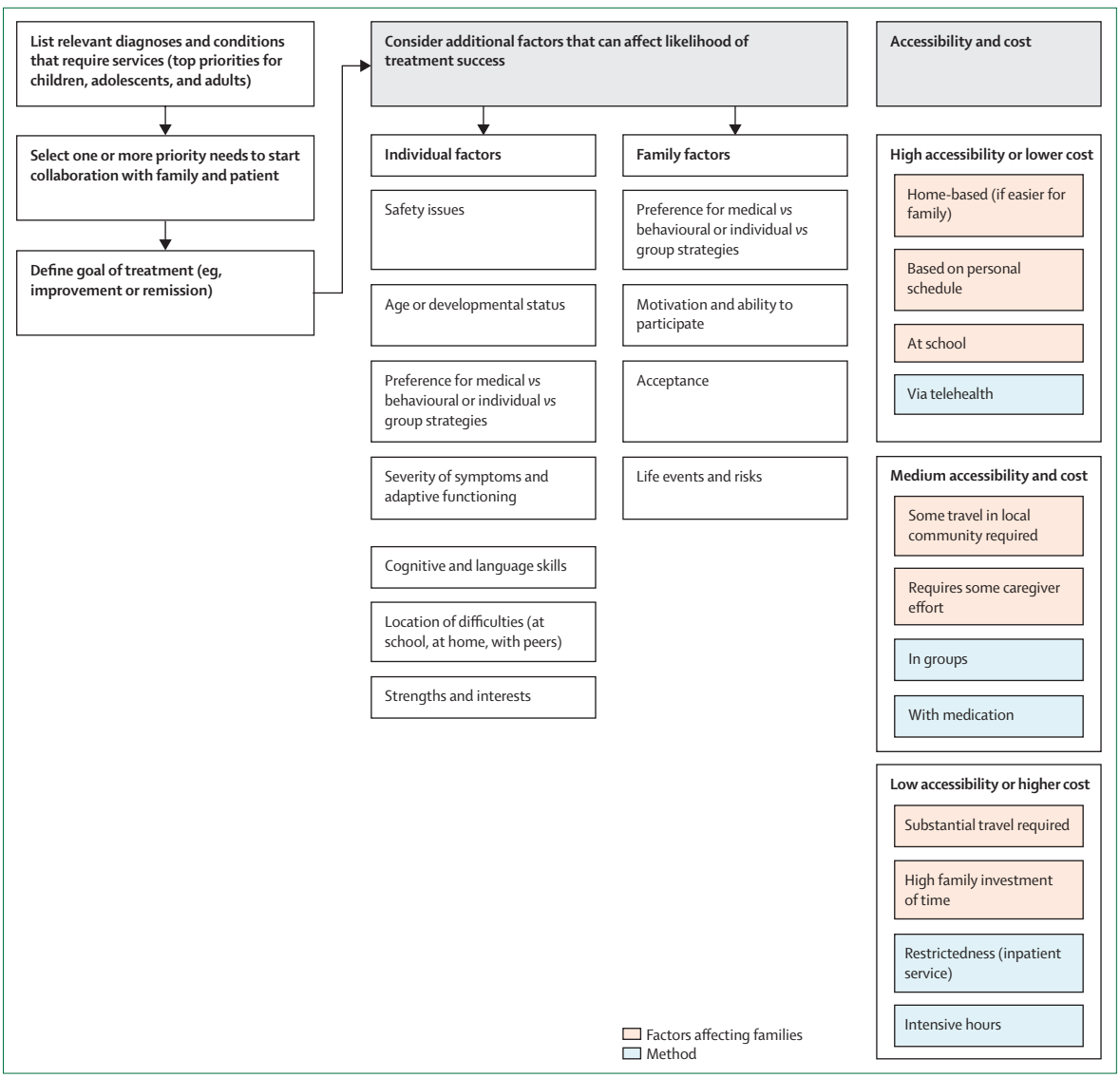


Figure 5: **Stepped care and personalised health interventions**

intervention approaches into three main categories: building skills, minimising barriers, and optimising person-environment fit.[72] For example, a minimally verbal 10-year-old child with autism whose non-verbal skills are more like those of a typical 3-year-old and who has substantial eating problems will need the help of a skilled therapist to build a communication system that could be implemented by a more general interventionist or teacher. To address the feeding problem using a stepped care and personalised health model, a behaviour programme might need to be developed by an expert in feeding difficulties in similar children, who demonstrates techniques and coaches the parents. Another 10-year-old child with autism whose language and reading comprehension are approaching typical age levels and whose mathematical skills are strong might benefit from an inclusive school programme with support to foster opportunities for peer interactions. If this approach is not sufficient to promote success, the school could organise a social skills group. Another child might benefit from cognitive behaviour therapy to alleviate anxiety and outbursts related to unpredictability. Put simply, the needs and strengths of autistic individuals and their families differ depending on their age, autism severity, general mental health needs, and language, cognitive, and adaptive skills, and interventions should address the multiple components of needs and consider personal preferences.[72]

As with other neurodevelopmental disorders, some aspects of interventions for autism aim to build skills that are absent or diminished. These skills can include social interaction, such as shared enjoyment or taking

turns, and communication, including spoken language, comprehension, and use of symbols (eg, through reading and pictures) and augmented devices. Psychoeducation is essential at every stage to help families understand where their children's skills fall developmentally, what are reasonable expectations for the next steps, and to learn techniques to support these aspects of development.[87] If a family or an individual with autism is actively involved in decision making and treatment planning,[72] they need opportunities to learn about autism in general, the specific characteristics of the identified patient, and the potential benefits and limitations of what professionals and systems can offer within locally available care systems. This information should include potential harms associated with clinical interventions.[88]

In contrast to skill building and supporting development, other interventions are aimed at supporting families or individuals to reduce behaviours or feelings that have negative effects, which Lai and colleagues[72] describe as barriers to progress. These interventions might include the development of alternative strategies for anticipating and dealing with behaviours such as aggression, tantrums, or severe distress, as well as the treatment of depressive feelings, irritability, or hyperactivity through medication or cognitive behavioural approaches. For many mental health problems, treating both skill development and reducing difficult behaviours or feelings is a standard part of an intervention plan. For example, in cognitive behaviour therapy for depression, goals include reframing troublesome thoughts and providing alternative behaviours and ideas to replace them. Because the two types of difficulty can cascade, substantial evidence and developmental theory support early initiation of services as soon as signs are observed.[89] Studies to date have not yet provided strong support for pre-emptive interventions, such as working with younger siblings who have no signs of autism or with infants showing early signs identified by community screening,[90,91] although interest in doing so is strong. Nevertheless, if families of very young infants are concerned about their child, these concerns must be taken seriously.

One implication for the integration of stepped care and personalised health approaches is that, for many children and adults, there will be multiple treatment goals. As shown earlier (figure 1), longitudinal studies suggest that the factors that predict positive outcomes in terms of independence and wellbeing are cognitive and language skills, severity of autism, connectedness with peers, adaptive skills, and mental health.[7,28,92] If these factors can be recognised and addressed together, or at least taken into account jointly, outcomes can be improved and services could be more effective and efficient. In addition, given the heterogeneity of autism, what works now might not work later for the same person, and what works later might not work now. Whether to step-up or step-down the intensity of an intervention or shift to a different approach should be based on data-informed progress monitoring and measurement-based care.[93]

How should a stepped care and personalised health model work in practice?

Few models exist of how to build skills and minimise barriers beyond some of the earliest therapist-mediated and parent-mediated interventions that combine approaches to improve social communication and support self-regulation (eg, Joint Attention, Symbolic Play, Engagement, and Regulation;[40] Enhanced Milieu Teaching;[94] Early Start Denver Model;[95] and Social ABCs[96]). With the exception of the Early Start Denver Model, most of these methods are short-term and involve only small re-adjustments of targeted behaviours within brief periods of time. Sequential Multiple Assignment Randomised Trial models, as we will discuss later, provide useful information about the effects of different sequences of strategies (eg, oral language only *vs* oral language and augmented communication). These models are a first step, but data about the relations between baseline features, initial rate of progress, type of intervention, and eventual outcome are still needed. The result of the absence of this information is a dependence on the clinician, the autistic individual (if possible), and their family to provide the first impetus for a treatment plan, and to be responsible for all decisions about what treatments should follow—treatments that are primarily short-term interventions for a disorder with long-term implications.

Thus, stepped care and personalised health begins with the identification of family and individual concerns (figure 5).[97] For most individuals and families, several needs or aims will be targeted at any given time. Next, factors related to the individual child or adult must be considered, beginning with safety aspects (eg, a child who wanders out of the house or has repetitive eye poking). Preferences of the individual that have an important effect on efficacy of treatment are then considered.[98] For example, does the autistic adult or a parent wish to avoid medication or, by contrast, seek a pharmaceutical treatment for depressive feelings or overactivity? Is the adolescent comfortable in groups or interested in participating in online interactions? Family circumstances, life events, and family preferences—eg, to be seen at home or in a clinic; to work in a group or individually; to use medication or not—are highly relevant to the potential effectiveness of a treatment, as are the family's acceptance of the diagnosis and resources to participate. Finally, as noted earlier, individual characteristics of the autistic person, including cognitive and language skills, severity of autism, strengths, interests, motivation to participate, and mental health all contribute to the likelihood of change over time.[8]

Having gathered this information, the idea of stepped care is to begin with the least costly approach. As mentioned before, costs include not just the economic

impact on health and other systems, but also the burden on the family and the person with autism in terms of time, effort, financial cost, and stress. Some locations or modes of intervention fall relatively easily in the first step of the stepped care model (figure 5). Priorities would include treatments at schools or preschools (eg, the Treatment and Education of Autistic and Related Communication Handicapped Children programme,[99] and the Joint Attention, Symbolic Play, Engagement, and Regulation approach[100]) or home-based treatments (eg, Social ABCs[96]). Yet, even with these obvious suggestions, important caveats remain, including whether there is sufficient support and time for school staff to provide treatments at school or preschool and the need for travelling therapists for home-based treatments. Supported employment programmes that take place in the workplace, such as Project Search[101] or Ready, Willing & Able[102] also fall in this first category of the most accessible services with the lowest cost. Telehealth could conceivably fall in the first step, but requires that families have internet access and that individuals are comfortable in this situation, which might not always be necessarily the case.

A subsequent step, more costly in terms of time, inconvenience, and funding, would involve some travel by the family or individual to a nearby clinic, or a substantial time commitment from the family. This step up would mean not just greater financial costs but a greater demand on the family to provide more intense parent-mediated treatments (eg, Early Social Interaction[38] and the Preschool Autism Communication Trial approach[37,103]), even if delivered at home. Treatment groups, generally done in clinics and often by non-specialists, and common medications, which can require regular visits to a local physician, might also fall into this category. The cost of these treatments is not negligible if they require time, effort, or travel for an autistic person or parent, even if they are considered affordable for a health system. Variability in how families or autistic individuals can and do use these treatments also needs to be recognised.

A third step would be highly specialised care that requires considerable travel to a tertiary care hospital or clinic, intensive hours, whether at home or in the clinic, or frequent clinic visits. This third step would include inpatient treatment and some naturalistic developmental behavioural interventions,[36] or interventions such as Parent-Child Interaction Therapy,[104] which typically require clinic visits by multiple family members. A range of circumstances share different but substantial costs for families and the health-care system, but are necessary for progress in some cases. One of the concerns with stepped care models is that individuals and families can get stuck in an early step of care, without consideration of needs that should be addressed in later, more costly steps. This risk is why assessments and monitoring or progress through measurement-based care with shared decision making is crucial to avoid resource wastage while ensuring appropriate allocation of needed services.

Shifting roles over time

The roles of the family, the autistic individual, and the community in provision of services and in decisions will change over time (figure 6), with family involvement being predominant in the early years, in most cases decreasing during school years, and often, but not always, increasing in adulthood.[65] The community, as represented primarily by schools for children aged 6–11 years, provides the greatest number of hours of potential focused support, with substantial reductions in community resources available after these years.[64–66] The type and intensity of interventions available vary greatly both within and between countries worldwide. For example, the number of hours of intervention (also known as treatment as usual) that preschool-aged children (generally meaning children younger than 6 years) received across different US regions varied from 3 h to over 15 h a week.[95] Similarly, a preschool-aged child living in one city in India might have access to a parent-mediated programme, but not to an organised preschool available in another city.[39] A preschool-aged child in a Scandinavian country might be in an inclusive child care programme, with services provided to support childcare workers, although the family might not receive autism-specific support until years after the diagnosis.[105]

The evidence base for autism interventions

Many clinical practice guidelines for autism exist, published by governmental bodies and professional associations worldwide,[106] although the quality, composition of such groups, and methodologies used vary considerably. Other articles also summarise the situation in different countries or regions, such as China,[107] Indonesia,[108] Iran,[109] south Asia,[110] sub-Saharan Africa,[21] and Vietnam.[111] Some of the methods of guideline development are similar, predominantly depending on the recommendations of an expert panel reaching consensus about appropriate interventions on the basis of systematic and expert review of the evidence.[112] However, conclusions vary, from those that only recommend approaches supported by meta-analyses of outcomes from multiple randomised controlled trials,[113,114] to others that recommend a broader range of interventions and practices based on expert consensus reviews, including evidence from case-control (so-called quasi-experimental), single-case, and cohort studies.[115,116] Furthermore, there is little agreement among practitioners about what is evidence-based and what is not, which calls into question the assumption that clinicians—who can have very different assumptions about what is good enough, or who come from different professional backgrounds with different biases—will automatically accept guidelines.[117] The utility of clinical practice guidelines in guiding practitioners through the complex (and often interdisciplinary) interventions and support strategies to provide adequate care for the heterogeneous autistic population will vary with the particular intervention under consideration, the nature of the service or care setting, and

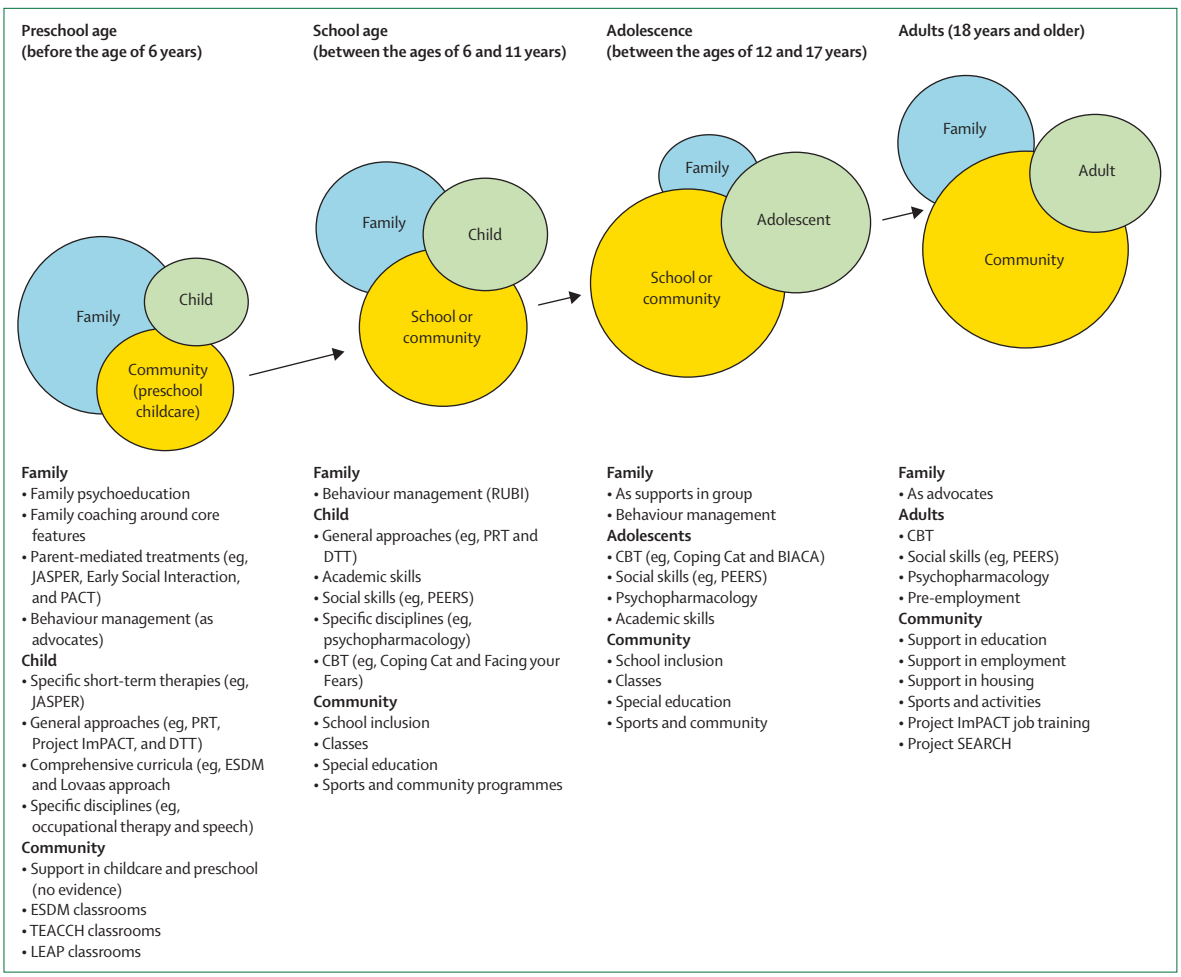


Figure 6: **Sources of support and locations of treatment**
The size of each ellipse represents the extent of care or intervention received. BIACA=Behavioural Interventions for Anxiety in Children with Autism. CBT=cognitive behavioural therapy. DTT=discrete trial training. ESDM=Early Start Denver Model. ImPACT=Improving Parents as Communication Teachers. JASPER=Joint Attention, Symbolic Play, Engagement, and Regulation approach. LEAP=Learning Experiences and Alternative Program for Preschoolers and their Parents. PACT=Preschool Autism Communication Trial. PEERS=Program for the Education and Enrichment of Relational Skills. PRT=Pivotal Response Treatment. RUBI=Research Units in Behavioural Intervention. TEACCH=Treatment and Education of Autistic and Related Communication Handicapped Children programme.

social and cultural contextual factors.[112] The growing number of clinical practice guidelines from different parts of the world (table 1) is an important step towards creating international standards for service provision and offering benchmarks for quality service provision. However, without critical appraisal, it is not a remedy in itself.

Historical and local cultural factors have a role in the approaches and thresholds that are used to judge levels of evidence of autism interventions. For example, in the USA, autism intervention research began with behavioural approaches (eg, applied behaviour analysis) that used the manipulation of the onset, offset, and resumption of treatment approaches across single cases rather than randomised controlled trials as a way of comparing different conditions. Such research designs are systematic, inexpensive, and flexible in their ability to address the needs of different children. Yet, they have clear limitations, such as biases associated with small sample sizes, absence of information on generalisation and the role of development, and, often, non-randomisation or non-blind outcome assessments.[135] Randomised controlled trials, when well conducted, provide the least-biased estimates of efficacy and often incorporate other rigorous methodological strengths, such as manualised interventions, prespecification of primary outcomes, attention to masking of assessors, and conservative intention-to-treat analyses. However, they also have well known limitations such as unrepresentativeness of highly selected samples, an over-reliance on research-directed programmes that might not be translatable to wider community practice, and restraints on individualisation and modification of an intervention based on responses, as would occur in clinical practice.[34] Despite differences in approaches to interpreting data,

	Authors or organisation	Guideline title	Year
National guidelines			
Australia	Autism Cooperative Research Centre	A national guideline for the assessment and diagnosis of autism spectrum disorders in Australia[115]	2018
Europe	Autism Europe	People with autism spectrum disorder: identification, understanding, intervention (3rd edition)[118]	2019
Belgium	Belgian Health Care Knowledge Centre	Management of autism in children and young people: a good clinical practice guideline[119]	2014
England and Wales	National Institute for Health and Care Excellence	Autism spectrum disorder in under 19s: recognition, referral and diagnosis[120]	2017
England and Wales	National Institute for Health and Care Excellence	Autism spectrum disorder in under 19s: support and management[113]	2013
England and Wales	National Institute for Health and Care Excellence	Autism spectrum disorder in adults: support and management[121]	2016
New Zealand	Ministries of Health and Education	New Zealand autism spectrum disorder guideline[116]	2016
Scotland	Scottish Intercollegiate Guidelines Network	Assessment, diagnosis and interventions for autism spectrum disorders[114]	2016
Professional association guidelines			
Canada	Brian, Zwaigenbaum, and Ip	Standards of diagnostic assessment for autism spectrum disorder[122]	2019
Canada	Ip, Zwaigenbaum, and Brian; Canadian Paediatric Society; Autism Spectrum Disorder Guidelines Task Force	Post-diagnostic management and follow-up care for autism spectrum disorder[123]	2019
Europe	European Society of Child and Adolescent Psychiatry (Fuentes, Hervás, Howlin, and ESCAP ASD Working Party)	ESCAP practice guidance for autism: a summary of evidence-based recommendations for diagnosis and treatment[124]	2020
India	National Consultation Meeting for Developing IAP Guidelines on Neuro Developmental Disorders under the aegis of IAP Childhood Disability Group and the Committee on Child Development and Neurodevelopmental Disorders; Dalwai and colleagues	Consensus statement of the IAP on evaluation and management of autism spectrum disorder[125]	2017
Ireland	National Disability Authority	Models of good practice in effectively supporting the needs of adults with autism without concurrent intellectual disability living in the community[126]	2017
Sweden	Swedish Agency for Health Technology Assessment and Assessment of Social Services	Autism spectrum disorders: diagnosis & interventions, organization of care and patient involvement[127]	2013
USA	American Academy of Pediatrics (Hyman and colleagues)	Guidance for the clinician in rendering pediatric care: identification, evaluation, and management of children with autism spectrum disorder[128]	2020
USA	American Academy of Pediatrics (Lipkin and Macias)	Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening[129]	2020
USA	American Academy of Child and Adolescent Psychiatry (Volkmar and colleagues)	Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder[130]	2014
Guidelines in languages other than English			
France	*Haute Autorité de Santé & Agence nationale de l'évaluation et de la qualité des établissements et services sociaux et médico-sociaux*	*Trouble du spectre de l'autisme: Interventions et parcours de vie de l'adulte*[131]	2018
Germany	Association of the Scientific Medical Societies in Germany	*Autismus-Spektrum-Störungen im Kindes-, Jugend- und Erwachsenenalter*[132]	2016
Italy	*Sistema Nazionale Linee Guida, Istituto Superiore di Sanità*	*Il trattamento dei disturbi dello spettro autistico nei bambini e negli adolescent*[133]	2015
Norway	*Regional kompetansetjeneste for autisme, ADHD, Tourettes syndrom og narkolepsi i Helse Sør-Øst*	*Regional retningslinje for utredning og diagnostisering av autismespekterforstyrrelse*[134]	2019

ASD=autism spectrum disorder. ESCAP=UN Economic and Social Commission for Asia and the Pacific. IAP=Indian Academy of Pediatrics.

Table 1: **Clinical practice guidelines by country or region**

there is increasing agreement about particular intervention techniques that are helpful, such as using positive reinforcement, visual materials to support behavioural expectations, and matching level of difficulty in language and play to child ability.[117,135] Researchers have more consensus than clinicians as to the value of different interventions, typically adhering to standards for randomised controlled trials and blinded assessment. However, clinicians have to make daily decisions about what interventions to recommend and deliver (figure 5) and so often have to move beyond the typically short-term, low-intensity interventions that have the strongest evidence.[31]

Not all forms of intervention and not all clinical practice across the fields relevant to improving outcomes for autistic individuals can be tested in conventional, so-called medical model, randomised controlled trial designs.[136] The absence of evidence from randomised controlled trials for a particular approach does not necessarily mean that the approach is ineffective (or effective). Moreover, several well intentioned attempts to introduce large-scale changes in schools with random assignment of different classrooms to different interventions have been unsuccessful for various reasons.[99,137] Despite calls for such research,[72] implementing double-blind, gold-standard, randomised controlled trial designs might not always be feasible in evaluations of longer-term, multicomponent, complex services that often involve populations in which randomisation is either practically difficult or ethically contentious. For example, in psychosocial trials, parent

reporting of adaptive function or child behaviour will be affected by parents' awareness of participation in the intervention, introducing a potential bias; the evidence for interventions is generally weaker when such studies are excluded (figure 7).[31] In efficacy trials with care as usual as a control in HICs, finding and sustaining a randomly assigned treatment-as-usual comparison group can be difficult because families might be able to access similar and sometimes even more personalised treatments through other means.[95] In fact, over time, community services change so much that comparisons to treatment as usual can vary considerably as this treatment changes.

We present common approaches to intervention at different ages recommended in many different sets of guidelines (figure 6). For children younger than 5 years, parent-mediated interventions such as the Joint Attention, Symbolic Play, Engagement, and Regulation approach (including as implemented by a teacher or therapist), the Preschool Autism Communication Trial intervention, Pivotal Response Treatment, Early Social Interaction, the Parent-Mediated Intervention for Children with Autism Spectrum Disorder in south Asia approach, and therapist-implemented and teacher-implemented versions of the Early Start Denver Model are the most commonly studied. Some, as shown in figure 7 (under naturalistic developmental behavioural interventions), have been supported by randomised controlled trials showing changes most commonly in the specific social communication behaviours taught, such as joint attention, synchrony, and social interactions.[138] General programmes of psychoeducation (eg, the More Than Words programme by Hanen) are often used as well, although evidence supporting them is more variable.[139] Direct treatments with similar approaches for very young children, usually involving a non-specialist (eg, a graduate student or a childcare worker), report a range of intensity from 1 h to 40 h a week. Well studied programmes have reported effectiveness primarily in increasing cognition, language, or both (eg, the Early Start Denver Model;[95] applied behaviour analysis and discrete trial training;[89] and pivotal response training[35]), or early social communication skills (eg, the Joint Attention, Symbolic Play, Engagement, and Regulation approach[40] and Social ABCs[96]). The potential effectiveness of classroom-based interventions, based on similar social-communication models, has been shown in several studies, but typically with weaker research designs (Early Start Denver Model[140]). WHO's Caregiver Skills Training programme focuses on teaching caregiving skills to parents of very young children and older children with developmental delays and disabilities, including autism, and is being evaluated in many sites worldwide.[141] This programme is a very important first step, but still leaves the primary burden of support and treatment on the family.

For school-aged children and some older preschool children, several short-term targeted interventions, either with parents (eg, Research Units in Behavioural Intervention[142]), directly with the child (eg, Behavioural Interventions for Anxiety in Children with Autism[143]), or with mental-health therapists (eg, An Individualized Mental Health Intervention for Children with ASD [autism spectrum disorder][144]), address common co-occurring difficulties such as behavioural problems, anxiety, and fears, with good evidence of efficacy from randomised controlled trials, systematic reviews, and meta-analyses.[70,71,145] Techniques such as writing social stories about anticipated events are widely used,[146] as are strategies to increase communication to decrease difficult behaviours. Within schools, the Treatment and Education of Autistic and Related Communication Handicapped Children programme provides principles for classroom organisation that are aimed at increasing predictability

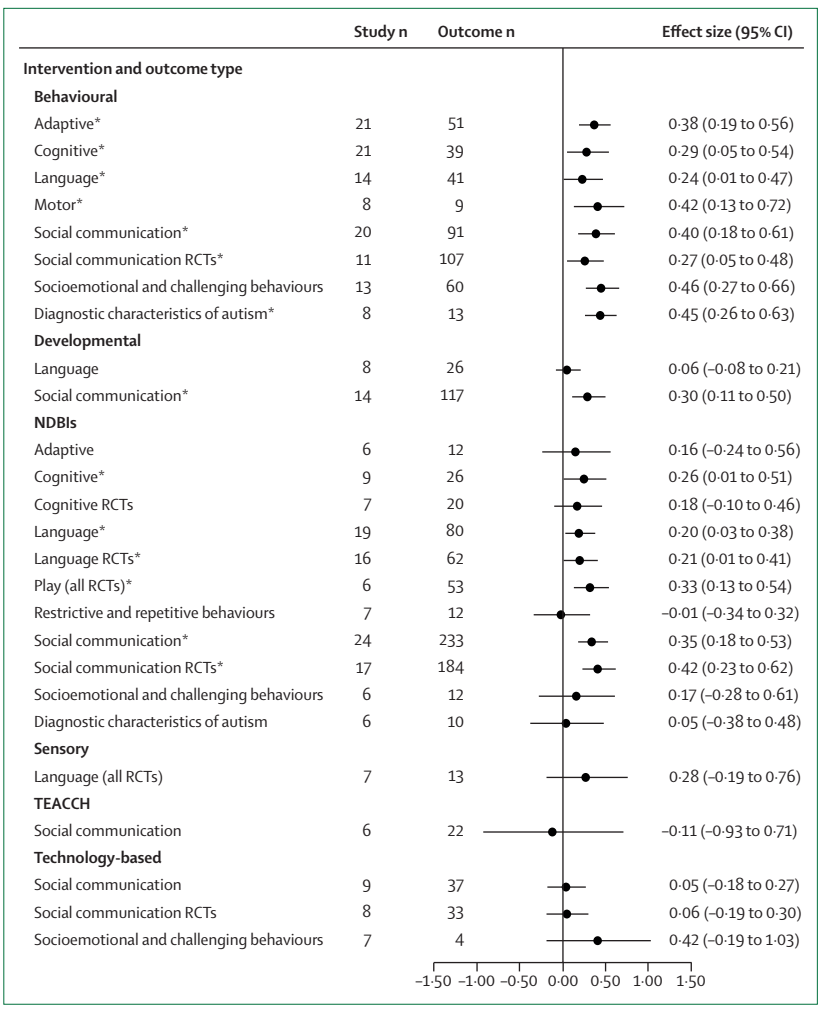


Figure 7: **Forest plot for robust variance estimation for outcomes by intervention type**
Adapted from Sandbank and colleagues,[31] by permission of the American Psychological Association. Forest plot of robust variance estimation summary estimates with small sample bias correction for each outcome by intervention type, when all outcomes from quasi-experimental and RCT group design studies are included. Summary estimates for all studies within a target area listed first, followed by estimates restricted to RCT findings. NDBI=naturalistic developmental behavioural intervention. RCT=randomised controlled trial. TEACCH=Treatment and Education of Autistic and Related Communication Handicapped Children programme. *Denotes summary effect size estimates with confidence intervals that do not overlap with zero.

and self-regulation,[43] although producing specific empirical evidence to prove its effectiveness has so far been difficult. Evidence for the efficacy of programmes in supporting social skills during school recess or breaks and increasing social interaction with peers is stronger and supported by the results of several multisite trials.[147,148] Outside of school, many social skills programmes have been designed (eg, the Program for the Education and Enrichment of Relational Skills,[149] summerMAX,[150] and the Frankfurt Social Skills Training for children and adolescents with autism[151]) that are supported by empirical evidence. Most of the change seen is in short-term, specific behaviours such as increased play and interaction with peers, with limitations in generalisability to broader social interactions, such as in school.[47] Many children in HICs also receive specific therapies, most commonly speech and language therapy and occupational therapy,[69] which are sometimes addressed in clinical practice guidelines.[113,128] Speech and language therapy and occupational therapy use a variety of techniques common in naturalistic developmental behavioural interventions, about which there is at least clinical consensus on their value.[117,135]

Issues in adolescence

Adolescents with autism have particular needs and strengths, and the development and evaluation of interventions for this group requires additional focused research attention. During adolescence, there is a general reliance on school-based education. Convergent data from several studies (for which randomisation was impossible) show that older autistic children and adolescents who attend inclusive schools providing general education have better outcomes than those in special education settings, including greater increases in intelligence quotient,[28,30,92] higher educational attainment, and better academic achievement,[77] even controlling for the likelihood that placement in an inclusive school is associated with different characteristics of the child. Psychopharmacology becomes a more typical component of treatment of co-occurring conditions in adolescence and later childhood, including attention-deficit hyperactivity disorder, anxiety, and aggression. Formal guidelines across countries and, not surprisingly, across professions differ in whether psychosocial approaches should always be attempted before medication is introduced (table 1). Social skills interventions and cognitive behavioural therapy[143,152] have been shown to be effective in reducing anxiety but not yet depressive feelings. However, too little is known about how to optimise mental health and develop independence across the heterogeneity of individuals with autism; another area where research is needed.

Issues in adulthood

Addressing the needs of autistic adults requires collaboration of the local community and stakeholders with researchers and clinicians involved in the development of appropriate programmes, as well as systemic change. The majority of autistic people are adults, and yet services and support available for this group are far fewer, and very few programmes for adults with autism have been rigorously evaluated.[135] Treatments similar to those used with adolescents (including cognitive behaviour therapy, medication, and social skills groups, such as the Program for the Education and Enrichment of Relational Skills) have all been shown to have some efficacy for adults.[153–155] Supported employment and job coaching programmes are available in some regions of some countries and there is growing evidence of their effectiveness.[101,156] Programmes and systems to support adult development of adaptive skills exist but are seldom documented in research.[157] Behavioural programmes for adults with autism have been described for many years, although few are randomised controlled trials and many involve individuals with more severe intellectual disabilities. The use of behavioural approaches is also controversial among some neurodiversity advocates.[26] Services for adults with profound autism and across the ability range are the area of greatest need in some HICs and require systemic support. In LMICs, because fewer services are available at any age, needs are even broader across the life span. The need for autism awareness, staff training, and, in some cases, specific support for individuals has become widely and increasingly recognised in statutory services in many communities, including unemployment and job support services, the polices, courts, and prisons.[158]

Finally, many interventions developed for autism, such as those addressing social communication, could be useful for children, adolescents, and adults with other neurodevelopmental disorders.[159] Not having a diagnosis of autism should not be an exclusion criterion for access to an effective intervention. Similarly, interventions developed for other populations might be helpful for autistic people, sometimes with adaptations that recognise the particular social impairments or sensory challenges in autism. For example, cognitive behaviour therapy for anxiety with autistic adolescents has been modified to account for differences in cognitive style, communication, and insight.[70,152] Interventions for autism cannot depend on being offered only by autism experts. The reality is that most treatment for autistic people of all ages, even in HICs, is not offered by specialists; most care is provided in educational and community settings that might or might not have consultation or support from experts.[160] Thus, as later discussed, training and supporting non-experts must also be part of research and systems planning. Crucial factors include understanding what works for whom and when, and what are some of the predictable needs and variations that need to be considered to support autistic individuals. This information, together with training and supervision, needs to be made available in an accessible way to

non-specialist providers, from preschool and school teachers, to job coaches, to school or community professionals, and to families.[161] These factors are another reason in favour of measurement-based monitoring; if progress on goals is not happening, clinicians, patients and carers should ask why not.

Panel 4 summarises intervention recommendations and considerations for clinical practice across the life span.

Screening, assessment, and diagnosis

The primary aim of a diagnostic assessment is to inform treatment planning with an individual and their family. Because no single treatment for autism exists, the assessment should not only describe autism features but also the individual's profile of strengths and needs and the family's circumstances, resources, and motivations that might affect outcomes and care.[162]

What is an adequate or appropriate assessment?

Although stating that more than a diagnosis is needed sounds simple, the reality is much more complex. Understandably, for many families and adults with autism, the primary concern at the point of an initial expert consultation is a diagnosis, which might be partly due to an unawareness that no single treatment for autism exists and that the course of an autistic individual's development is determined by other factors as much as by the condition itself. Nevertheless, in some countries and regions, having a formal diagnosis of autism results in access to services and funding otherwise not available, which reflects the influence of health-care systems.

Beyond providing documentation that grants access to services within systems of care, the primary recipient of most assessments is the family, or for verbally fluent adolescents and adults, the individual. Diagnostic assessments need to consider what the family already knows, what they want to know, and what information will help them to understand, support, and advocate for their child or affected family member. These factors can be lost when a provider makes a quick diagnosis without compiling more information, or sometimes even in long, detailed written reports with little attention to questions raised by the family (eg, including long lists of expensive treatments that the family cannot afford).

Many formal guidelines propose a multidisciplinary assessment to address the basic characteristics of the child (or adolescent, or adult) and family (figure 8). There is widespread agreement about gathering a history, observing the individual clinically, and evaluating current functioning and family contexts more broadly. However, the practical outcome of this process (beyond arriving at a diagnosis), how to do it (eg, through standardised or informal methods, questionnaires, interviews, or medical record review or direct testing), and in what context (eg, in a standard office visit, in a waiting room, or in a formal observation in clinic or school) is seldom delineated. For most guidelines, a clinical consensus diagnosis by expert diagnosticians is considered the gold standard, but few attempts have been made to test the reliability over time or between clinicians of such assessments, or even to consider how such a test could be done. Studies that have addressed these questions within autism (comparing various previous subtypes of autism spectrum disorder) have found much variation.[163]

Some factors that have been repeatedly identified as major moderators of outcomes, such as language skills, cognitive ability, adaptive skills, and co-occurring mental and physical health conditions,[28,30,164] are specified as crucial in some guidelines, but not in others, partly depending on the region and professional class of the guideline writers. In some clinical practice guidelines, the assessment of such variables is considered the responsibility of schools or of social services (ie, outside of the health-care system), both of which might not exist in some contexts. Research has established that lifelong outcomes are affected by factors beyond diagnosis, including cognitive or language skills or co-occurring conditions; yet few systematic studies of how these variables contribute to responses to different treatments exist. This paucity of knowledge comes back to previously discussed questions about the need to know which interventions work for whom and when, which in turn have implications for what needs to be evaluated.

Raising the question of when a formal diagnosis of autism makes a difference (beyond consideration of other factors such as cognitive or language delays, mental health issues, and other features) is also reasonable. A diagnosis clearly makes a difference in many circumstances: for example, in obtaining early intervention for young children who are verbal but clearly autistic, in creating an appropriate cognitive behaviour therapy programme for an anxious adolescent with autism, or in selecting a suitable medication for an older child with autism and attention-deficit hyperactivity disorder. However, sometimes a diagnosis might not make a difference. A valid diagnosis is a necessary step in developing an adequate treatment plan, but it should be considered a beginning, not an end. As stated previously, the lack of a diagnosis should not prevent the initiation of an intervention, although, in the long term, adequate assessments are important to match the needs of a child or adult with autism and their family with services.

Another important consideration is whether single-provider assessments are sufficient to make a diagnosis of autism, or if multiple disciplines are necessary. Single-provider assessments are less expensive, more realistic for LMICs, and easier to organise and reimburse even in HICs. In some studies, families prefer them.[165] Multiple providers participating in the same assessment require time to maximise team efficiency and maintain a clear internal communication with the family or individual, and often also result in families and autistic

Panel 4: **Recommendations and considerations for clinical practice interventions**

1. Appropriate personalised health interventions in a stepped care model for a given child or adult require integrating information from previous assessments, current providers and teachers, the family, and the individual within the context of existing or possible local care
2. Each treatment plan should include the identification of appropriate formal treatments, community resources, and everyday activities that can address treatment goals and of ways to support use of these resources, as well as reducing or eliminating services that are not effective or no longer needed; health-care systems must support this communication, navigation, and continuity
3. Interventions must take into account the preferences of individuals and families and the implications of implementation in culturally diverse contexts; evidence-based interventions in low-resource settings should be implemented, but adaptations and innovative strategies might be required
4. Families and autistic adults who can speak for themselves should be involved at each step, but should never be expected to assume societal and community responsibilities for individuals who need support
5. Autistic individuals and their families are a population vulnerable to false claims of effectiveness and unstudied treatments that might have substantial adverse effects
6. Psychoeducation and interventions for families and autistic individuals that promote autonomy and personal choice and decrease vulnerability through knowledge are essential components of equitable global and local models to support decision making across steps of care
7. Prompt interventions (ie, as soon as difficulties are identified) are vital:
   - Early, problem-focused interventions for neurodevelopmental disorders should be accessible and based on screening and needs identified through a stepped care model, without waiting until a comprehensive assessment or formal diagnosis of autism is made
   - Co-occurring conditions, including medical, developmental, behavioural, and psychiatric disorders, should be addressed with adequate treatments as soon as they are recognised
   - Stepped care models based on personalised data and systematic monitoring should allow rational, graded increases or decreases in intensity of intervention when needed
   - Systems should prioritise evidence-based interventions, recognising that most of these treatments are short-term and focused, and that other ongoing approaches, including education and employment support, are also necessary to support autistic individuals over time
8. Modifications to existing evidence-based treatments, including cultural adaptations, might be necessary to optimise both behavioural-psychological and medical approaches, together and separately, for co-occurring conditions in autism and to increase effectiveness and participation
9. Adolescents with autism have particular needs and strengths; the development of clinical practices for them, most notably interventions, requires more focused research attention
10. The typical life span involves more years in adulthood than childhood; addressing the urgent needs of autistic adults requires collaborative participation by researchers, clinicians, self-advocates, and families in the development of intervention programmes and systemic changes

individuals having to provide the same information repeatedly. On the other hand, some single providers might not have the skills necessary to observe, measure, and discuss with families the range of issues affecting individual children or adults.[166,167] Kanne and Bishop[162] highlight that, despite a waitlist crisis for evaluations at particular centres in many countries and communities, shortcuts to speed up the diagnostic process (eg, remote video capture or biological tests) do not actually address the problem. The shortcuts overlook the fact that the crucial outcomes of a diagnostic assessment are fed back to the individual, family, and other providers about the individual's profile of strengths and needs together with the provision of individualised recommendations for intervention and care across development (for an example of research concerning the provision of feedback for a different condition see Schechter et al[168]).

Moreover, much evidence indicates that diagnoses with standardised information are more reliable across sites and more valid over time than single-clinician asesssments.[169] Including information from both caregiver report and clinical observation increases the reliability and validity of diagnoses.[170,171] The intention of any diagnostic tool, such as a medical instrument (eg, a thermometer or a stethoscope), is not to deliver an inarguable answer, but to provide standardised data to a clinician who can use it, together with other information, to allow the clinician to provide a diagnostic formulation and appropriate care plan over time. Thus, requiring clinicians to use at least one standard instrument in the documentation of severity of autism signs, with an awareness of the strengths and limitations of that instrument, appears to be an appropriate minimal standard, particularly if the instrument can be used as a benchmark in later assessments. Knowing that a potential for change exists places a responsibility on the provider to document improvements, which currently happens relatively rarely. The scarcity of standardised instruments presents a challenge in LMICs, particularly those with many different languages, but is beginning to be addressed by the development of nationally designed instruments that can be translated at least into the major languages used by providers, if not by all families.[172]

The stepped care and personalised health approach to autism assessment

Accompanying the stepped care and personalised health model we proposed for interventions, we also recommend an integrated stepped and personalised approach to assessment of the developmental and functional profiles of all neurodevelopmental disorders, with a focus on individual and family needs (figure 8). This approach allows inclusion of a broader, more heterogeneous group of children and adults beyond only those who receive an autism diagnosis, and avoids sequential disorder-specific assessments (eg, one assessment pathway for autism, followed by another for attention-deficit hyperactivity disorder), with a focus on developing a personalised intervention plan and on monitoring change. This model links to our stepped and personalised intervention approach, which moves from matching assessed needs to broader, non-specific interventions to increasingly intense and specific interventions, according to identified priorities for the individual and family.[173]

Many children with autism are first referred for difficulties characteristic of other neurodevelopmental disorders, such as language delay or attention problems.[174] Conversely, children who are referred for concerns about possible autism can have other neurodevelopmental disorders but not autism. A stepped and personalised approach allows consideration of these disorder overlaps from the start, which is different from systems in which individuals with autism and other neurodevelopmental disorders are referred on to different services (eg, education *vs* mental health services, or social *vs* medical services, depending on their diagnoses or needs) from an early age. We propose a stepped and personalised care model that can be adjusted as heterogeneous needs change with development and overlaps emerge across diagnostic categories and intellectual ability levels. In contrast to our intervention section, we first provide descriptions of empirical findings about surveillance and screening and assessments, and then return to consider the stepped care and personalised health assessment model in more detail.

Diagnostic criteria for autism

The diagnostic criteria in the current versions of the DSM-5 and the ICD-11 are applicable at any age and level of language and intellectual functioning, with a range of possible manifestations. Social communication difficulties should be greater than those expected, considering the individual's general developmental level. Several different repetitive or restricted behaviours are required for a diagnosis, but evidence of these, as for social communication deficits, can be obtained from a developmental history. A diagnosis of autism also requires evidence of clinically significant impairment in current functioning, such as limited daily living skills, psychological distress, or need for support in everyday settings such as nursery, school, employment, or the community.

An important change in DSM-5[12] and ICD-11[13] was the removal of autism spectrum disorder subtypes (eg, autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified), folding them under the single diagnosis of autism spectrum disorder, or autism. Instead of unreliable categorical subtypes, the DSM-5 and the ICD-11 require profiling of individual strengths and weaknesses, including the level of intellectual, language, and adaptive functioning, and any co-occurring neurodevelopmental, mental health, and medical conditions (see also the UK's National Institute for Health and Care Excellence clinical guideline 128[120]). As mentioned before, these changes have the potential to radically reconceptualise the field by making the primary aim of a diagnostic assessment to inform needs-based treatment planning and service provision, and to provide data for monitoring of progress and anticipation of later needs (with the assumption that needs change and improvements can occur), rather than to provide a categorical diagnosis. The introduction of the term profound autism in this Commission (panel 2) is intended to amplify the clinical specifiers that are included in both diagnostic systems, with the aim of informing and helping to individualise interventions, support, and care for some of the most vulnerable autistic individuals—who, notwithstanding, have the potential to live better lives.

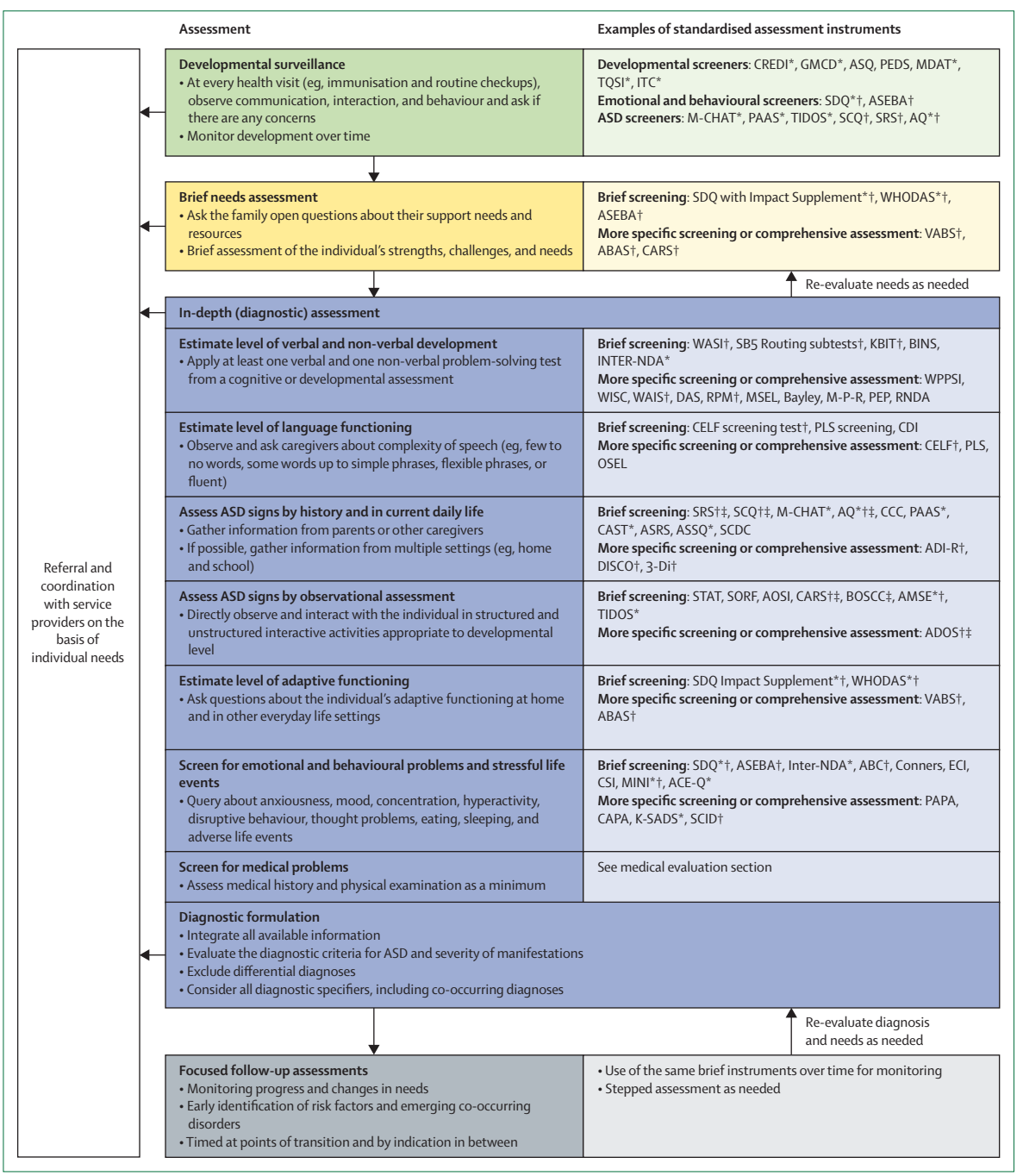
Early identification and surveillance

Early identification of clinical signs of autism is the first step to facilitating prompt referral for an assessment and diagnosis. In many cases, features of autism and other neurodevelopmental disorders are apparent early in development, although the specificity of these signs is still unclear. Retrospective and prospective studies, including those based on high-risk sibling designs,[175] have shown that the onset of autism signs is variable across the first years of life, with suggestive, neurobiological group differences potentially measurable earlier,[176] and with clearer behavioural differences emerging from the age of 12 months.[177] Some children show delayed and atypical development from early in life, others a plateauing of development over time, and some show a loss of skills already acquired. Incidents of such regression (mostly in social skills, including language) at about 15–18 months of age seem to be relatively unique to autism and some rare genetic neurological conditions, such as Rett syndrome.[178] Other children show signs that only become clearly visible later, usually during more complex social interactions with peers and unfamiliar adults.[179] Thus, heterogeneity is present from an early age, including in patterns of onset and progress.

Screening is done through the administration of a brief questionnaire or examination, usually at a single or a few predetermined ages, to rapidly identify individuals in need of in-depth assessment. A wide range of screening instruments for autism, general developmental delays, and emotional and behavioural problems is available (figure 8). However, views contrast, with some strongly supportive[128] and others unsupportive,[180] on the strength of the evidence for their use in universal autism-specific screening in the absence of any parental or clinician concern. A meta-analysis of the parent-rated Modified Checklist for Autism in Toddlers, Revised with Follow-up,[181] the most researched autism-specific screener, reported an overall sensitivity of 0·83 (95% CI 0·75–0·90) and overall specificity of 0·51 (0·41–0·61).[182] Nevertheless, although identifying some children with autism before parents or professionals have expressed concerns is possible, in studies with systematic follow-up to mid-childhood, autism is missed in many screened children.[183] Positive predictive values are low in general population studies (15% in Guthrie et al,[183] 6% in Yuen et al[182]), with higher, but still moderate values (eg, 53%) in individuals from high-risk populations with already identified developmental concerns.[182] On the other hand, the process of screening, even when so-called false

positives occur, can result in primary care physicians making earlier and more referrals that lead to intervention and support, including for children with other neurodevelopmental disorders (but not autism) who are identified by the screening process.[184] There is a balance between the relative costs and benefits of false positives and false negatives in screening; false positives can lead to unnecessary assessment and parental concern, whereas false negatives can lead to under-identification, late diagnosis, and delay in intervention.[128]

In countries other than the USA, the broader concept of developmental surveillance is the ongoing, systematic monitoring of development over time, including the integrated use of clinical observation, asking parents about their concerns, family history, and use of screening instruments repeated over time.[185] Autism screening instruments also identify children with broader neurodevelopmental disorders.[128,180] Universal developmental surveillance of infants is common in some countries and regions.[114,186] Variability in the emergence of early signs of



autism, another example of its heterogeneity, highlights the utility of surveillance in which children are monitored at regular intervals during their early years[185] and families can be referred on for support. However, access to universal health care is limited or even absent in many places, especially in LMICs.[187] In such circumstances, opportunistic contacts, such as immunisation visits, can be used as a means of identifying early atypical development.

Recognising that many health practitioners (including community physicians and paediatricians) do not have specialised skills and training in the manifestation of neurodevelopmental conditions in infancy is important. Therefore, training professionals on the early signs of atypical neurodevelopment remains a high priority if the identification, diagnosis, and interventions for autism are to be done in a timely manner.[128] Descriptions of early signs of autism are available to support professionals and raise public awareness.[114,188] In addition, well established risk factors for autism have been identified and include parents expressing concerns that their child might have autism,[189] preterm birth, a family history of autism, and a number of genetic syndromes such as tuberous sclerosis complex and fragile X syndrome.[132] Similarly important is an awareness of referral and recognition biases related to sex, ethnicity, and social disadvantage that can affect the timely identification of neurodevelopmental concerns, a diagnosis of autism, and access to provision such as education support.[190,191]

Despite the availability of this information on the early signs and known risk factors for autism, the reality for many families in both HICs and LMICs is that children are not identified early, and are only recognised when they enter formal educational settings such as preschool or school, if at all.[192,193] Often, later manifestations of autism coincide with periods of transition, such as entry into high school or leaving school. These are, therefore, important developmental stages, and professionals involved in these systems should be aware of the signs of autism to adequately refer families for advice.[120] In accord with the belief that lives can be improved with help, all individuals should be promptly referred for assessment at whatever age concerns regarding neurodevelopment are identified.

Assessment of functioning and support needs

At the initial recognition of difficulties, the priority should be to identify the areas in which the individual (and their caregivers) has needs and to identify services within the community that can provide support and intervention. As shown earlier (figure 8), a needs assessment can be brief, but should identify key strengths, concerns, and functional impairments. A clinical interview with caregivers (and individuals able to self-report) or standardised instruments that cover a range of signs and symptoms, strengths, and challenges, and provide red flags for follow-up about support needs can be used. Findings from all these sources should be summarised in a written report, available to the family and appropriate for their level of language and understanding. Although standardised instruments can be useful to structure a clinical interview, they are no substitute for in-person, open-ended questions about concerns and needs. Professionals should be aware that parents vary in their understanding of their child's needs, particularly with a first child or when the child is very young. Questioning must take into account the family's sociocultural background.[194] Most important is to recognise that evaluating needs is an ongoing process, which—in current systems—is often overlooked. For example, at the time of diagnosis, some families believe that once their child can speak, they will have no further issues; yet, as the child develops or as they encounter more information about autism, they become aware of other needs and challenges. Other families can begin

Figure 8: **Assessment flow and examples of standardised instruments for the assessment of autism**

3-di=Developmental, Dimensional and Diagnostic Interview. ABAS=Adaptive Behavior Assessment System. ABC=Aberrant Behavior Checklist. ACE-Q=Adverse Childhood Experiences Questionnaire. ADI-R=Autism Diagnostic Interview, Revised. ADOS=Autism Diagnostic Observation Schedule. AMSE=Autism Mental Status Exam. AOSI=Autism Observation Scale for Infants. AQ=Autism-Spectrum Quotient. ASEBA=Achenbach System of Empirically Based Assessment. ASD=autism spectrum disorder. ASQ=Ages & Stages Questionnaire. ASRS=Autism Spectrum Rating Scales. ASSQ=Autism Spectrum Screening Questionnaire. Bayley=Bayley Scales of Infant and Toddler Development. BINS=Bayley Infant Neurodevelopment Screener. BOSCC=Brief Observation of Social Communication Change. CAPA=Child and Adolescent Psychiatric Assessment. CARS=Childhood Autism Rating Scale. CAST=Childhood Autism Spectrum Test. CCC=Children's Communication Checklist. CDI=MacArthur-Bates Communicative Development Inventories. CELF=Clinical Evaluation of Language Fundamentals. Conners=Conners Comprehensive Behavior Rating Scales. CREDI=Caregiver Reported Early Development Index. CSI=Child Symptom Inventory. DAS=Differential Ability Scales. DISCO=Diagnostic Interview for Social and Communication Disorders. ECI=Early Childhood Inventory. GMCD=Guide for Monitoring Child Development. INTER-NDA=INTERGROWTH-21st Neurodevelopment Assessment. ITC=Infant-Toddler Checklist. KBIT=Kaufman Brief Intelligence Test. K-SADS=Kiddie Schedule for Affective Disorders and Schizophrenia. M-CHAT=Modified Checklist for Autism in Toddlers. MDAT=Malawian Developmental Assessment Tool. MINI=Mini-International Neuropsychiatric Interview. M-P-R=Merrill-Palmer-Revised scales. MSEL=Mullen Scales of Early Learning. OSEL=Observation of Spontaneous Expressive Language. PAAS=pictorial autism assessment schedule. PAPA=Preschool Age Psychiatric Assessment. PEDS=Parents' Evaluation of Developmental Status. PEP=Psychoeducational Profile. PLS=Preschool Language Scales. RNDA=Rapid Neurodevelopmental Assessment. RPM=Raven's Progressive Matrices. SB5=Stanford-Binet Intelligence Scale, fifth edition. SCDC=Social and Communication Disorders Checklist. SCID=Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5th edition Disorders. SCQ=Social Communication Questionnaire. SDQ=Strengths and Difficulties Questionnaire. SORF=Systematic Observation of Red Flags. SRS=Social Responsiveness Scale. STAT=Screening Tool for Autism in Toddlers & Young Children. TIDOS=Three-item Direct Observation Screen. TQSI=Ten Questions screening instrument. VABS=Vineland Adaptive Behavior Scales. WAIS=Wechsler Adult Intelligence Scale. WASI=Wechsler Abbreviated Scale of Intelligence. WHODAS=WHO Disability Assessment Schedule. WISC=Wechsler Intelligence Scale for Children. WPPSI=Wechsler Preschool and Primary Scale of Intelligence. *Instruments available free of charge. †Instruments designed for use with adults (individuals older than 18 years). ‡Instruments including dimensional symptom measurement (ie, measures that provide interpretable continous scores instead of a categorical label only).

with many identified areas of need and narrow them down as they prioritise particular issues of greatest current relevance in the context of the resources of the family, the person with autism, and the wider community.

Diagnostic assessment and treatment planning

Whereas a brief needs assessment can be used for access to broad-level services, a more in-depth assessment is essential to give families and individuals information and to develop a personalised plan for targeted interventions, as exemplified in figure 5. Core components of a diagnostic assessment for autism (and for neurodevelopmental disorders more broadly) are to document relevant aspects of the individual's developmental history and to construct an individualised profile of treatment-relevant strengths and difficulties, which will include verbal and non-verbal skills, adaptive functioning, social communication difficulties, behavioural flexibility, and emotional, behavioural, and medical functioning. A stepped and personalised assessment can be used for each component, meaning that the clinician can consider what information is already available (eg, achievement tests or intelligence quotient from school reports) and what is absent (eg, a detailed assessment of receptive language if this is in question, or a description of peer interactions), do a brief assessment or screening to check for issues, and then, if indicated, do a more comprehensive evaluation. Clinicians from many disciplines (eg, physicians, psychologists, speech-language pathologists, and social workers) can lead the assessment process, if they have training in autism and related disorders. Because of the need for assessment of multiple domains of functioning, input from clinicians of multiple professional disciplines is ideal (table 1). If a multidisciplinary assessment is deemed unnecessary or is not possible (eg, in low-resource settings in HICs and LMICs), the lead clinician is responsible for ensuring that all other components are addressed, if appropriate. For example, if a child is seen only by a physician or nurse practitioner, the health-care professional should attempt to measure the child's verbal and non-verbal skills (if they have the training to do so) or refer them for additional testing.

Core assessment components

Assessment of social communication and restricted, repetitive, or sensory behaviours

A diagnosis of autism requires integration of information across multiple contexts (eg, in daily life at home, in the clinic setting, or at school). An array of standardised diagnostic instruments (figure 8) allows evidence-supported documentation of signs of autism in social communication and of restricted, repetitive, or sensory behaviours, and can provide benchmarking for later re-assessments of changes over time (instruments that can be used in this way are marked with a double dagger symbol in figure 8), although putting this information together still requires a competent clinician. Evidence supports use of a combination of instruments based on parent account and direct clinical observation.[170,171] The Autism Diagnostic Interview, Revised[195] and the Autism Diagnostic Observation Schedule, 2nd edition[196] have been most widely used in clinical practice (mostly in tertiary health-care settings), in larger school systems in the USA, or in research studies in HICs. The need to take a global perspective on autism is driving attempts to develop scalable (ie, usable in different places and situations) open-access tools that are not limited by their proprietary costs, but this work is currently in an early stage.[187] A validated open-access diagnostic tool was developed in India and has now been made available online, but would benefit from being evaluated across diverse populations and compared with gold-standard approaches.[172]

Language, general developmental level, and adaptive skills

The diagnosis of autism entails an assessment of social communication skills and behavioural flexibility in the context of the individual's language and developmental level. An estimate of overall developmental level should precede the assessment of social communication and repetitive behaviour. Studies show that standard cutoffs on many instruments for autism have a low capacity to differentiate between individuals with autism and individuals with severe global developmental delay without autism.[170] The Autism Diagnostic Observation Schedule, 2nd edition provides age-standardised and language-standardised cutoffs and dimensional scores for social communication difficulties and repetitive behaviour patterns (separately and combined). These features allow the clinician to consider developmental level,[197] which can be especially important in the differential diagnosis of an intellectual disability or identification of a co-occurring diagnosis.

Language and intellectual functioning are also among the most reliable predictors of prognosis in autism (figure 1). For example, first words by the age of 2 years and flexible phrase speech by the age of 3 years are predictive of better social functioning in adolescence and adulthood.[198] Furthermore, a non-verbal intelligence quotient within the average range by the age of 3 years is predictive of a more positive developmental course and outcomes in adolescence and adulthood,[75] and might be directly or indirectly related to differential treatment responsiveness. Assessments of the individual's receptive and expressive language skills, non-verbal problem-solving, and adaptive skills are necessary to assign DSM-5 clinical specifiers relevant to ICD-11 subtypes and have implications for prognosis and treatment planning.[128] Informal estimates do not provide the same information as standardised assessments and can limit reliable and valid focused follow-ups, which should be a priority even in LMICs.[167] Efforts are underway to develop more scalable methods for LMICs.[199] Brief, norm-referenced tests of non-verbal and verbal ability are

available to provide a rough estimate of developmental level; these can be administered by providers who are experienced in clinical assessment but are not psychologists in as little as 10–15 min.[200]

Screening for emotional and behavioural problems

Given the frequency and importance of co-occurring conditions, assessment of potential difficulties beyond autism is essential. Several questionnaires and norm-referenced screening tools are available to detect signs of emotional and behavioural disorders. These measures are available in versions for parents, teachers, day-care staff, and self-report; some are free, and some are available in many languages (figure 8), although they do not generally have empirically validated cutoffs for autistic populations, so they should be used descriptively. Identification of early signs calls for further assessment to evaluate severity and diagnosis of a co-occurring condition. For example, parent-reported hyperactivity can be an indicator of concomitant attention-deficit hyperactivity disorder, which can then be further assessed through a range of questionnaires and more structured observation and interviewing.[201]

Medical evaluation

The purpose of the medical evaluation is to identify potential aetiologies and co-occurring medical conditions that require further assessment, inform recurrence risk, or that should be integrated into intervention planning (table 2). Several organisations have published guidelines for medical evaluations (table 1). What constitutes an adequate medical examination of a child or adult with autism varies widely across countries and professional associations. There is agreement that a medical history, family history, and a physical examination are essential to document growth parameters and physical and neurological abnormalities (including tics), motor function, and dysmorphic features or congenital anomalies suggestive of genetic syndromes that warrant further testing. If any concerns about a lack of previous standardised assessment of hearing and vision exist, these should be recommended. Additional examinations, such as blood tests, electroencephalography, or MRI are pursued only if indicated by presenting symptoms or history. Oral hygiene should also be addressed in every person with autism on a regular basis. In some, but not all countries, genetic tests are a standard part of a medical assessment.

Assessment process and diagnostic formulation

Similarly to treatment decisions, a stepped and personalised approach can be used for time-efficient and resource-efficient assessments. In some cases, the presentation of autism is clear, and a standardised instrument might only be needed to benchmark the severity and types of social communication difficulties and repetitive behaviour patterns for treatment planning. In other cases, the presenting signs are unclear or complex—for example, a child who clearly has an attention-deficit hyperactivity disorder but also other difficulties, requiring further assessment of signs of autism. A study of sequential assessment strategies showed that about two-thirds of 280 toddlers referred to an autism specialty clinic received sufficiently high (145 [52%]) or low (56 [20%]) scores on the Autism Diagnostic Observation Schedule, 2nd edition, to confirm or exclude an autism diagnosis, with a high

	Indication	Rationale
Prenatal, perinatal, and family medical history taking	All individuals with ASD	Useful to clarify risk factors, guide future investigations, and identify and treat comorbidities
Physical examination (growth parameters [eg, height, weight, and head circumference], skin examination [eg, for tuberous sclerosis complex or neurofibromatosis], neurological examination, and dysmorphology)	All individuals with ASD	Useful to clarify risk factors, guide future investigations, and identify and treat comorbidities
Hearing and vision assessment	All individuals with ASD	Useful to clarify differential diagnosis and provide adequate support and interventions
Genetic testing*	Depending on jurisdiction, all individuals with ASD or those with intellectual disability, dysmorphic features, or congenital anomalies	Useful to assess the genetic aetiology of ASD, predict recurrence, clarify, follow up, and treat co-occurring conditions, and avoid further unnecessary testing
Electroencephalography (prolonged or sleep record preferred)[203]	Individuals with seizures or late or atypical regression	Rule out epilepsy, Landau-Kleffner syndrome, and electrical status epilepticus of sleep
MRI	Individuals with atypical regression, dysmorphology, microcephaly, macrocephaly (seizures, severe intellectual disability, focal neurological findings, severe hypotonia or muscle weakness, and other clinical indicators[130,204]	Identify neurological conditions that provide aetiological insights and often require monitoring and treatment
Metabolic testing†	Individuals with cyclic vomiting, lethargy with minor illnesses, atypical regression, seizures, and other clinical indicators[205]	Although rare, metabolic disorders associated with autism spectrum disorder can be treatable
Blood levels for lead	Individuals with pica or known exposure to lead[122]	Pica increases the risk for lead intoxication

ASD=autism spectrum disorder. *Currently, genetic testing includes chromosomal microarray and fragile X testing; new emerging data might change this recommendation to next-generation sequencing in the future.[202] †No evidence in favour of routine testing of hair, blood, or urine for environmental toxins or heavy metals.

Table 2: **Medical evaluation procedures for autism spectrum disorder**

probability that another autism measure (eg, the Autism Diagnostic Interview, Revised) was unlikely to provide incremental diagnostic prediction.[206] We further examined the efficacy of this decision rule for this Commission and found that of 448 toddlers screening positive in the population-based Autism Birth Cohort Study in the Norwegian Mother, Father and Child Cohort Study (MoBa),[189,207] 27 (6%) had sufficiently high scores and 358 (80%) had very low scores on the Autism Diagnostic Observation Schedule, thus potentially reducing the need for further autism testing except for the 14% of children at risk.

Diagnostic classification criteria derived from standardised assessment instruments (eg, scores, classifications, and likelihood ratios) should be integrated with other relevant clinical information, including factors known to influence instrument efficacy (eg, sex, level of intellectual ability, emotional and behavioural difficulties, and cultural context). Clinicians should use at least one standardised instrument over time, although none of the available instruments are perfect. An important clinical question is whether the pattern of signs is better explained by another condition. For example, a child with a language impairment but developmentally appropriate social communication might be diagnosed with a developmental language disorder.[208] A child with social impairments characterised by impulsive behaviour or discordant relationships but insufficient social deficits otherwise might be diagnosed with attention-deficit hyperactivity disorder. When the diagnostic conclusion is autism, relevant diagnostic specifiers (eg, language delay) are warranted and will inform treatment planning.

Dimensional scores, such as the Autism Diagnostic Observation Schedule Calibrated Severity Score and the Social Responsiveness Scale T-scores, are useful to benchmark the degree of social communication difficulties and repetitive behaviour patterns.[77] Even if the diagnostic conclusion is not autism, the degree of autism-related signs should be documented because of its relevance for treatment planning and tracking potential changes over time.[197] When a clinician is unsure about a diagnosis, additional information can be gathered (eg, home videos, teacher reports, and parent observations) and another visit within weeks or months might be necessary. A second visit, occurring during a reasonable length of time (ie, weeks) or after a transition (eg, starting school) can be particularly valuable for very young children or older children and adolescents with complex difficulties to rule in or out a diagnosis of autism. Continued surveillance and re-assessment might be necessary but, even in children or adults for whom the diagnosis is not yet confirmed, support strategies and interventions addressing the needs of the child or adult and the family should be initiated.

Communicating the assessment results

Guidelines for communicating information about a diagnosis are available in numerous sources (table 1). Most guidelines include meeting in person with the individual or child and family to describe the profile of strengths and challenges, the diagnostic conclusion, what it means for prognosis, and individualised recommendations for support options and interventions. Acceptance and understanding of their child's difference will vary according to familial, community, and cultural perspectives. A second meeting for consideration of the family's cultural perspectives and views on child development might be necessary. For families, learning to work with providers and systems is a process that takes time. Participation in a thoughtfully led assessment and feedback can make a key difference and increase continued engagement.[209]

Focused follow-up evaluations

The strengths and challenges of individuals with autism change across developmental periods and over time,[30,210] and the clinician's responsibility is to ensure that families have ongoing care. In many countries, including HICs, there is an emphasis on initial diagnostic assessments, but less so on follow-up. Focused follow-up assessments should be used to monitor progress and to anticipate vulnerabilities, social difficulties (eg, bullying) and disorders (eg, depression), as well as family circumstances, particularly at times of transition (eg, entry into high school or moving from paediatric to adult services). Theoretically, within a stepped and personalised care model, the primary care provider could assume the lead in ongoing care, monitoring risk, advocating for the family's needs, and referring to specialty care as needed,[128] although how often this happens currently is unclear.

Core assessment components for adolescents and adults

Adolescence is a unique period in development that shares some aspects (eg, sexuality) with adulthood, and others (eg, parental interactions) with childhood. Similarly to a neurotypical adolescent, the autistic adolescent might assert a desire for more privacy and independence. However, parents are still responsible for their care and are usually the primary reporters of signs and symptoms and instigators of evaluations. In adolescence, assessments will be very different for young people with profound autism, those with average or higher intellectual ability, and those in between. As much attention as possible should be given to the questions and priorities of the young person and their caregivers. Referrals are often made because of immediate difficulties related to co-occurring disorders or life transitions. Depending on the purpose of the evaluation, establishing appropriate cognitive and language tests for adolescents and adults with intellectual disabilities is possible, but difficult. Assessment of adaptive skills is particularly important.[210] Parents' memories of early histories can be scant; and at this age, teachers might know students less well than teachers of younger

children. However, diagnostic measures do exist, as do assessments of potential co-occurring conditions such as attention-deficit hyperactivity disorder, limited executive functioning, depression, anxiety, and irritability.[201]

The general expectations for the assessment of adults seeking a possible diagnosis of autism are similar to those for children and adolescents, but differ in the reason for assessment and the parties involved (eg, if the impetus for the evaluation came from the adult individual, spouse, family member, or a social or legal service).[211] Assessments of children and adolescents depend heavily on parent reports, which are often not available for adults. Siblings, with permission of the adult, can provide important historical information when parents cannot. Typically, self-reports of autistic adults might yield discordant information from standardised clinical observations or reports of others close to them,[212,213] calling into question research that relies solely on self-reports and highlighting the need for supportive information. On the other hand, patient-reported outcomes are a major interest in many HICs.[214] In HICs, adults coming for a first diagnosis usually do not have intellectual disabilities,[215] and often have other mental health conditions such as anxiety, depression, attention-deficit hyperactivity disorder,[15] vulnerability to sexual exploitation, and learning disabilities,[216] as well as disorders that are less commonly associated with autism but have some overlapping features, such as schizophrenia.[16] Thus, the diagnostic assessment of adults requires familiarity with autism and other adult mental health conditions, and knowledge of associated services. Standardised measures have lower specificity and sensitivity in adults, but have been very helpful in some studies.[217]

Autism in women and girls

Another aspect of the heterogeneity of autism is reflected in the current interest in whether autism presents differently in females compared with males. This interest is to be welcomed, not least because in one UK population-based study, girls with signs of autism similar to those of boys were less likely to receive a diagnosis of autism from clinical services.[218] This disparity might reflect sociocultural factors in the application of the diagnostic criteria, differential sensitivity in the commonly used screening and diagnostic measures (although this differential sensitivity has been fairly consistently disproven in large-scale studies), or greater resilience or protective factors in girls that appear to reduce the need for clinical services up to a given level of autistic traits.[219] In epidemiological studies, the prevalence of autism is 3–4 times higher in males than females, although the ratio is lower in those with a severe intellectual disability.[5,220] Under-recognition and underdiagnosis in females might account for a proportion of this difference. Findings on age at diagnosis are not consistent but, when sex differences were found, females tended to receive a diagnosis later than males.[5,221]

Much of what is known about autism has been learned from clinical presentation and scientific investigation in males, notwithstanding the fact that Kanner[3] included descriptions of girls in his seminal early accounts. In studies that have examined sex differences in phenotypic presentation, the most consistent finding is lower severity of restricted and repetitive behaviours and greater social communication impairment in females with autism (shown in some but not all studies), although effects sizes are small.[222,223] In addition, some studies have reported higher levels of externalising behaviour in females than in males.[222] Clinicians need to be aware of the potential for under-recognition of signs of autism in women and girls and different expressions in particular sign and symptom clusters. In the social communication domain, some hypothetically female traits (eg, higher social attention or motivation for friendship) can result in the presentation of autism in girls being somewhat different from that seen in boys.[224] In the domain of rigid and repetitive behaviours and interests, behaviours can be misinterpreted if viewed through the cultural lens of activities that are typically considered gender-appropriate. For example, young autistic girls might, like their peers, have a large collection of dolls, but only play with them in an isolated, repetitive, and non-imaginative manner. Few replicable findings on cognitive differences have been reported, although the notion that females with autism can in some ways camouflage or compensate for autistic difficulties has attracted much attention (including from autistic women who identify with the concept), which still requires further empirical validation.[225] Personal accounts from women and girls describing growing up with autism are helpful for families and clinicians working with autistic girls and women, and provide models of female autistic self-identity.[226] Questions of how some interventions can have different effects in females and males have seldom been addressed and should be taken into account by clinicians and families.

Gender non-conformity

Gender non-conformity, or gender variance, including transgender identity and non-heterosexual sexual orientation, is more common in autistic individuals (and those with other neurodevelopmental conditions) than in the general population.[24] This difference might be part of a different concept of self, less reliance on or reference to social norms, or part of a neurodiverse lived experience of (and outlook on) the world. For some individuals, gender non-conformity in combination with an autistic self-identity is an example of social and cultural intersectionality. Clinically, recognition and assessment of these differences is important to help identify individuals, both male and female, who might be vulnerable to (sexual) exploitation and bullying from peers. There is also an elevated prevalence of gender dysphoria (the term used in the DSM-5; it is called gender incongruence in the ICD-11) in autistic individuals.[227] Recognition of possible autism in

this clinical population is important because it would indicate the need to tailor interventions that can be used to ameliorate potential resulting distress and self-harm or neglect, as well as potential medical interventions such as puberty suppression and cross-sex hormone intervention. Clinicians and parents can sometimes dismiss gender dysphoria as an autistic trait; an unusual or over-focused interest. Conversely, autism might be under-recognised in an adolescent if their social difficulties are ascribed to gender dysphoria in isolation instead of with other potential signs and symptoms of autism.[227]

Barriers to access and global differences in approaches to assessment and diagnosis

Some groups in HICs and LMICs are more likely to be diagnosed with autism later in life; these include females, children with age-appropriate language and cognitive skills or attention-deficit hyperactivity disorder signs, and children in families of low socioeconomic status, of a minority ethnic group, or those living in non-urban areas.[228,229] Most individuals with autism remain undiagnosed in LMICs[230] and other low-resource settings, where developmental surveillance is rarely done for any neurodevelopmental disorder. Parents with concerns about developmental delays might struggle to obtain a referral to a service with capacity for developmental assessment. Many LMICs have low levels of literacy, which restricts families' abilities to access appropriate services. Children might be brought to clinics by adults other than their biological parents, limiting historical information. Despite parental concerns about their child's development, many families do not start the journey to assessment and diagnosis due to poor understanding and awareness of the signs of autism, stigma, or financial barriers. Families can even receive false reassurance in primary care settings due to insufficient staff knowledge about neurodevelopmental disorders such as autism, and can then face long delays to reach a specialist level of care because of the scarce numbers of specialist centres. In LMICs and in low-income regions within HICs, children who finally receive a diagnosis tend to be those with more complex clinical presentations, including intellectual disabilities or epilepsy. Children with milder social communications delays might not come to clinical attention until adolescence, or at all.[231]

Summary of stepped care and personalised health approach

We advocate for a stepped, personalised, transdiagnostic approach that addresses development and multiple dimensions in identification, assessment, and treatment. This approach moves away from an emphasis on a categorical diagnosis as an endpoint and towards a focus on treatable problems that affect the quality of life of the individual and families within their communities. This model recommends that assessments focus on information that is relevant for treatment planning in collaboration with families, both in HICs and LMICs. Follow-up care should consider mutual goals set out by the clinician and the autistic individual, family, or both to monitor progress and ongoing service needs. In addition to an emphasis on family and individual priorities, personalised stepped care can use brief caregiver reports and validated screening measures to identify the need for further investigation, to rule out particular concerns (eg, developmental delays or co-occurring conditions), and to highlight ways to use community resources within the context of the family and community. Panel 5 summarises screening, assessment, and diagnosis recommendations for clinical practice.

Designing research that has meaning for clinical practice

Prediction of treatment response: from assessment to intervention

With a better understanding about who is most likely to respond to which interventions, when, at what intensity, and for what duration (eg, the interaction between heterogeneity of manifestations of autism and treatment response), resources could be allocated more equitably to those most likely to benefit from them. In addition, more input is needed from autistic individuals and their families about their experiences, needs, and aspirations. This information is also relevant to prioritising capacity building to provide different interventions in LMICs and underserved communities. Some studies have shown that children with better skills at baseline make the greatest gains from an intervention.[89,232] By contrast, other studies found that children with the fewest skills progressed whereas more skilled participants did not improve.[139,233] This divergence is especially relevant for clinical trials, in which investigators are expected to define the minimal level of change needed to justify the treatment. The number of adequate outcome measures is scarce, but even scarcer is the ability to identify mediators of treatment response, which are very rare, and moderators (factors that predict greater treatment responsiveness, including the factors that affect individuals' responses to various treatments). The specification of minimally meaningful improvement might be more straightforward for medication studies than, for example, teaching parents who begin with different levels of skill or knowledge to support their children's communication, which also varies. Computing these metrics for many autism treatments is possible, but seldom done.

Matching treatment type (eg, parent-mediated or direct; cognitive behaviour therapy or medication, or both) and intensity (eg, 5–20 h per week in a structured programme for preschool-aged children) to need and benefit is particularly important in planning services in LMICs but also in HICs, where expensive, intensive treatments might be prescribed when not needed or unlikely to result in the promised change. Analyses in autism studies that identify moderators of treatment response are rare because of insufficient sample sizes,

Panel 5: **Screening, assessment, and diagnosis recommendations for clinical practice**

1 Developmental surveillance within health-care and education systems can identify young children with autism and other neurodevelopmental disorders whose difficulties have not previously been recognised or characterised; screening instruments can provide useful information but should not form the sole basis for triage for further assessment and support; parental concerns should always be included as part of ongoing developmental surveillance

2 The aim of a diagnostic assessment is to inform intervention and service planning for the individual and family
- The assessment must be more than an enumeration of autism features and a formal diagnosis, and should include the identification of strengths (eg, visual-spatial skills and attention to detail) and difficulties (eg, language and motor skills), general delays, adaptive skills (eg, toileting and dressing), behaviour problems (eg, temper tantrums and aggression), and overall health that might not fit into formal diagnostic categories, but are relevant to short-term and long-term outcomes and care decisions
- Co-occurring conditions, including intellectual disability, should be considered with the same diagnostic and treatment standards in people with autism as in other children and adults
- Personal and family concerns, preferences, resources, and needs should be considered from the start in any evaluation

3 Use of at least one standardised instrument for documentation of the severity of signs of autism and to provide a benchmark for later reassessments is recommended when empirically tested instruments that are appropriate for the culture and community are available; clinical consensus is the gold standard in many countries, but available evidence for the reliability of these diagnoses is seldom reported and other data strongly suggest that clinicians make more reliable decisions when they have access to standardised information from caregivers and observations

4 Because needs and skills change over time, reassessments are essential for adjusting interventions and services; in addition to reviewing original treatment goals and overall functioning, validated measures of behavioural problems and adaptive functioning allow evidence-based monitoring of progress

5 Given the rapid developmental changes in preschool years (generally meaning up to the age of 6 years), focused re-evaluations within a year of the first diagnosis are strongly recommended; during childhood, adolescence, and adulthood, follow-up visits should address transitions, specific concerns, and progress

6 Medical evaluations identify potential causes and co-occurring medical conditions that might require further assessment or specific treatments; the medical evaluation can also prompt genetic testing that might not affect treatment but can inform recurrence risk and families' access to information

7 Evaluations of adolescents and adults might require adaptations from traditional approaches to address the role of parents and families. Recognition of the rights and desires of the teenager or adult, of the somewhat differing concerns (eg, sexuality), and of co-occurring disorders that arise in this age group (eg, anxiety or depression) is also warranted

8 Girls, children with co-occurring disorders, those with age-appropriate language and cognitive skills, and children from socially disadvantaged backgrounds, minority ethnic groups, or living in non-urban areas are at higher risk of late diagnoses; increased clinical awareness and policy changes are needed to improve detection in these subgroups

variability in measuring informative predictors (eg, some studies do not include language level or intelligence quotient; others do not include family factors), and because randomised clinical trials often deliberately impose stringent entry criteria to control variability. For example, participants with a very low intelligence quotient or severe behaviour problems are excluded from many studies.[234] Studies that have the power to address actual mediators are even rarer.[235] An area of increasing interest that might, in future, improve the precision of measuring potential moderators is the identification of relevant stratification biomarkers (eg, biochemical indices, genotypes, electroencephalograms, or neuro-imaging signatures).[80,236,237] However, these measures first need to meet basic standards for replicability and validity and then be tested in trials to provide evidence that biological differences do relate to different intervention mechanisms and responses. Such work is currently underway in several international consortia (eg, European Autism Interventions—A Multicentre Study for Developing New Medications;[238] Autism Biomarkers Consortium for Clinical Trials;[236] and Province of Ontario Neurodevelopmental Network[237]), but translation to routine clinical practice, even in expert centres in HICs, is at least several years away.

Evidence-based approaches to streamline assessments

A more efficient approach to moving from assessment to effective treatment in the face of the heterogeneity of autism is based on the psychometrics of diagnostic and dimensional assessment instruments that make use of what is already known about treatment-related issues, such as presenting problems, referral concerns, developmental level, or age (figure 8). This approach recognises that practitioners are often dealing with more than one disorder and, if they can use relatively brief questionnaires to rule out some conditions, more assessment time can be spent on crucial matters. In line with stepped care and personalised medicine, this approach is focused on supporting the clinician in

A

Instrument	AUC (95% CI)	Cutoff	Single instrument		Combined with ADOS-2 (ASD cutoff)	
					Both positive	Both negative
			LR+ (95% CI)	LR– (95% CI)	LR+ (95% CI)	LR– (95% CI)
SCQ	0·80 (0·73–0·86)	≥11	1·8 (1·5–2·1)	0·3 (0·2–0·5)	7·2 (5·0–10·5)	0·02 (0·00–0·25)
		≥15	3·3 (2·4–4·4)	0·5 (0·3–0·6)	12·2 (7·0–21·2)	0·07 (0·02–0·2)
M-CHAT crucial 6 items	0·73 (0·66–0·80)	≥1	3·0 (2·3–4·1)	0·5 (0·3–0·6)	15·5 (8·4–28·8)	0·07 (0·02–0·2)
		≥2	5·0 (2·9–8·6)	0·7 (0·6–0·8)	23·7 (8·4–67·0)	0·1 (0·04–0·2)
SDQ prosocial scale	0·75 (0·68–0·82)	≤6	1·7 (1·5–2·1)	0·4 (0·2–0·6)	7·6 (5·3–11·1)	0·07 (0·02–0·3)
		≤4	3·4 (2·4–4·7)	0·5 (0·4–0·7)	10·6 (6·0–18·6)	0·06 (0·02–1·2)
ADI-R Toddler	0·90 (0·87–0·94)	Clinical	7·2 (4·9–10·7)	0·4 (0·3–0·5)	19·9 (10·1–39·0)	0·04 (0·01–0·2)
		Research	**11·5 (6·2–21·2)**	0·6 (0·5–0·7)	66·6 (16·3–272·1)	0·1 (0·05–0·2)
ADOS-2	0·93 (0·89–0·96)	ASD	5·3 (4·1–6·9)	0·1 (0·1–0·3)	..	..
		Autism	10·2 (6·7–15·7)	0·3 (0·2–0·4)	..	..

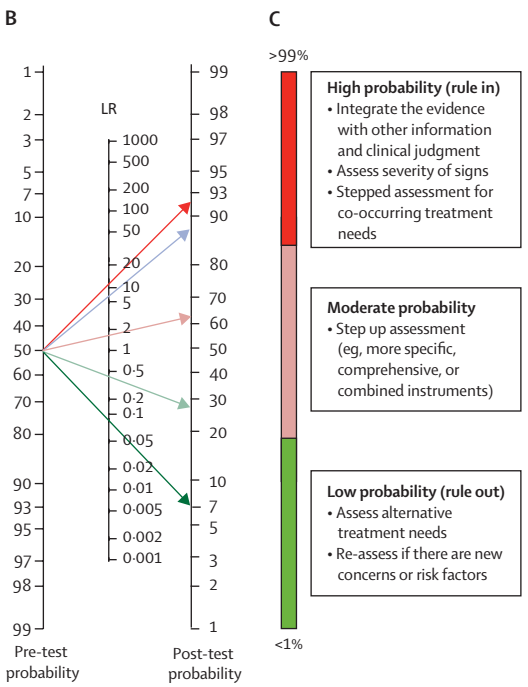


Figure 9: **Probability-based approach to assessment**

LRs were derived from the comparison of toddlers diagnosed with autism versus other psychiatric disorders without autism in the Autism Birth Cohort Study nested in the Norwegian Mother, Father and Child Cohort Study. LRs should be estimated from samples representative (eg, in age and comparison group) of the population in which the instrument is applied.[239] Use of the revised probability from one instrument as the pre-test probability for the next instrument requires that the two instruments are based on different information and make independent and additive contributions to predict the diagnosis,[240] such as parent account from daily life at home and direct observation of interaction with an unfamiliar adult. (A) LRs of autism based on results from single instruments and combinations of parent-based instruments and the clinician-based ADOS-2. (B) Example of a toddler with a 50% starting probability of having autism. An SDQ prosocial score of 6 or less would increase the probability of autism to 63% when considered alone (light red), and to 88% if combined with an ADOS-2 result above the autism spectrum disorder cutoff (purple). By contrast, an average-range (>6) SDQ prosocial score would reduce the probability to 29% (light green) when considered alone, and to 7% if combined with an ADOS-2 score below the ASD cut-off (dark green). In some cases, a single instrument result could change the probability sufficiently to exceed the rule-in or rule-out threshold (red). (C) Thresholds for ruling in or out a diagnosis or service need, which need to be personalised. ADI-R=Autism Diagnostic Interview, Revised. ADOS-2=Autism Diagnostic Observation Schedule, 2nd edition. ASD=autism spectrum disorder. AUC=area under the receiver operating characteristic curve. LR=likelihood ratio. LR+=positive likelihood ratio. LR–=negative likelihood ratio. M-CHAT=Modified Checklist for Autism in Toddlers. SCQ=Social Communication Questionnaire, SDQ=Strengths and Difficulties Questionnaire.

offering the most appropriate services for a child, adult, or family's needs.[239] Here we again present epidemiological data from MoBa to illustrate how to apply these strategies.

Figure 9 illustrates how the pre-test probability that an individual has a given diagnosis or treatment need can be estimated. A likelihood ratio (LR) is then used to combine this probability with information from risk factors and with results from standardised instruments to question whether the probability is high enough to rule in or out a particular diagnosis or treatment need. This approach is a more sophisticated version of the earlier discussion on whether the Autism Diagnostic Observation Schedule alone is sufficient or if the additional time for an Autism Diagnostic Interview is warranted.[206]

In the MoBa population sample of 679 children aged 35–47 months assessed in the Autism Birth Cohort Study clinic,[170] LRs of diagnosis of autism were derived for single and combined instrument criteria[189] for children who were diagnosed with autism (n=66) or other neurodevelopmental disorders (n=303). Figure 9A shows the LRs of autism based on results from single instruments and combinations of parent-based instruments and the clinician-based Autism Diagnostic Observation Schedule, 2nd edition, which can help to estimate the post-test probability of autism in an individual case. Positive LRs are informative for ruling in the diagnosis or treatment need, with an LR of 2 corresponding to approximately 15%, an LR of 5 corresponding to approximately 30%, and an LR of 10 corresponding to approximately 45% increases in probability. Negative LRs, on the other hand, are informative for ruling out the diagnosis or treatment need, with a negative LR of 0·5 corresponding to approximately 15%, a negative LR of 0·2 corresponding to approximately 30%, and a negative LR of 0·1 corresponding to approximately 45% decreases in probability.[241] In this approach, the recommendation is to start with a broadband screener, and move to more specific and comprehensive instruments as necessary to increase or decrease the probability sufficiently to rule in or out the diagnosis or

treatment need.[239] Figure 9B shows an example of a toddler with a 50% starting probability of autism. In this case, an Autism Diagnostic Interview, Revised Toddler score that meets the more stringent research threshold would increase the probability of autism to 92%. If this score exceeded the personalised probability threshold and the clinician's interaction with and observations of the child also supported a diagnosis of autism, the individual, family, and clinical team could decide to finish the stepped and personalised assessment.

The clinician needs to personalise the threshold for ruling in or out a diagnosis or service need (figure 9C), taking into account the benefits and costs associated with the diagnosis and intervention and the family's perspectives and preferences (figure 5).[240] For example, a moderately high probability threshold might be sufficient when the goal is to evaluate if a child with anxiety is in need of autism-specific adaptations in cognitive behaviour therapy treatment; or in deciding if a language-delayed child in preschool should receive a low-intensity, parent-mediated, early intervention aimed at improving social communication. On the other hand, in a diagnostic evaluation for long-term treatment planning, or beginning an intensive autism-focused behavioural treatment, the clinician and the individual or family can decide together on a high probability threshold.

This approach is common in evidence-based medicine. In mental health, published papers based on similar approaches are available for bipolar disorder[242] and attention-deficit hyperactivity disorder.[243] Printable visual probability nomograms (eg, figure 9B), online calculators, and apps are freely available to calculate post-test probability.[244] These probabilities are not necessarily something a clinician would calculate for an individual patient, but rather a way that clinicians could use group data to make recommendations for sequences of assessments and potential cutoffs (which would depend on the context and the characteristics of the individual). Clinicians must integrate information beyond reading scores on instruments to move through personalised steps (figure 8).

Mechanisms of change

Despite the growing body of empirical support for a small number of treatment approaches that work in autism and for the use of interventions with clear or probable evidentiary support, relatively little is known about how or why evidence-based treatments work, either in terms of mechanisms of change or active components. The focus of many research funders in HICs has been on the identification of neurobiological factors that could contribute to a positive treatment response (as previously summarised).[236–238] To date, however, the usefulness of these research efforts to families and clinicians has been alluring, but less fruitful.[1] The difficulties of identifying the role of biomarkers in treatment response are manifold. First, because of the heterogeneity of autism, the putative biomarker might only be present in a subgroup and therefore evade detection in broader populations. Second, the developmental nature of autism suggests that a given biomarker might be relevant at some stages of development, but not at others. Finally, the replicability of neurobiological measures and their applicability to individuals beyond specific subgroups is unclear.[245] More focused consideration of behavioural factors that mediate change and that can be reliably measured and are more accessible to most providers might provide more immediately useful information.

Moreover, the efficacy of an intervention in a randomised controlled trial can be affected by known or unknown (and measured or unmeasured) intervening variables (eg, improvements in co-occurring sleep problems or decreased parental stress during an intervention study can contribute to improvements in disruptive behaviour).[246] In these examples, determining the time sequence or the direction of change can be difficult: for instance, did a decrease in the child's disruptive behaviour reduce parental stress, which then contributed to improved parental efficacy and further reduction in disruptive behaviour, or vice versa?[247] Collectively, these considerations indicate the need for more tailored intervention approaches with a priori hypotheses about mechanisms of change, including psychosocial factors and neurobiological measures, built into research designs with sufficient sample sizes to detect them.[233,235]

In the meantime, studies of environmental and active behavioural components do exist. Findings on the importance of changes in parental behaviour for social communication outcomes and core diagnostic features in the child have been replicated.[103,248] In fact, the documented feasibility of many parent-mediated interventions even provide what is known as implementation data, which are sorely needed for interventions in the community. Proximal improvements in joint engagement have been linked to downstream effects on social communication skills and language development.[41] Successful engagement in school playground activities predicts positive response to social interventions.[249] Parental and caregiver preferences and beliefs in a treatment might be relevant to child treatment response and potential change.[98]

Intensity and duration

Knowledge about how much and for how long a given intervention should be delivered is scarce, and few systematic comparisons have been done to date.[40,95] A recent study by Rogers and colleagues,[74] done across three different sites, compared two types of intervention (applied behaviour analysis and Early Start Denver Model) at two different, relatively high intensities (12 h per week *vs* 20 h per week) for 2-year-olds with autism. There was no difference in outcome according to either treatment

type or treatment intensity on autism manifestations, although greater improvement was found at one of the three sites with greater intensity. This finding is a start; the next step would be to determine if regular, relatively intense, face-to-face interventions of this kind have effects different from those of typical clinic visits or low-intensity, parent-mediated interventions that occur even less frequently.

Current public policy debates on the format and resources for early intervention are taking place in many countries in the relative absence of reliable data. In both HICs and LMICs, decisions about timing and intensity of treatment should be based on evidence rather than on whatever is most avidly promoted, recognising that change is possible but cannot be taken for granted. Questions about the timing and intensity of intervention are not just relevant to early childhood. As discussed in the Potential for change section, these concerns extend to adolescence and adulthood because developmental changes are still occurring during these periods, and individuals continue to be susceptible to the onset of co-occurring conditions during these stages. As stated earlier, concerns about the timing and intensity of intervention are highly relevant to designing programmes in low-resource environments, where selection decisions about resource management are crucial. Where such gaps exist, systematic studies are needed to provide evidence on which decisions should be made.

Another important but often overlooked factor is post-treatment follow-up. Post-intervention booster sessions have been offered in some cases and might be helpful,[37] but have not yet been formally evaluated in autism trials. Some studies have shown continued benefit for up to 6 months after treatment.[142,144] However, many empirically supported interventions, such as parent-mediated, early social communication programmes, parent training for behaviour problems, social skills training, and cognitive behaviour therapy for anxiety have primarily been shown to have short-term effects,[70,71] and relatively little is known about longer term outcomes.

Issues in research design and outcomes

Amid these quandaries, strikingly little is known about the practical issues involved in implementing the most common and well studied interventions beyond a few parent-mediated interventions. The number of review papers, meta-analyses, and guidelines on autism interventions far exceeds the number of high-quality randomised controlled trials of any intervention.[31,72] Randomised controlled trials are essential to expand the evidence base for short-term specific interventions. However, the recommended and trusted sequence for developing and testing complex interventions (ie, model development, pilot feasibility, efficacy and tolerability, effectiveness in a wider sampling frame, and implementation into community settings) has rarely been achieved in autism.[250] The beneficial effects of combinations of psychosocial and pharmacological treatments are widely recognised, but there is almost no research about such combinations.[72] Although fundamentally rational, the traditional pathway of randomised controlled trials is time-consuming and expensive, and few interventions in autism are likely to go through this entire sequence. Some researchers have called for a massive investment in high-quality, systematic, well designed, multisite randomised controlled trials for the many different interventions currently in use. The assumption is that an individual child or adult and respective family will move from one short-term modular intervention to another throughout life.[72,103] Yet, this approach to creating a clinically useful evidence base is unrealistic. Even if funding were available for the many large-scale trials that would be needed to study interventions at different ages and for different subsets of autistic children and adults, particularly if the aim was to test for mediators, most psychosocial interventions last only for 3–4 months, and there is limited evidence supporting their generalisation beyond proximal intervention targets.[251] As the child or adult faces new demands and requires different approaches, other modular interventions that could be effective would be put in place. However, the practical challenges of doing brief randomised controlled trials at each point in time for different groups of people with autism are immense. Modular interventions make sense on the assumption that they teach a specific skill that could potentially be generalised or evoke a cascade of learning (eg, helping a family of a young child play and communicate with the child leads to improved later language or social skills).[41,103,252] However, to our knowledge, no funding mechanisms exist for such research programmes, even in HICs with the largest research spending; nor are such programmes likely to be feasible to implement over a long period of time without shifts in priorities in funding agencies. Moreover, few follow-up studies document the continued progress beyond the immediate goals of such interventions; even then, causal connections are very difficult to identify.[253]

Showing the efficacy of an intervention does not guarantee adoption or sustainability in the wider community.[254] The recognition that implementation of approaches is separate from empirical support is at the root of implementation science.[255] Evidence showing that effect sizes in university-based interventions are larger than those in the community[256] is not surprising, but neither does it mean that interventions in the community cannot be effective. Rather, this difference in efficacy should be an impetus for refining methods on how to implement interventions in the community.[257] The gap between what research currently offers and the needs of individuals, families, and communities concerned about autism calls for action and rethinking of the science of clinical practice in this field. More systematic consideration of the essential intervention components and adaptations required to promote adoption in the community is a

pressing matter to improve the lives of people with autism and their families.[49,72] Perhaps more so than in other fields such as psychiatry and paediatrics, most randomised controlled trials of psychosocial interventions in autism have remained closely tied to the university-based programme developers. Although these close ties have the advantage of ensuring expert supervision and fidelity of each so-called bespoke treatment model, they limit the number of independent replications of different approaches and the identification of common and effective components—which are common to many programmes—that can be tested more broadly in community services by non-expert practitioners, and that are necessary for the study of wider implementation.

Randomised controlled trials are the gold standard of evidence and the most recognised approach for studying interventions. Notwithstanding, autism research could benefit from alternative approaches developed in other areas of public and mental health,[258] which would require changes to systems that currently rely on the traditional standards of high-quality research, such as guideline writing. A range of approaches that can be used to assess causality are available. Engaging stakeholders (eg, consumers, clinicians, administrators, family members, and autistic people) in the development and adaptation of interventions is a starting point. Building the capacity of systems to receive the intervention and strategies to facilitate successful introduction and sustained adoption of a new programme are other essential steps.[141,259–261] To build an evidence base and test interventions in real-world conditions, with due consideration of human resources and cost, a wide range of research designs will be needed. Effectiveness can be tested with implementation by researchers in the practice setting, such as peer-mediated approaches in schools.[148] Implementation can be done by community personnel (eg, teachers and child-care workers) with monitoring and outcome measures collected by researchers.[147]

Psychosocial randomised controlled trials often compare a study intervention to treatment as usual. As noted, usual care varies widely and its effects can equal or exceed the benefits of the study intervention.[95] Designs can test the order of interventions through a series of sequenced randomisations of study participants based on initial response, such as in a sequential multiple assignment randomised trial design. These research designs have begun to be applied in autism[40,93] to show the benefits of different treatments (eg, direct therapy only *vs* use of speech-generating devices) and are an embodiment of stepped care and personalised health in some ways. However, they could be used even more efficiently, with deliberate planning and sufficient sample sizes, to show which treatments worked best with which children and how much of an early response to a treatment predicts eventual outcome with that intervention, another approach, or both. Sequential multiple assignment randomised trial designs are promising, but require large samples and sophisticated data analysis.[246] Many interventions share common elements, some of which can be essential. Studies focused on testing active components or combinations of components, such as multiphase optimisation strategy designs, can be used to test a streamlined treatment package that is scalable and less expensive.[258] Another application of multiphase optimisation strategy designs could involve a randomised evaluation of implementation strategies with a focus on scalability.[262]

Observational, non-randomised controlled trials have many methodological limitations, including unmeasured confounding, reverse causation, and other biases. However, because the long-term follow-up required to establish effects from randomised controlled trials can be too expensive or too difficult to reach due to attrition, observational studies can be a practical way to identify treatment targets and evaluate interventions. A range of approaches exist that can be used to assess causality, such as natural experiments and instrumental variable analysis. A further approach to reduce the lag between efficacy and implementation is the application of hybrid study designs that combine effectiveness and implementation.[263] In a hybrid design, a study can test specific implementation strategies in the context of an efficacy study. For example, in a population with little access to mental health professionals, an implementation–effectiveness study could compare two approaches for training parents to train other parents in behaviour management.[259] The results could reassure policy makers, clinicians, and consumers about which implementation strategy is ready for wider application.

Systematic epidemiological studies, careful single-case studies with systematic efforts to reduce biases, and designs such as stepped wedge trials offer ways to approach the inherent challenges of research with a heterogeneous and developmentally changing population.[264] Yet, most current practice guidelines would not include such studies. In addition, there is great interest in the use of novel modalities to deliver and assess interventions and training in hard-to-reach communities, such as digital technology and remote monitoring.[265] However, to date, there is little evidence that such methods reduce the time lag from research to practice, or reduce disparities in access between HICs and LMICs.

Research in schools

Schools are a system that provides a unique opportunity to bridge research and practice, although how often, or how well, this bridging occurs is variable. In most HICs, public schools cannot legally exclude children with special needs. In LMICs, parents might struggle to have their children included in mainstream schools and advocate for appropriate services for students who need an adapted structure.[266] The mandate to include children with autism in schools should be a primary public policy

focus. In addition to academic skill building, appropriate teaching in school should increase adaptive skills and promote independence. Schools provide daily environments that can be incredibly helpful or difficult (for example, when bullying occurs), depending on the person–environment fit. Barriers to school-based research include challenges in obtaining compensation from administrators and community personnel, which is essential to support school providers' use of a novel intervention. Challenges also exist in training providers to deliver interventions with fidelity.[49,267] Notwithstanding the difficulties, if school-based research is properly designed and supported, the large number of children with autism served in schools provides a natural context to test interventions at scale with a focus on relevant outcomes, such as retention in the classroom setting, acquisition of life skills, and better peer interactions. School-based research can be particularly useful in underserved communities and in LMICs.

Intervention research across the life span with a targeted focus on adolescents and adults

Intervention research with adolescents and young adults with autism has primarily focused on social skills or social cognition[149,268] and co-occurring anxiety.[143,152] Some newer programmes, however, have addressed executive functioning[46] and practical issues such as employment.[101] Most of this research has not included individuals with intellectual disabilities. Future research that tests interventions to promote achievable independence for autistic adolescents and adults is needed, focusing on outcomes such as employment,[101] meaningful and generalisable social skills, improvement of common co-occurring mental health conditions,[156,269] and broader functioning and wellbeing (eg, as per the WHO International Classification of Functioning, Disability and Health).[270] Research on autism in adulthood in general is scarce and relatively recent (with most studies dating of the past 20 years); that on older adults is almost non-existent, and a pressing need exists for funding agencies and researchers to prioritise intervention and evaluation research across the whole ability range and life span. In addition, the inclusion of people with lived experience of autism in the planning of and doing such research is increasingly recognised as essential. The brevity of this paragraph reflects the little data available in this area, not its importance.

Inclusion of under-represented and underserved communities and individuals

Most of the evidence derived from intervention research in autism is based on research in middle-income countries and HICs, with White children constituting the majority of participants.[21,271] The growing evidence of the transportability of adapted versions of well documented approaches is encouraging;[39,141] more research in low-income countries is clearly needed. Research on moving effective interventions into underserved areas, culturally and linguistically diverse communities, and socioeconomically disadvantaged locations is scarce. Research efforts in LMICs and underserved communities require cultural adaptation and documentation of intervention implementation and effectiveness.[87] Finally, more research attention is warranted for subgroups of underserved individuals with autism, such as minimally verbal children, individuals with profound autism, adults, females, minority ethnic groups, immigrants, and refugees.

Considerations for research in LMICs

Although we support and aim for research to occur across diverse settings and communities, these nascent research efforts need to be done with mandated ethical guidelines. In some LMICs, ethics review boards might not exist; a power imbalance between researchers and participants can occur; and some families and individuals might be unfamiliar with the meaning of informed consent and their right to refuse to participate. To ensure that vulnerable families are not subjected to unethical practices, research oversight of the highest quality is imperative. As is true in any context, research in LMICs should embrace a participatory approach that includes autistic people, their families, and potential providers to maximise the utility and relevance of the research.[272]

Understanding the relative cost–benefits of empirically supported interventions

Resources are never enough to meet all the needs or satisfy all wants. Therefore, decisions about which interventions to deliver are usually informed not only by whether they are effective, but also by how much they cost. This issue is a pressing public policy matter both in HICs and LMICs. Unfortunately, the cost-effectiveness of autism interventions is drastically understudied (with rare exceptions[273]), and we recommend this study as a priority for future clinical research (panel 6). Furthermore, both short-term and long-term perspectives warrant consideration. For some interventions, small initial effects, such as in social communication, might translate into longer-term gains, whereas the effects of other interventions can be limited to the immediate context. These interventions could, in turn, have very different economic implications. To advocate for the needs of autistic people and their families wherever they live, the challenge is how to implement scalable strategies for the delivery of evidence-based interventions or best practices to improve access to care within the constraints of available human resources and budgets.

Measuring outcomes

Current empirical data on interventions is fraught by the scarcity of comparable outcome measures across studies. Although many measures have been used in autism treatment research,[274] only a few have been validated as

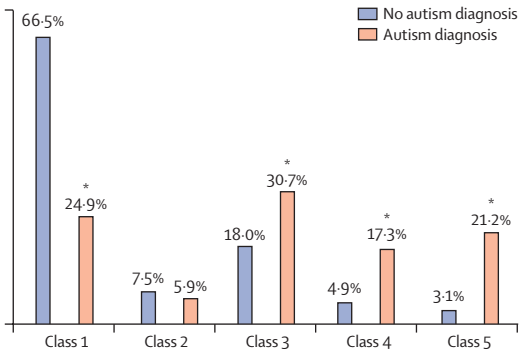
outcomes[275] that reflect meaningful changes in the lives of people with autism. More standard measures, designed to be meaningful and sensitive to changes in core sign and symptom domains or co-occurring conditions and that can be compared across treatments, are necessary.[4,276–278] Patient-reported outcome measures, often completed by parents or carers and teachers for children, are important,[279] but many autism interventions are psychosocial, hindering the masking of participants, parents, and teachers who are best placed to report on meaningful everyday outcomes. Placebo effects are also well known to be strong. In other neurodevelopmental disorders, such as attention-deficit hyperactivity disorder, unblinded outcome measures (eg, parent reports of the benefits of parent training) produced biased (ie, higher) estimates of effect sizes than blinded, objective, performance-based measures.[280] By contrast, more objective measures (eg, the Autism Diagnostic Observation Schedule) are less susceptible to bias, but are expensive and relatively insensitive to short-term changes. Other measures do not have ecological validity (ie, might not be generalisable to real-world settings). Practical outcomes such as participation in school or parent-stress measures are less often reported, even when available. To do large-scale trials in community settings, outcome measures need to be usable across different studies, inexpensive, accurate, unbiased, and relate to treatment targets, as opposed to diagnoses only. Poor outcome measurement, the presence of placebo or expectancy effects,[281] and the difficulty of finding untreated control groups in HICs hamper efforts to distinguish ineffective treatments from invalid measures.

Measures that allow for mechanistic analyses and better ongoing progress monitoring are also needed.[235] The use of formative (and not just summative) measures also fits within current advanced methodological approaches being used to examine treatment efficacy in autism, such as in multiphase optimisation strategy and sequential multiple assignment randomised trial designs.[40] In some areas of mental health, there has been a push within clinical research to develop ways to document progress regularly in standardised ways, often digitally, and provide feedback to the provider and the family or an adolescent or young adult during treatment.[282] Applied behaviour analysis has a long tradition of documenting children's responses in detail, with those data sometimes shared with the family. Other approaches, such as Youth Top Problems, Parent Target Problems,[252] and other patient-reported outcomes engage the parent, and adolescents when possible, in nominating the most pressing problems. Progress on these problems is reviewed at follow-up visits. Both the act of reporting and the providers' review of the information have been linked to greater progress,[283] although measuring progress is complicated in a heterogeneous disorder for which progress is sometimes slow. However, some examples of measures in autism could suit the dual purpose of

Panel 6: **Recommendations for clinical research**

1 The most urgent questions involve what works for whom, when, and in what intensity or amount
   - Answers to these questions would allow appropriate development of scalable interventions worldwide and are essential to improving the science underlying practice decisions in low-income and middle-income countries (LMICs); future research both in high-income countries and LMICs must be sufficiently powered to address these questions
   - Research with adolescents and adults is particularly needed, although a better understanding of developmental differences in early years (where changes are more rapid) and their variance with interventions (as a moderator and as predictors) is also important
2 Randomised controlled trials for short-term interventions (including medication and behavioural trials) are a priority, but the field needs to move on from basic two-group trial designs comparing a targeted intervention against treatment-as-usual to test the relative efficacy of different types or intensity or combinations of interventions
3 Implementation and effectiveness trials are needed to address gaps such as effectiveness outside clinics, effectiveness with diverse populations across age ranges, developmental levels, and socioeconomic and cultural backgrounds, and the implementation of required training and systems changes required to make interventions scalable
4 Randomised controlled trials should assess generalisation beyond treatment-specific assessments and parent reports of short-term changes to address long-term follow-up of focused interventions, including cost-effectiveness and budget impact analyses in their design; potential mechanisms of change, including child, family, and social factors, and moderators of outcomes, should be prioritised as much as proving that a given short-term intervention is effective
5 Alternatives to traditional randomised controlled trials should be developed and supported to address other challenges, including difficulties in finding comparison groups for treatment as usual, circumstances where randomisation is not feasible, studies of use of already-in-place approaches and tools, and therapies commonly used in clinical practice (eg, speech-language therapy, occupational therapy, or educational approaches); systems supporting guidelines should address the need for such designs and consider how to evaluate them beyond traditional standards
6 Along with predictors of progress and outcomes, research should address factors that drive resilience and capabilities in some families and individuals and those that serve as barriers and challenges to others
7 Inclusion of stakeholders in the development of clinical trial designs and outcome measures is vital, including on how to best use patient-reported outcome measures
8 Research on early identification in preschool-aged children (generally meaning up to the age of 6 years) should shift the focus from short-term evaluations of the accuracy of autism-specific screening instruments to effectiveness of broader surveillance strategies tailored to local models of service provision, which should aim to identify both autism and other early-emerging and commonly co-occurring neurodevelopmental conditions and include longer-term follow-up and evaluation of costs and benefits to the whole population
9 High-quality research in LMICs is possible; support for such studies is crucial and should address implementation and feasibility as well as outcomes
10 Technology has the potential to reduce disparities and improve clinical care and quality of life for individuals and families who live with autism and other neurodevelopmental conditions; to realise this potential for autism, rigorous scientific scrutiny in partnership with the autism community and infrastructural developments will be required to bridge the worldwide digital and knowledge divide

A



B

	Class 1 (reference): stably low E and B	Class 2: transient E and B	Class 3: persistent B and low E	Class 4: increasing E and low B	Class 5: high and increasing E and B
Children with autism, n	186	44	229	129	158
Probability of outcomes at the age of 8 years					
Academic problems (MoBa)	0·07	0·00	0·20	0·22	0·27
Educational support needs (MoBa)	0·43	0·36	0·71	**0·85‡**	**0·72‡**
Not enjoying school (MoBa)	0·10	0·48	**0·33‡**	0·23	**0·42‡**
Little or no time with friends (MoBa)	0·49	0·50	0·52	**0·94‡**	0·60
Daily life impairment (MoBa)	0·72	0·58	0·92	0·90	0·94
Anxiety† (SCARED)	0·07	0·34	0·07	0·27	0·28
Depression† (MFQ)	0·06	0·20	0·35	0·43	0·50
Attention problems† (RSDBD)	0·14	0·10	**0·69‡**	**0·77‡**	**0·79‡**
Hyperactivity† (RSDBD)	0·04	0·07	**0·50‡**	**0·60‡**	**0·74‡**
Defiance or non-compliance† (RSDBD)	0·11	0·17	0·54	0·32	**0·67‡**
Aggressive behaviour† (RSDBD)	0·07	0·30	0·61	0·20	0·59
Language difficulties† (CCC-S)	0·38	0·20	0·48	**0·89‡**	**0·75‡**
Social communication difficulties† (SCQ)	0·24	0·36	0·37	**0·74‡**	**0·50‡**
RRB† (SCQ)	0·39	0·35	0·62	**0·84‡**	**0·71‡**

Figure 10: **Heterogeneity in early childhood trajectories of emotional and behavioural difficulties and mid-childhood outcomes in the Norwegian Mother, Father and Child Cohort Study**
A latent class growth analysis identified five distinct patterns (classes) of emotional and behavioural difficulties in early childhood in 73 838 children in the MoBa study, for whom Child Behaviour Checklist data at 18 months, 36 months, and 60 months were available. 516 (69%) of 746 of the children with an autism diagnosis in the Norwegian Patient Registry were assigned to one of the three classes characterised by persistent or increasing difficulties (classes 3, 4, or 5). Panel B shows, for the autism group, the probabilities (0–1) of mid-childhood (8 years of age) functional difficulties and signs in each of the trajectory classes. The results remained similar when excluding children with a co-occurring diagnosis of intellectual disability. B=behavioural difficulties. CCC-S=Children's Communication Checklist 2 short scale. E=emotional difficulties. MoBa=items specific of the MoBa cohort. MFQ=Short Mood and Feelings Questionnaire. RRB=restricted and repetitive behaviours. RSDBD=Rating Scale for Disruptive Behaviour Disorders. SCARED=Screen for Child Anxiety Related Emotional Disorders. SCQ=Social Communication Questionnaire. *Proportions differ at p<0·001. †Continuous variables dichotomised at the 90th percentile (ie, probability of being in the top 10%). ‡p<0·05 for a higher probability than in the reference class (class 1).

providing formative and summative data, including the Autism Behavior Inventory.[284]

Another need is to develop outcome measures that can be scaled for larger samples within the complexity of existing systems (eg, schools and community-based mental health centres), including low-resourced communities and LMICs, perhaps by making use of technology. The Brief Observation of Social Communication Change is one example of a new measure, developed for use with young children with autism, that allows for more frequent re-administration and that could thus potentially fill this role.[285] It consists of a 12–16 min videoed interaction (eg, on a mobile phone) with a family member, teacher, or non-expert research assistant that can be done at home, school, or in a clinic, with instructions but no formal training. However, it requires human coding, which means training masked coders or collaborating coders from existing centres. The intention is to find automatic methods of coding the video and audio recordings that would minimise costs and burden across the life span, but this approach is still in development.

The use of digital tablets or other commonly available technological devices to support data collection and outcome measurement is of interest, but meaningful results of their effect to date are unclear.[286] Eventually, audio recordings might yield automatic codings of language; videos might be used to code proximity to others; and information about sleep, activity, or arousal might eventually be interpretable. However, these audio and video recordings will need to meet standard psychometric standards (eg, test-retest reliability on an individual basis), safety standards of security, and validation against more recognised outcomes. Linkage of data across databases for education, health, and social care is also important and has provided evidence of longer-term benefits of an intervention in other neurodevelopmental disorders, such as attention-deficit hyperactivity disorder.[287] Finally, an outcome is more than the patient's response to intervention, but also the potential for implementation and the fidelity with which the intervention was done.

Evaluation and management of co-occurring conditions

An important aspect of the heterogeneity of autism is that most people with autism have co-occurring conditions (ie, developmental, physical, behavioural, or psychiatric conditions) throughout their life. These conditions are treatable, but often affect quality of life as much as autism core features at different points of life. Evidence-based treatment can result in increased wellbeing for autistic people and their families and can enable better access to other services and supports. For example, new epidemiological data from the MoBa study analysed for this Commission show that the proportion of autistic children with increased emotional (eg, anxiety) and behavioural difficulties (eg, hyperactivity and aggressive behaviour) far exceeds the proportion of these concerns in the general population, even in the age range from 18 months to 5 years (figure 10). In many cases, concerns increase with age. In early childhood, 516 (69%) of 749 children (data collected for this Commission) with autism were classified in one of the classes characterised by persistent or increasing emotional or behavioural difficulties; early trajectories of emotional and behavioural difficulties were also associated with outcomes at

mid-childhood (at the age of 8 years) such as daily life impairment, school enjoyment, and friendships.

Many people with autism are initially referred for signs of co-occurring conditions rather than for core autism signs. Anxiety, aggression, and sleep problems are often the greatest focus of parents' concerns.[288] These conditions adversely affect quality of life (eg, by introducing difficulties with friendships and at school or work) from early childhood all the way to adulthood. Therefore, identifying and treating co-occurring conditions is an essential component of personalised interventions and should be included in the formulation of short-term and long-term intervention targets from assessment. In the initial diagnostic evaluation and follow-up, other behavioural and psychiatric conditions are considered as potential differential diagnoses. The same diagnostic and treatment standards for these disorders should apply to people with autism as to other children and adults, although manifestations of these conditions can vary. Once a diagnosis of autism is made, integration of co-occurring conditions and core features is essential for the stepped care approach.

As shown in figures 5 and 8, the same system of decisions needs to be applied for co-occurring conditions as for an autism diagnosis. Because many putative autism rating scales are confounded by other behavioural conditions (eg, the Social Responsiveness Scale[289]), specific screening and diagnostic assessments of the differential behavioural and psychiatric disorder diagnoses need to be done during evaluation.[170] Stepped care and personalised health procedures and data from novel systems (eg, figure 9) that use probabilistic data from autistic samples can be applied to streamline choices for areas of focus. A clinical environment with a knowledgeable provider, that is culturally appropriate, adapted to the needs of the stakeholders, and that allows sufficient time for assessment, discussion, and participatory decision making is necessary to support a successful diagnostic evaluation of co-occurring conditions.

Figure 11 shows the prevalence of common co-occurring conditions according to population-based or clinical studies. The wide range of prevalence for many conditions (also evident in meta-analyses[16,311]) results from ascertainment biases and measurement differences across studies and from real differences across age, sex, and samples. Because similar factors vary in studies of the general population, we do not show comparative prevalence rates but rather indicate robust evidence that rates are higher in autistic people. Despite these confounding factors, heterogeneity in the prevalence and incidence of these conditions is clearly associated in different ways with different ages, resulting in higher rates of attention-deficit hyperactivity disorder in children and increased rates of depression, schizophrenia, and bipolar disorder in adulthood.[7,16] The underlying shared risk for autism and co-occurring conditions can be related to a shared genetic risk, such as for attention-deficit hyperactivity disorder, intellectual disability (eg, fragile X syndrome), or different forms of epilepsy (eg, tuberous sclerosis complex).[15,16] Shared psychosocial risk is a possible factor for other conditions, but there is scarce evidence about this possibility.

Conceptualising co-occurring conditions

Whenever two conditions occur at rates that exceed a chance probability, interest in the nature of the association is inevitably prompted. The term comorbidity is typically applied to the co-occurrence of two conditions (eg, autism and anxiety) with the implication that they are independent, but the two conditions might not be separate, and instead overlap or be associated in complex ways. For example, non-compliant, irritable, and oppositional behaviour can be related to rigidity or impaired verbal communication, which can also mask anxiety as the underpinning driver of the externalised behaviour.[312] Anxiety can be related to cognitive style aspects that are more common in autism, such as poor executive function[313] and intolerance of uncertainty.[314] Similarly, depressive symptoms can follow social interaction problems with peers, but might also be related to other environmental risk factors. Therefore, we use the term co-occurring conditions with the understanding that the relations between autism and other conditions can be complex.

The overlap of manifestations of autism and other mental health issues is a clinical challenge for both assessment and intervention. For example, social avoidance can be a sign of either an anxiety disorder or of autism; apparent separation anxiety can reflect a child's strong reaction to a change in routine rather than to the actual separation; and an emotional outburst in a novel environment might be a consequence of rigidity and intolerance of uncertainty and not of generalised anxiety. Regardless of whether these issues are truly additional conditions or part of autism, they must be addressed. Alternatively, co-occurring symptoms such as those related to anxiety might be missed, especially with standardised instruments, because of their atypical presentation.[315] They therefore require careful assessment and corresponding intervention formulation. From a practical standpoint, however, clinicians should avoid either attributing all maladaptive behaviours to autism or, on the other hand, neglect to take into account the role of core aspects of autism in treatable co-occurring conditions.

Infants, toddlers, and preschool-aged children and issues addressed at first diagnosis

Physical conditions co-occurring with autism must be diagnosed and addressed as a priority. Among these are hearing and vision impairments, epilepsy, and medical conditions associated with some genetic syndromes (eg, tuberous sclerosis complex, Prader-Willi syndrome, or Klinefelter syndrome).[128] In autistic children with behavioural or cognitive regression, the possibility of epilepsy and related conditions, such as

Landau-Kleffner syndrome, must be considered. Different forms of epilepsy and seizures frequently co-occur with autism, with one peak of incidence in early childhood and a second peak in adolescence and young adulthood.[17,307] The presence of an intellectual disability and female sex are associated with higher rates of epilepsy in autistic individuals (figure 11).

Sleep problems in autism are also frequent, affecting all ages, and have adverse effects on daily functioning, learning, and behaviour in the individual and on the whole family.[316] Diverse problems related to the gastrointestinal tract, such as selective eating, constipation, diarrhoea, and gastro-oesophageal reflux, are more frequent in individuals with autism (figure 11) and can co-occur with behavioural

	Typical age of onset	Prevalence in individuals with ASD (data from population-based studies and epidemiological surveys)*	Prevalence in individuals with ASD (data from clinical populations)*	More frequent in individuals with ID than in individuals with no ID?*	Effective evidence-based treatment for individuals with ASD†	Effective evidence-based treatment for individuals without ASD†
Intellectual disability	NA	Highly variable within and between global regions;[290] 30–70% in HICs (studies since 2000); rates might be higher in studies limited to children younger than 5 years and in LMICs	Systematic review, no aggregated data	NA	Treatment can improve IQ but seldom results in moving out of ID	No
Speech and language problems or delay	NA	Few population-based studies; 56% in 10–14 year-olds[291]	Systematic review, no aggregated data	Yes	Yes	Yes
Motor problems	NA	No population-based studies on motor development or coordination problems; 30·3% (95% CI 22·7–37·9%) on the basis of the Child and Adolescent Twin Study in Sweden[292] (not direct examination)	Systematic review, no aggregated data	Yes	No	Yes
Urinary incontinence only	NA	2–11% in children aged 5–16 years[293]	16–30% in children aged 5–17 years[293]	Yes	No	Yes
Combined urinary and faecal incontinence	NA	Daytime urinary incontinence in 4–22% of children up to 18 years; faecal incontinence in 2–7% of children aged 5–14 years	Daytime urinary incontinence in 25% of children aged 5–16 years; faecal incontinence in 12–29% of children aged 5–16 years[293]	Yes	No	Yes
Constipation	Childhood	Population-based and clinical ASD samples combined: 4–46% (median 22%)[294]		Unknown	No	Yes
Diarrhoea	Childhood	Population-based and clinical ASD samples combined: 2–76% (median 13%)[294]		Unknown	No	Yes
Overweight and obesity	Childhood and adolescence	No population-based studies	BMI ≥85th percentile: 37·0% (95% CI 33·5–40·5); BMI >95th percentile: 22·2% (18·1–26·9)[295]	Unknown	Yes	Yes
Selective eating	Childhood	No population-based studies	No aggregated prevalence data available[296]	Unknown	No	No
Anorexia	Adolescence	Lifetime prevalence: HR 5·3 (95% CI 4·4–6·6)[297]	Lifetime prevalence: 2–7% (95% CI 1–8%)[298,299]	No	No	Yes
Sleep–wake disorders	Childhood	Pooled prevalence: 11% (95% CI 7–17%)[16]	Pooled prevalence: 13% (95% CI 16 9–17%)	Unknown	Yes	Yes
Attention-deficit hyperactivity disorder	Childhood	Pooled prevalence: 22% (95% CI 17–16 26%)	Pooled prevalence: 28% (95% CI 16 25–32%)	No	Yes	Yes
Anxious behaviour and anxiety disorders	Childhood	Pooled prevalence: 15% (95% CI 11–19%)[16,300]	Pooled prevalence: 20% (95% CI 17–23%)[16,300]	No	Yes	Yes
Obsessive-compulsive disorder	Adolescence	Pooled prevalence: 4% (95% CI 2–6%)[16]	Pooled prevalence: 9% (95% CI 7–10%)[16]	No	No	Yes

Developmental conditions
Behavioural, psychiatric, or medical conditions, depending on health-care professional making diagnosis
Psychiatric and behavioural conditions
Medical conditions

(Figure 11 continues on next page)

	Typical age of onset	Prevalence in individuals with ASD (data from population-based studies and epidemiological surveys)*	Prevalence in individuals with ASD (data from clinical populations)*	More frequent in individuals with ID than in individuals with no ID?*	Effective evidence-based treatment for individuals with ASD†	Effective evidence-based treatment for individuals without ASD†
Depressive disorder	Adolescence	Pooled prevalence: 8% (95% CI 5–11%)[16]	Pooled prevalence: 11% (95% CI 9–13%)[16]	No	Yes	Yes
Bipolar spectrum disorder	Adolescence and adulthood	Pooled prevalence: 3% (95% CI 2–5%)[16]	Pooled prevalence: 5% (95% CI 3–6%)[16]	No	No	Yes
Oppositional defiant disorder	Childhood	28% (95% CI 14–42%; data from one population-based study in children with ASD)[301]	..	No	Yes	Yes
Aggressive behaviour and conduct disorder	Childhood	Pooled prevalence: 7% (95% CI 4–11%)[16]	Pooled prevalence: 12% (95% CI 10–15%)[16]	No	Yes	Yes
Internet gaming disorder	Adolescence	No population-based studies	Systematic review, no aggregated data	Unknown	No	Yes
Schizophrenia spectrum	Adolescence and adulthood	Pooled prevalence: 2% (95% CI 1–4%)[16]	Pooled prevalence: 4% (95% CI 3–5%)[16]	No	No	Yes
Non-suicidal self-injury	Childhood, adolescence, and adulthood	27–50%	Pooled prevalence: 42% (95% CI 38–47%)[302]	Different types (including suicide attempts *vs* repetitive self-injuries)	For some types	No
Suicidality	Adolescence	Suicide 0·3%[303]	Suicidality in children, adolescents, and adults: 11–50%; suicide attempt: 7–15%[304,305]	Suicide decreased in ID	No	Yes
Gender dysphoria	Childhood and adolescence	6·5–40·0% with widely varying definitions and age groups; generally higher in adults[306]		Unknown	Yes	No
Gastro-oesophageal reflux	Unknown	Population-based and clinical ASD samples combined: 0–22% (median 7%)[292]		Unknown	No	Yes
Seizures and epilepsy	Childhood	Median 10·8% (95% CI 2·5–60·0%); 15·5% (0·0–60·0%) in girls; 8·8% (3·7–30·0%) in boys[307]	Lifetime prevalence: 1·8% (95% CI 0·4–9·4%) in children younger than 12 years with no ID; 8·9% (3·7–15·7%) in children older than 12 years with no ID; 6·1% (3·8–9·0%) in children younger than 12 years with ID; 23·7% (17·5–30·5%) in children older than 12 years with ID[17]	Yes	No	Yes
Genetic syndromes and specific genetic disorders	NA	Population-based and clinical ASD samples combined: 10–30% recognised genetic disorder or de novo mutation		Yes	No	No
Peripheral hearing loss	NA	5–7%	0–10% in children[308]	Unknown	No	Yes
Vision difficulties	Usually in childhood	2–12% blindness or sight loss	Myopia: 2–16%; hyperopia: 8–18%; astigmatism: 3–26%: anisometropia: 1–12% (in children and adolescents)[309]	Unknown	No	Yes
Cerebral palsy	NA	2·9–4·3%[310]	..	Yes	No	No

Developmental conditions
Behavioural, psychiatric, or medical conditions, depending on health-care professional making diagnosis
Psychiatric and behavioural conditions
Medical conditions

Figure 11: **Common co-occurring conditions in people with autism**
ASD=autism spectrum disorder. HICs=high-income countries. HR=hazard ratio. ID=intellectual disability. IQ=intelligence quotient. NA=not applicable (ie, inborn or developmental condition). LMICs=low-income and middle-income countries. RR=relative risk. *Data based on systematic reviews and meta-analyses of population-based studies or (if population-based studies are not available) of systematic reviews of studies in autism. If the studies differentiated between lifetime and prevalence at 3–6 months, this is indicated; otherwise, this differentiation is absent from the studies. If aggregated data are missing, only ranges are shown. †Data based on at least one randomised controlled trial of children or adolescents with ASD, intellectual disability (non-ASD), or in the general population with the respective condition (non-ASD).

problems.[317] Researchers are currently exploring possible associations with altered microbiomes,[318] serotonin concentrations,[319] cytokines,[320] and stress response.[321] Nutritional deficiencies can occur and lead to decreased bone density and increased fracture risk.[322] Individuals who are underweight, have symptoms of dysphagia, or food allergy might benefit from further medical investigations.

In general, the characteristics of each of these problems are varied and not specific to autism, but commonly co-occur in all children with neurodevelopmental disorders. For sleep problems, empirical data supports parent education, sleep hygiene, and other behavioural interventions as first-line interventions,[323] and the use of melatonin when other therapies are not effective.[324] Other medications are often prescribed in some countries, but evidence to support their use is variable (tables 1, 3). Standard treatments are often effective, but might require adaptations, a longer duration of intervention, and more frequent follow-up by providers. Practice pathways and consensus guidelines for evaluation and

	Medication class	Medication	Strength of evidence	Effect size*	Usual dose range†	Common adverse effects	Comments
ADHD	Stimulants	Methylphenidate‡	Systematic review of RCTs[325]	Medium to large	0·5–1·0 mg/kg per day	Insomnia, anorexia, and irritability	Information on amphetamine compounds in ASD is scarce, although these compounds are widely used; benefit to adverse effects ratio is not yet established; efficacy is lower and adverse effects are more frequent in individuals with ASD than in those without ASD
ADHD	Selective norepinephrine reuptake inhibitors (non-stimulants)	Atomoxetine	Systematic review of RCTs[326]	Medium	0·5–1·2 mg/kg per day	Anorexia, nausea, and irritability	Starting below the recommended dose and titrating slowly might prevent or reduce side-effects
ADHD	α agonists (non-stimulants)	Extended-release guanfacine (not available in all countries)	Two RCTs[327,328]	Large	1·0–3·0 mg/day	Fatigue, sedation, drop in systolic blood pressure and pulse, and mid-cycle insomnia	Strength of evidence and expert opinion suggest guanfacine can be used as an alternative to stimulants for the treatment of ADHD; usual dose range is based on children younger than 14 years of age; evidence supports higher doses for adolescents in the non-ASD population
ADHD	α agonists (non-stimulants)	Extended-release clonidine	No RCTs in ASD targeting ADHD signs	Not available	0·1–0·3 mg/day	Fatigue and sedation	Scarce information on clonidine for ADHD signs in ASD; extended-release clonidine is FDA-approved for the treatment of ADHD in children aged 6–17 years
Irritability, tantrums, and aggression	Atypical antipsychotics§	Risperidone	Systematic review of RCTs[329]	Moderate to large	0·5–3·0 mg/day	Sedation, weight gain, potential metabolic complications (ie, hyperlipidaemia and diabetes), hyperprolactinaemia, tardive dyskinesia (low); weight gain from atypical antipsychotics might be attenuated with concomitant use of metformin[330]	Maladaptive behaviours might serve a purpose (assessment of the function of the behaviour is warranted); if irritability and aggression are primarily due to co-occurring conditions (eg, anxiety, ADHD, depression, or discomfort due to medical conditions), consider medications or treatments that target these conditions before atypical antipsychotics; weight, diet, and metabolic monitoring are necessary; the addition of parent training in behavioural modification might improve the response to antipsychotic medications;[331] a lower dose range applies to children weighting less than 25 kg
Irritability, tantrums, and aggression	Atypical antipsychotics§	Aripiprazole	Systematic review of RCTs[329]	Moderate to large	2–10 mg/day	Sedation, weight gain, metabolic complications, and akathisia	Same as for risperidone
Irritability, tantrums, and aggression	Supplements	Acetylcysteine	Two RCTs[332,333]	Uncertain	1800–2700 mg/day	Gastrointestinal distress	Because only small studies have been done, data to identify a usual dose range is scarce
Anxiety, depressive disorder, and obsessive-compulsive disorder	SSRI	Fluoxetine, sertraline, citalopram, and escitalopram	No RCTs in ASD for anxiety	Not available	5–20 mg/day for fluoxetine; 25–100 mg/day for sertraline, 10–20 mg/day for citalopram; 5–10 mg/day escitalopram	Behavioural activation (eg, emotional lability, agitation, aggression, hyperactivity, and insomnia);[334–336] the FDA has issued a black box warning for suicidality	Evidence supports use of SSRI in children, adolescents, and adults with anxiety in the general population, but little information available for use in ASD; usual dose ranges for SSRIs provided are for non-autistic children and adolescents (doses for individuals with ASD are not established); on the basis of clinical experience, the Commission recommends that SSRIs be initiated at low doses (one-fourth or half of the target dose) and titrated slowly;[145] treatment of obsessive-compulsive disorder can require higher than usual dose ranges compared with anxiety and depression

(Table 3 continues on next page)

	Medication class	Medication	Strength of evidence	Effect size*	Usual dose range†	Common adverse effects	Comments
(Continued from previous page)							
Repetitive behaviour	SSRI	Fluoxetine and sertraline	At least two RCTs[335,337]	Nil	Not recommended	Same as above	Two large scale RCTs found no difference between drug and placebo
Repetitive behaviour	Atypical antipsychotics	Risperidone and aripiprazole	At least two RCTs[329]	Medium	0·5–3·0 mg/day for risperidone; 2–10 mg/day for aripiprazole	Same as above plus irritability	In trials of atypical antipsychotics for irritability, an additional benefit on repetitive behaviours was observed; the use of antipsychotics for repetitive behaviour has not been specifically tested
Initial insomnia	Not applicable	Melatonin	At least two RCTs[338]	Large	2–10 mg nightly	Most studies reported no associated side-effects[338]	Expert opinion and studies showing benefit support parent-mediated behavioural interventions as a first-line intervention; non-pharmacologic interventions should be considered first

Epilepsy is not included in the table because no trials have been done specifically for the treatment of epilepsy in patients with ASD. Treatment of seizures should be done as per epilepsy guidelines. ADHD=attention-deficit hyperactivity disorder. ASD=autism spectrum disorder. FDA=US Food and Drug Administration. RCT=randomised controlled trial. SSRI=selective serotonin reuptake inhibitors. *Data from autism trials provided when available. Effect sizes of standardised mean differences (Cohen-Lenstra heuristics) were considered small if ≥0·2, medium if ≥0·5, and large if ≥0·8. †Jurisdictional variation in recommended doses is possible. ‡Various formulations of variable duration are approved for ADHD by the FDA, the European Medicines Agency, and Health Canada. §The use of other atypical antipsychotics is supported by some evidence of efficacy.

Table 3: **Commonly used medications for children and adolescents with autism by target sign or diagnosis**

treatment of common gastrointestinal and sleep conditions in autism are also available.[339]

The most common co-occurring behavioural and emotional difficulties during preschool and school age are hyperactivity, irritability, oppositional problems, anxious behaviours,[340] and elimination disorders.[293] These conditions can be measured via standard approaches, whether they represent distinct conditions or increased behavioural signs associated with autism. Parent training strategies through psychoeducation, positive parenting, and behavioural techniques[71] have been shown to be effective, especially regarding irritability and oppositional behaviour. Behaviours such as peering at objects, unusual movements, talking to oneself, or fixated interests and unusual preoccupations, which used to be described as psychotic in children, are now generally considered part of the core features of autism.[341]

Co-occurring conditions during school age and adolescence

The term wandering describes the propensity that 25–50% of autistic children have to leave a supervised safe space or to escape from the supervision of a caregiver.[342] Wandering, which is not a diagnosis but a behaviour that causes much concern, is associated with an increased risk of accidental drowning and traffic injuries.[343] Younger age, intellectual disability, and behavioural or psychiatric conditions in children with autism increase the risk of wandering.[342] Dyslexia and dyscalculia are often not identified in autism but are common and can be addressed with standard educational approaches adapted for autism.[77] Bullying, beginning in childhood but continuing on through adolescence and beyond, is also a serious concern.[344]

Other behavioural issues during school age and adolescence overlap with those emerging earlier, but more treatment options are available. These include the direct treatment of children and adolescents, often in groups (including caregivers in most successful treatments), adaptation of cognitive behaviour therapy approaches for anxiety,[70,143,152] and common use of medication. Attention-deficit hyperactivity disorder is typically addressed with psychostimulants.[325] Irritability, aggression, oppositional behaviours, and severe repetitive behaviour are not diagnoses, but behaviours that need to be carefully evaluated and considered in relation to physical and environmental issues. They can be addressed with parent training (as discussed in the section "Infants, toddlers, and preschool-aged children and issues addressed at first diagnosis"). Antipsychotics such as risperidone or aripiprazole[329] are sometimes prescribed, ideally after other approaches have been tried, although effectiveness and side-effects are more variable in autism than in some other conditions. Thus, prescribers should use a titration approach (ie, starting with a low dose and increasing it slowly) when initiating medication to treat co-occurring behavioural and psychiatric conditions. Additional expertise might be required when considering doses outside the usual ranges (table 3). Even in adolescence and adulthood, psychosocial, environmental, and sometimes physical issues can contribute to problematic behaviours, so considering these factors is important during an initial assessment. In general, psychosocial approaches are recommended to be used before psychopharmacological interventions in children (table 1).

The recent expansion of genomic and system neuroscience findings have provided several targets for psychopharmacological manipulation of underlying biology, with the hope that targeting such aetiological pathways might have broad effects across domains, including core signs and symptoms. Potential compounds targeting excitatory and inhibitory balance, mediators of synaptic plasticity (eg, γ-aminobutyric acid and glutamate modulators), and neuropeptide systems involved in social

perception, cognition, and affiliation are currently in clinical trials in children, adolescents, and adults with autism.[345]

Co-occurring conditions in older adolescents and adults

Adolescents and adults with autism are at a higher risk, increasing with age, of being overweight or obese.[15,346] However, research often groups adolescents either with younger children or with adults.[347] Insufficient physical activity, prescription of atypical antipsychotics, autism severity, sleep problems, and family history of obesity all contribute to this risk, which is accompanied by an increased propensity for metabolic sequelae, such as diabetes, hypertension, and non-alcoholic fatty liver disease.[346] These conditions can, in turn, contribute to a nearly three times increased risk of premature mortality in individuals with autism, highlighting the urgent need to focus on preventive care interventions.[303] Nutritional counselling, behaviour modification, physical activity, and adjunctive metformin for young people taking antipsychotics can be effective in reducing body-mass index.[330]

Various mental health disorders first become apparent during adolescence, and adolescents with autism might be even more vulnerable than neurotypical adolescents. Eating disorders, depression (especially in girls and women), anxiety, suicidal ideation, non-suicidal self-injury, and psychotic symptoms all occur in adolescents[145] and in adults[16,269,300] (figure 11). These symptoms must be taken seriously and addressed. Psychotic and psychotic-like signs can occur in developing adolescents,[16,145] and are especially associated with depressive episodes.[348] Some people with autism show formal thought disorders, such as restricted thinking, and others might have psychotic-like episodes, which can sometimes be incorrectly interpreted as psychosis.[132] Better primary health care, mental health services, and evidence-based guidelines for the evaluation and treatment of co-occurring conditions are needed. There is also a huge knowledge gap about co-occurring disorders such as dementia and Parkinson's disease in older adults with autism.[349]

Overall, modifications to existing evidence-based treatments are often necessary to optimise both behavioural and psychological and medical approaches for co-occurring conditions in autism and to ensure effectiveness and participation. Modifications range from the provision of multimodal information and materials, including visual guides; work on emotional literacy and understanding; the crucial role of engaging and joint working with parents and carers and ideally across environments (eg, at school and at home); and consideration of the role of sensory behaviours and their effects. Until evidence is generated for these modified approaches, autism-informed and autism-friendly modifications to existing evidence-based practice should be used. Systematic efforts to reach non-autism specialist therapists with information about these adaptations are important because most interventions will not be delivered by autism experts; again, stepped care and personalised health approaches might be particularly valuable (figures 5 and 6).

Financial and personal costs

Alongside the social justice and social equity values that underpin our approach, more information is urgently needed about the financial as well as personal consequences of autism, to inform the economic, social, and political case for action worldwide. The pervasive scarcity of resources (both in HICs and in LMICs) requires difficult decisions to be made. Knowing not only which interventions are effective, but which are affordable given budget constraints and which make the best use of society's scarce resources becomes necessary. Economic evaluations, such as cost-effectiveness analyses, compare the outcomes and cost implications of two or more interventions.

Costs can range widely across many sectors. Buescher and colleagues[350] estimated the lifetime costs of supporting an individual with autism and intellectual disability to be US$2·4 million in the USA and $2·2 million in the UK; the cost of supporting an individual with autism without intellectual disability would be $1·4 million in either country. In childhood, special education services and parental productivity loss are the highest costs; in adulthood, the highest costs are residential or supported living costs, individual productivity loss, and medical costs. Although, in HICs, expenses are often discussed in the context of early intervention, over an individual's lifetime, adult costs far outweigh childhood costs, in part because adulthood is a far longer phase of life than childhood.

Cost-effectiveness analysis examines whether the outcomes achieved by one intervention compared with another are sufficiently important (in scale and relevance) to justify the additional resources needed to generate them. An intervention could be cost-effective even if it was more expensive than the comparator if the beneficial effects for autistic people and their families were viewed by the decision maker (eg, a government) to be worth the higher costs. The decision is a value judgement, but it is rarely easy: how much is society (represented by the government, in this context) willing to pay to improve the lives of autistic people and their families?

If the task is to decide which is the better of two interventions for autistic people, a measure of social communication or adaptive functioning, for example, would be appropriate to measure effectiveness. However, if the decision is on how to allocate across different clinical areas (eg, interventions for autistic children, or adolescents with depression, or adults with cancer), then generic outcome measures are needed, such as quality-adjusted life-years or disability-adjusted life-years. A substantial challenge for the field of autism is that these generic outcomes might not be sufficiently sensitive to measure

change in autistic people, which leaves autism in danger of being overlooked in the perpetual battle for resources.

The situation is not helped by the paucity of cost-effectiveness evidence. A systematic review focused on children and adolescents[351] identified only two robust studies: one randomised controlled trial-based evaluation that suggested that the Preschool Autism Communication Trial intervention did not appear to be cost-effective in the short-term when added to treatment as usual,[273] and another that used modelling to estimate the potential costs and benefits of developmental early intervention programmes (ie, Early Start Denver Model) up to the age of 65 years, concluding that there would be cost savings and cost-effectiveness gains.[352] Another modelling study concluded that, even under optimistic assumptions, applied behaviour analysis was not cost-effective.[353] Other studies based on modelling methods point to economic gains for some interventions, such as cognitive behaviour therapy and supported employment.[113,354] However, the very small number of valid and reliable cost-effectiveness studies highlights the need for future intervention studies to incorporate rigorous health economic analyses in their design from the outset.

The already noted under-recognition and under-diagnosis of autism, combined with the scarcity of evidence on the economic costs and benefits of interventions and services, exclude autistic people and those with other neurodevelopmental conditions from access to an equitable share of public and private resources that would improve their life choices and outcomes. More information about the financial and personal costs and consequences of autism is required in every country and region in the world. A requirement to record individuals with an autism diagnosis within health-care, education, and social care systems would inform local service planning and provision, contribute to a future ability to estimate the real-world costs and the personal and societal consequences of autism relevant to each community, and help to monitor equity of provision.

Family experiences with autism

Historical and cultural context

In the 1960s, autism was thought to be the result of poor parenting. Mothers were singled out as bad parents and called "refrigerator mothers", too cold to provide the love and warmth a child needs to thrive.[355] They were told the best they could do for their children was to send them to live in an institution and were pressured to undergo psychoanalysis to determine why they (the mothers) were such bad parents. As a result, there was a tremendous stigma associated with having a child with autism. Autism is now known not to be caused by parenting style. Nevertheless, in some parts of the world, there is still substantial stigma associated with a diagnosis of autism and families are often reluctant to take their children to be diagnosed or to seek help.[356] This stigma varies widely by region, culture, and availability of services. A review that included studies of caregivers (predominantly mothers) across three cultural regions (east Asia, the Middle East, and Australia and USA) reported a negative effect of autism-related stigma on caregiver mental health.[356] In some cultures, those who are identified as deviating from group harmony are vulnerable to being devalued, rejected, and stigmatised. Families fear such stigmatisation and consequently hide their circumstances (and sometimes their child with autism) from the community, leading to a range of harmful consequences.[356]

In addition, culture influences explanatory models for autism. For example, in some African cultures, autism is conceptualised as resulting from witchcraft and poor parenting.[357] Similarly, Alqahtani[358] has shown how Saudi Arabian parents might rely on cultural interventions involving religious healers. In some countries, there is still a psychoanalytic approach to autism or a strong cultural belief that early diagnosis is equal to prematurely labelling the infant, and so the diagnosis of autism is delayed.[359] These variations emphasise the importance of creating partnerships and using language that can synthesise cultural and biomedical views so that families can engage in services. The situation for parents today (at least in many parts of the world) is much improved, and they are rightly seen as the primary carers and key advocates for their child. Nevertheless, many community care systems inappropriately place an over-reliance on parents to negotiate, coordinate, and sometimes even assume the role of the primary service provider, bringing additional disadvantage to those with the least personal and financial resources.

Effects of autism on family members

A diagnosis of autism affects not just the individual, but the entire family. Parents of children with autism have higher levels of stress and depression than parents of typically developing children or of children with other types of disabilities.[8,360] Factors that contribute to these high levels of stress and depression include parental mental health issues, low support, severity of autism symptoms and behavioural problems, extensive care needs, financial difficulty, problems with school, low satisfaction with health-care providers, and concern about their child's future.[8,360] In some cases, parents' greatest concerns stem from a poor acceptance of autism by society and sometimes by other family members, worries over the permanency of the condition and long-term care, feelings of isolation, and the effect on siblings.[361]

Effects on siblings

Siblings of children with autism are at higher genetic risk of autism and other mental health conditions than typically developing children without siblings with autism.[362] Growing up in a household with a brother or sister with autism also results in unique environmental stressors, with siblings showing higher levels of internalising and externalising disorders, social and

behavioural problems, and distressing emotions such as guilt and embarrassment about their sibling's behaviour.[363] In cultures where there is stigma linked to disabilities, autism in the family can affect the marriage prospects of siblings.[51] On the other hand, some siblings have a positive response to growing up with a sister or brother with autism, including greater empathy, resilience, maturity, and self-confidence.[363] Having a sense of control of the future and understanding of autism, access to time alone with parents, supportive and inclusive environments, and the chance to relate to other siblings are protective factors that facilitate positive psychological outcomes in siblings of autistic people.[363]

Effects on grandparents

Having already raised children, grandparents are often in a unique position to spot early signs of autism and encourage developmental screening. Findings indicate that frequency of interaction with a grandmother might result in an earlier diagnosis.[364] A study of 1870 grandparents by the Interactive Autism Network in the USA indicated that a majority had a role in the diagnosis and treatment of autism in their grandchild.[365] These contributions ranged from being the first to raise concerns, supporting others who raised concerns, and involvement in treatment decisions, to providing financial support and even moving closer to their grandchild's family so they could help with managing the different aspects of autism.

Vulnerability to non-evidence-based treatments

Families and caregivers can be particularly vulnerable to poorly evaluated fads and false claims about efficacy of so-called alternative treatments in the popular press,

Panel 7: **Vulnerability of parents or carers to non-evidence-based treatments**

Despite research advances in the neurobiology of autism, many questions regarding causes and effective treatments remain unanswered. In this context, many families of individuals with autism have turned to unproven medical treatments and to complementary or alternative medicine treatments.[166,366] In some cases, unscrupulous providers might prey on a family's desire for a cure or urgent needs to address challenging behaviours, such as aggression or self-injurious behaviour, or on families living in low-resource settings where there is no access to evidence-based approaches or advice.

Complementary or alternative medicine approaches include natural products (eg, herbal remedies, homoeopathy, vitamins, and minerals), mind and body interventions (eg, music therapy, yoga, and meditation), and specialised diets (eg, gluten-free and casein-free). There has been little rigorous testing of the efficacy of some of these approaches, such as homoeopathy. For others that have been tested in randomised controlled trials, such as gluten-free and casein-free diets, no evidence of effect was found.[367] For facilitated communication (as distinct from the independent use of augmentative devices), consistent evidence emerged of manipulation by the therapist.[368] However, emerging evidence shows a modest benefit of omega-3 and vitamin supplementation both for autism and associated behaviours,[367] although the mechanisms of the effect and the specificity to autism versus other neurodevelopmental disorders are not well understood.

Of greater concern are various non-mainstream biomedical therapies (eg, antifungal treatment, ayurveda, chelation, hyperbaric oxygen, leuprorelin, secretin, and stem-cell treatments) that have been advertised as autism treatments by word-of-mouth, social media, or the internet with sophisticated marketing, unsubstantiated testimonials, and unproven claims. Most of these are not supported by evidence; some are costly or take time away from potentially more effective therapies (eg, stem cells[369]), and others have been shown to be potentially harmful to the health of the individual (eg, secretin[370] or chelation[371]).

By evaluating evidence and potential for harm, health-care providers fulfil an important role in helping families to make responsible decisions about complementary or alternative medicine and non-mainstream biomedical approaches.[372] However, several studies indicate that autistic people and their families frequently do not disclose use of complementary or alternative medicine to their health-care providers, often due to a fear that their providers might disapprove of these approaches.[166] Studies of health-care providers indicate poor knowledge about complementary or alternative medicine treatments for autism and concerns about the potential for harm and the burden of time and cost that unproven therapies place on families.[166] There is a need to strengthen the partnership between providers and families to reduce decisional conflict and foster treatment plans that are safe and effective. Providers who gain trust by providing longitudinal primary care within an ongoing relationship can have a positive effect on helping families to make responsible decisions about treatment and gain access to therapies that are evidence-based and safe.[373] As discussed earlier in the context of a stepped care and personalised health approach, the concept of shared decision making provides a framework for the respectful discussion of potential treatments with families and providers to engage in bidirectional exchange of information, review potential risks and benefits of treatment options, and ultimately arrive at decisions that respect the knowledge and values of both parties.[166] Our Commission recommends that providers gain knowledge of the evidence base behind benefits and potential harms of complementary or alternative non-mainstream biomedical treatments; ask families about the use of complementary or alternative medicine; and partner with families by providing information about potential risks and harms to enable responsible decisions about treatment.

social media, and on the internet. Many of these interventions have subsequently been shown to be ineffective, and some to have adverse effects. Because of this vulnerability, clinicians have a responsibility to be informed on what are evidence-based and non-evidence-based treatments, and to advise and guide parents through the ever-changing minefield of misinformation about autism and specifically about what autism interventions are available (panel 7). At a systems and societal level, one protection against unevidenced treatments is the equitable provision of evidence-based care through existing health-care systems.

Parent and family advocacy

Parents and families have, for many decades, held a crucial role in policy, practice, and research advocacy worldwide. Because of their work, autistic people today benefit from earlier diagnosis and have more evidence-based treatment options. In many countries, parent and voluntary groups have successfully lobbied for legislation (eg, the National Autistic Society in the UK [for the 2009 Parliamentary Autism Act] and Autism Europe with the European Commission). In the USA, parents lobbied for the Individuals with Disabilities Education Act (1975), which guarantees individuals with disabilities the right to a free and appropriate public education. Parent advocacy groups such as Cure Autism Now, the National Alliance for Autism Research, Autism Speaks, and the Autism Science Foundation were the driving forces behind the Combating Autism Act (2006) and the Autism Collaboration, Accountability, Research, Education and Support Act (2019), which nearly doubled National Institutes of Health funding for autism research. In Germany, parent advocacy groups were the driving force to establish any kind of intervention in the 1980s, and still work together with professionals in developing national clinical guidelines on diagnosis and intervention. In Argentina, autism advocacy groups joined to create Red Espectro Autista, an autism network involved in awareness campaigns and advocacy to create political and social changes, and 150 organisations formed the Artículo 24 group that promotes and guarantees educational inclusion. In Australia, the Helping Children with Autism initiative, introduced by the federal government in 2008, was a direct result of parent lobbying and provides support for children with autism under the age of 6 years, their families, and caregivers. In South Africa, the Right to Education Campaign was led by the Western Cape Forum for Intellectual Disability. Children with severe disability were deemed not to be educable, but after many years of lobbying, the parent-led Western Cape Forum for Intellectual Disability launched and won a court case enshrining the right to education for all children, including those with severe to profound intellectual disability. Similar events took place in India, where the Persons for Disabilities Act of 1995 did not recognise autism as a distinct disorder. Parents lobbied the government to pass the National Trust for Autism, Cerebral Palsy, Mental Retardation and Multiple Disabilities Act of 1999, the first ever legislation to be passed in India that recognised autism as a distinct condition. It allowed the setting up of State Nodal Agencies across the country to support families and, in 2009, the Right of Children to Free and Compulsory Education was passed. Continued pressure from families and other stakeholders led to their inclusion in the committee that drafted the Rights of Persons with Disabilities Act of 2016, which includes autism and expands the right of individuals to education and social care benefits. In Bangladesh, a parent advocate chaired a National Advisory Committee for Autism and Neurodevelopmental Disorders, which had a key role in the development of a Strategic and Convergent Action Plan on autism and other neurodevelopmental disorders—the result of interministerial collaboration to provide an integrated framework for action in the country. In Canada, where health care and education are managed at the provincial level, autism organisations partnered under the umbrella of the Canadian Autism Spectrum Disorder Alliance to advocate for a National Autism Strategy and to develop country-wide standards. Together, these examples highlight the importance and impact of parents and, increasingly, self-advocacy worldwide, as well as the difficulties individuals and families have faced in accessing services over time.

Global and cultural diversity

Assuming a minimum prevalence of 1–2%, a figure that varies by region,[290] an estimated minimum of 78 million individuals worldwide have autism. Outside urban areas in most countries, families have virtually no access to either assessments or evidence-based interventions. The assessment and intervention gap seen across the world is compounded by a knowledge gap in LMICs and other low-resource settings.[75] 95% of all children under the age of 5 years with developmental disabilities (including autism) live in LMICs;[374] and yet, little research is done outside of HICs. For example, although sub-Saharan Africa and southeast Asia showed the greatest rise in the diagnosis of developmental disabilities of all world regions over the past 30 years, a scoping review found that less than 1% of the world's autism research originated from sub-Saharan Africa.[21] In addition, this research was mostly done with families already receiving services, so it was not representative of the other approximately 90% of families who received none. Panel 8 shows how our main themes of heterogeneity, potential for change, and systems are particular challenges in LMICs.

WHO has recognised autism as a global health priority and passed a resolution calling for "comprehensive and coordinated efforts for the management of autism spectrum disorders", with key

Panel 8: **Particular challenges for families who live with autism in low-income and middle-income countries (LMICs) and other low-resource settings by domain**

Heterogeneity

Despite similiar manifestations of autism:

- Low awareness and knowledge about autism and available interventions can lead to misdiagnosis, late diagnosis, or non-identification
- Because the identification of autism in most LMICs is limited to the most severely affected individuals, autism might be perceived solely as a severe disorder
- Co-occurring conditions might not be identified and receive appropriate interventions
- Validated, affordable, and appropriate tools for identification and quantification of heterogeneity are scarce
- Cultural and linguistic heterogeneity are not represented in validated, open-access tools available in LMICs and other low-resource settings
- Poverty and socioeconomic status is a substantial barrier to care because families often have to prioritise basic needs over health care for a chronic lifelong disorder

Potential for change

- Stigma and discrimination, combined with the lack of knowledge about autism and other neurodevelopmental conditions, are major barriers to families seeking help
- Knowledge of and access to early intervention in community settings is scarce
- Most specialist care is available in a few highly specialised centres with minimal communication between specialist, targeted, and community levels of care
- Access to evidence-based or evidence-informed interventions is scarce; many non-evidence-based practices and interventions are thus pursued and cause negative financial effects on families
- Cost of interventions is often prohibitive to most families
- Models of task-sharing for training and supervision to bring accessible interventions to communities are scarce
- Capacity and skills to support children with autism in school is insufficient and education for children with autism is of poor quality
- Access to intervention and training for adults with autism is restricted

Systems of care

- Knowledge and understanding about autism are very low in most levels of care, including at the government and policy development levels
- Government and care systems do not recognise autism as a specific condition that requires targeted and specialist services in addition to services for all children with developmental disabilities
- Care and resources in communities might be so scarce or unclear that identifying existing care systems where early detection and early intervention for autism can be embedded might be difficult
- From mid-childhood, existing care systems within which ongoing identification and intervention for emerging physical and mental health difficulties of people with autism can be embedded are not clear
- Developing and implementing intersectoral autism policies is necessary given the reluctance of different sectors (eg, health, education, and social care) in taking primary responsibility for autism

recommendations for all member states to implement.[230] The needs of families who live with autism worldwide are universal: to understand their child's developmental differences; to seek support that can improve and optimise outcomes; to be included as active members of society; and to receive appropriate support to empower their child's journey into and throughout adulthood.[375,376]

Platforms of care

The Disease Control Priorities project[377] has recommended platforms of care for the delivery of evidence-based interventions for mental health and neurological problems, including autism and other neurodevelopmental disorders. These platforms expand beyond the vertical levels of health, education, and social welfare, which too often leave families stranded between these levels and create blocks to transitions. These platforms are "the level of the health or welfare system at which interventions or packages can be most appropriately, effectively, and efficiently delivered".[378] Matching our systems theme, population-level platforms aim to inform policy to support the development of cross-departmental community strategies and health-care approaches. Within the health-care platform, specific delivery channels are centred around individuals (or families), or primary, secondary, or specialist care. These channels can guide resource allocation while also directing best practices at various levels of care.

Many of the priorities for global action have been highlighted during this Commission. These priorities include engaging families as key stakeholders; remembering that most autistic people are adults; addressing the need, particularly in LMICs, to find scalable models to raise awareness, identification, assessment, and care that will, in most cases, take place across a lifetime; recognising the importance of systems and economic implications; and acknowledging the continual need to take into account heterogeneity and diversity not just in individuals with autism but in their cultures, contexts, and personal preferences.

The importance of cultural diversity in global settings

Cultural diversity encompasses broad social constructs including sex, race and ethnicity, class, income, language, religion, sexual orientation, and gender identity. Many autistic individuals will have a so-called minority or non-dominant status across several of these social and cultural factors, and recognition is growing that the intersectionality of these factors makes individuals vulnerable to both discrimination and exclusion from appropriate services. Autism is defined worldwide by a recognisable pattern of behaviours and signs, but the cultural context in which these are interpreted has a great effect on the awareness of difference, identification, access to care, development of care systems, and individual and family interactions within such systems.[357] Cultural context can foster acceptance of autism, or alternatively, might induce stigma or harm. People with autism or other neurodevelopmental disorders are more vulnerable to maltreatment, sexual exploitation, neglect, and other human rights violations,[379] along with inequitable access to health care and education. Stigma associated not just with autism, but with mental health and neurodevelopmental conditions, is a substantial concern in many cultures.[50,377,380] For example, in a

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comparison between Swedish and South African caregivers of autistic children, participants from both countries identified their families as sources of support, but caregivers from South Africa also reported that families were sometimes barriers to progress because of fathers' attitudes and family members' expectations for children's behaviours.[381] By contrast, Swedish parents were more negative about health professionals, reporting concerns about the providers' knowledge and the degree to which they were supportive, whereas this complaint was rare in South Africa.

Two examples of cultural differences that could affect engagement with services are illustrated by Shaked and Bilu,[382] who describes mothers' struggles to get their autistic child's behaviours accepted in an ultra-orthodox Jewish community. In Pakistan, parents found comfort from spiritual healers' explanation that looking after their child was a divine duty.[50] Despite increased initiatives to address cultural diversity, approaches that could work well for individuals with autism across culturally diverse settings are only just starting to be explored.[380] This disparity is most obvious in the dearth of evidence from LMICs. However, disparities are important factors within and across many HICs, where substantial ethnic, racial, and socioeconomic disparities exist, with minority ethnic populations and disadvantaged socioeconomic groups (and, in some studies, females) having less access to services and later and less accurate diagnoses.[218,383,384]

Developing high-quality, scalable, and sustainable clinical services

Making services scalable should not compromise standards of evidence, meaningful outcomes, and efficacy.[385] As previously noted, which treatment or assessment strategies in autism are most effective, when, and for whom is still not fully known. A better understanding of the key components and mechanisms underlying change will allow appropriate treatments, assessments, and methods of monitoring for all autistic people and their families to be established. However, practicalities also apply in LMICs around the availability of specialists who, at least in urban environments in HICs, are often sought out for care or, at least, consultation. Even in urban areas in HICs, the reality is that most interventions are not done by specialists, but by teachers and education staff, early intervention workers, and social service providers.[386] In a few LMIC settings, stepped care is in place, but often not to the degree it could be, nor in a well supported or supervised way. In LMICs, there is a great need for task-sharing approaches where specialists train and supervise community-based health-care and education workers to optimise their inputs to individuals with more complex support needs.[82,385,387]

Another question is the degree to which research and programmes developed in HICs can and should be applied, with appropriate cultural and contextual adaptations, in other settings, including both LMICs and other HICs. Panel 9 provides an example. Use of strategies and tools developed in HICs for screening and diagnosis have been used in several other countries or regions,[187,388] such as Jamaica,[389] Africa,[390] and south Asia.[110] In addition, studies have examined specific instruments, such as the Autism Diagnostic Observation Schedule, in South Africa.[391] Results of these studies showed general applicability across countries[187] and also in diverse populations within the USA.[392] Simultaneously, efforts have been made to develop and validate open-access tools that can be used with minimal contextual adaptation

Panel 9: An example of an adapted intervention for autism supporting evidence-based care in low-resource settings

The only way to provide equitable care for children and families in India is to consider innovations and systems that can deliver evidence-based interventions in settings with scarce specialist resources. One such innovation is the Parent-mediated intervention for Autism Spectrum Disorders in South Asia Plus (PASS Plus), an expanded version of the Preschool Autism Communication Trial (PACT) intervention,[37] which was systematically adapted and evaluated over two pilot trials in south Asia.[39,261] The adaptation process took an intervention delivered by specialists in a high-income country (the UK) and developed a package that could be delivered by non-specialists with no previous exposure to autism and still maintain fidelity. Whereas PACT and the adapted PASS focused only on social communication, the need to support coexisting behavioural and mental health difficulties for families resulted in the development of a manualised clinical decision algorithm and expanded the package with the Plus component.

The key strengths of the PACT intervention that permitted the adaptation process were, first, the development of a clinical decision algorithm and careful manualisation, which allowed it to be translated into three languages and provided content for the non-specialist counsellors to communicate to parents of varying literacy; and second, its parent-mediated approach, which permits the PASS Plus counsellor to deliver strategies to the caregiver without requiring expert knowledge beyond the intervention components itself. The non-specialist counsellor helps the parent to build on their strengths and recognises the caregiver as their child's expert, sharing strategies for them to adopt in a systematic phased manner. The direct work with parents results in quicker generalisation and more therapy time across routine activities and supports the low intensity (fortnightly sessions), which in turn increases acceptability and engagement for families and scalability for the health system.

The adaptation and expansion aimed to preserve the mechanistic component of the original social communication intervention identified as parent synchrony, which was facilitated by personalised video feedback, a key component of the original intervention. Each session is centred around a short episode of play between the parent and their child, which is recorded. During feedback, clips of the play are reviewed by the parent and the non-specialist counsellor; the parent is encouraged to identify moments in the play when their behaviours supported their child to communicate. This use of video requires the counsellor to personalise their inputs to meet the needs of individual parents, allowing a reflective discovery of their own efficacy in supporting their child's social communication.

An important part of the adapted PASS Plus package is the training and supervision cascade that includes an objective competency measure, ensuring the fidelity of delivery of a quality session while also ensuring that more complex problems are supported by the specialist who leads the service. This package is currently being evaluated in a cost-effectiveness trial in India (the COMPASS trial [MR/R006164/1]).

(eg, the International Clinical Epidemiology Network Diagnostic Tool for Autism Spectrum Disorder in India).[172]

Research about what is colloquially described as home-grown versus transported models of intervention in children's mental health generally suggests that transported models can be adapted and implemented in different cultural contexts with good clinical outcomes.[393] However, such implementation requires sustained attention to adaptation processes, supervision to maintain fidelity over time, and a clear understanding of implementation challenges.

Interventions developed in the UK and the USA have been successfully adapted and applied in research settings in other countries. Notable examples include adaptations of the Parent-mediated intervention for Autism Spectrum Disorders in South Asia Plus package and expansion of the Preschool Autism Communication Trial approach (panel 9), and the Chinese[394] and Australian[140] adaptations of the Early Start Denver Model. Evaluations of well established behavioural techniques have also been reported for parent-mediated interventions in Nigeria[395] and rural Bangladesh.[396] Effect sizes from the better controlled trials were sometimes even larger than when similar interventions were used in HICs, potentially because treatment as usual in the comparison groups was less available.[385] Notably, for these studies and others done in preparation for similar trials,[60] similarities and differences in implementation barriers and facilitation factors were not always as predicted. For example, in India, families preferred the delivery of parent-mediated interventions at home, whereas in Pakistan, families preferred to come to a local centre.[39] South African caregivers were positive about the opportunities to watch parent-mediated strategies provided in videos of other parents with their children,[397] although African providers were sometimes sceptical about using US videos.

The most successful projects in LMICs, and elsewhere, have consistently welcomed families as active participants; not only in service design, evaluation, and development, but also in interventions. One issue, across all contexts but particularly relevant to LMICs, is general public awareness of autism and neurodevelopmental disorders. Earlier, in our stepped care and personalised health model (figures 5 and 8), we emphasised that diagnoses should be followed both by provision of information to families about autism and by discussion with families about the needs they perceive. For families in LMICs, evidence-informed parent education, training programmes, and early access to information online can also connect them to other families, teach skills to support their child, and empower them as advocates for their child, contributing to self-management.[87,247,375] Capacity building and implementation of evidence-based programmes of care in LMICs is crucial to support the rights of people with autism and other neurodevelopmental disorders to have their needs met within the context of the Universal Declaration of Human Rights, UN Convention on the Rights of the Child, and Sustainable Development Goals. A recent scoping review outlines a framework to overcome barriers to universal health care for autistic children in LMICs that includes recommendations for practice, policy, and research.[398]

Based on the available evidence showing the benefits of parent-mediated interventions delivered by non-specialist providers,[160] the WHO Caregiver Skills Training[141] is an evidence-informed parenting intervention to support caregivers, both tapping into their existing competences and developing new skills that can foster their child's learning, social communication, and adaptive behaviour. The programme was designed to be implemented by trained non-specialists and adopts a family-centred approach that fits within a stepped care model for caregivers of children with developmental delays (including, but not limited to, autism). Caregiver Skills Training can serve as a transdiagnostic first step to support families who have children with developmental delays and neurodevelopmental disorders.

Technology and autism

Technology has been explored for various purposes, including screening, diagnosis, intervention, outcome monitoring, assisting autistic people to participate in society, and to provide information, training, or remote consultation to families and providers.[399] A wide range of technologies has been developed, including personal computers and mobile technologies, shared activity surfaces (eg, sensing technologies to measure sounds or distances), robotics, and virtual reality, aimed at different users in different settings;[399,400] many of these are now available to the autism community.[401] Digital technologies provide opportunities to address geographical inaccessibility, delayed provision of care, and low adherence to clinical protocols. However, digital technologies should enhance and complement functioning health systems and cannot replace important skilled human resources and adequate financing.[81,82,402]

The COVID-19 pandemic provided a powerful impetus for families, professionals, and businesses worldwide to move towards digital technologies for communication, information, education, and health care, including in the autism community.[403] Working remotely, treating remotely, and coming together through virtual meetings have become much more commonplace in some regions. However, most relevant to autism, technologies have often been developed without rigorous scientific evidence and without active participation of key users.[399,404] Little consideration has yet been given to the feasibility of implementing such technologies, particularly in LMICs, where the greatest potential effects might be seen.[403] Limitations in feasibility include affordability, accessibility, cultural appropriateness, and sustainability.[405] A 2016 report by the World Bank highlighted that the rise in access to internet and mobile

	Robotics	Virtual reality	Shared active surfaces	Sensing technologies	Personal computers	Mobile technologies
User	Researcher, clinician or therapist	Researcher, clinician or therapist, educator, person with ASD	Researcher, clinician or therapist, educator	Researcher, clinician or therapist, educator, person with ASD, family or carer	Researcher, clinician or therapist, educator, person with ASD, family or carer, non-specialist provider	Researcher, clinician or therapist, educator, person with ASD, family or carer, non-specialist provider
Setting	Research facility, clinic	Research facility, clinic, school, home, community	Research facility, clinic, school	Research facility, clinic, school, work, home, community	Research facility, clinic, school, work, home, community	Research facility, clinic, work, home, community
Purpose	Intervention and education	Screening and diagnosis, intervention and education, functional assessment	Intervention and education	Screening and diagnosis, intervention and education	Screening and diagnosis, intervention and education, functional assessment	Screening and diagnosis, intervention and education, functional assessment
Relative cost	Very high	High	High	Medium	Medium	Low
Feasibility	Very low	Low	Low	Low	High	Very high

Adapted from Kumm.[408] Feasibility is defined in terms of cost, access, and ease of use. ASD=autism spectrum disorder.

Table 4: **Potential applications of evidence-based technologies for autism**

connectivity has been far greater in HICs than in LMICs, risking an increase in the existing digital divide unless concerted efforts are made to enable universal internet and mobile access.[406] The COVID-19 pandemic certainly magnified these pre-existing digital disparities.[403] In addition, somewhat unexpected factors, such as gender differences in access to both smartphones and computers, will be important to consider as assumptions are made about the usefulness of different approaches.[407] In the context of these implementation challenges, table 4 shows the potential feasibility of a range of technologies for autism.[408]

Current and future uses of technology for autism

WHO has recently generated a classification of digital health interventions organised around four key user groups: those living with health conditions and their families, health-care providers, health systems and resource managers, and data services.[405] Each of these four groups is relevant in the use of technology in autism. In this Commission, we propose five pragmatic uses of technology for autism in the coming years.

The first is technology to connect people to people. Current social media technologies (eg, WhatsApp, Facebook, and similar systems) can be powerful tools to connect families and individuals who live with autism to one another. Online platforms can also connect families and individuals with autism to professionals (eg, electronic appointment bookings for someone with autism who would struggle to book appointments over the telephone or in person), while also supporting the formation of user groups (eg, a group of trained therapists for a specific intervention).

The second is technology to connect people to knowledge and training. An increasing number of online resources is available to individuals with autism and their families, offering research summaries, state-of-the-art information updates, and toolkits on a range of topics. These include information about specific tools, suites of local and national resources for families and practitioners about young children, and an electronic textbook from an international association of providers of children's mental health services.[409] Formalised training and certification courses for specific interventions can also make good use of technology. Virtual and augmented reality is also being explored for both interventions and training purposes.[410]

The third use is technology for screening, surveillance, diagnosis, consultation, and clinical care. Complex electronic systems for medical records, surveillance, targeted communication, decision support, and data management, as well as affordable and accessible tools for webinars and video conferencing, are now widely available. These tools allow for new models of clinical care, such as for screening and surveillance,[411,412] and for the Extension for Community Healthcare Outcomes model to be used for remote peer-on-peer consultation.[66] A series of digital tasks based on eye-tracking and fine motor coordination has shown promising early results to differentiate typical and delayed development in Indian children aged 2–6 years.[199] Electronic health records will continue to improve in sophistication and will support further improvement in data management and communication.

The fourth use is technology for alternative and augmentative communication. Various alternative and augmentative communication devices and therapeutic tools exist,[413] and many innovations are possible in this domain. These innovations include speech-generating devices[93,414] and less high-tech methods of communicating using pictures (eg, the Picture Exchange Communication System[413]).

Finally, technology can be used for new types of data collection and analysis. Technological advances might become particularly transformative in the collection of new types of data, including behavioural analyses (eg, through wearable devices[415]), potentially with the use of increasingly sophisticated artificial intelligence and big data methodologies. Data are needed to support their validity and reliability.

For **examples of technology resources for autistic people** see http://www.thinkingautismguide.com

Risks and pitfalls of technology for autism

Despite the increasing potential benefits of technology for autism, multiple risks and pitfalls should also be considered, such as technical challenges including the calibration of tools (eg, tablets, eye trackers, and smartphones); the need to validate and generate an evidence base for the technology, including how it is actually used; the risk of false claims, misinformation, and predatory commercial practices; privacy and confidentiality issues and ownership and curation of data; safeguarding and protection against exploitation of potentially vulnerable users; and screen addiction. Cost and accessibility of the technology and acceptability to different users will remain a substantial risk to be considered in ensuring that the digital divide that currently exists between HICs and LMICs does not become larger, thereby increasing rather than decreasing current disparities.[406]

Building workforce capacity and competency

WHO has set out key recommendations for building capacity to support individuals with autism and other neurodevelopmental disorders across several levels (from institutional and academic activity to civil society and government) that support our proposed models of stepped care and personalised health in assessment, treatment, and support.[416] While using the relevant evidence, interventions must match local contexts.[398] In LMICs or sparsely populated regions, one strategy is the development of broad skills to equip staff to work with the population within their specific context.[83] Such task sharing, as discussed earlier within the stepped care and personalised health model, requires reconfiguring tasks between professionals, ensuring that the complexity and demands of the work match the skill level of the provider, and task sharing between professionals and non-professionals, each of which is essential in LMICs (where the number of professionals available is scarce). As previously discussed (panel 6), to inform how evidence-based interventions can be scalable and adapted for use in LMICs and other under-resourced settings, more trials that study effectiveness and implementation factors are needed instead of simplistic efficacy trials of one intervention compared with treatment as usual.

In rural Australia, for instance, researchers introducing a rural allied health generalist role delineated 337 discrete tasks across six allied health professionals, with 45% of the tasks already delivered by more than one profession, and 38% by more than two. Reconfigured tasks were repackaged into 13 categories based on functional and diagnostic categories (rather than traditional professional repertoires) and made available to all allied health professionals.[83] Increased skill flexibility is achieved in several ways: by enabling one professional to do tasks traditionally allocated to others to cover a wider range of care needs;[39] delegating tasks requiring less training so that the highest skilled individuals can do the most complex activities; task sharing between professional and non-professional groups (eg, parents) while expecting experts or professionals to retain particular responsibilities; and broadening skills across the workforce to support more integrated care.[416]

In HICs, well established systems and competency frameworks set by professional regulatory bodies might act as barriers to flexible working and task sharing.[83] Radical and more controversial solutions include shortening professional training and focusing on specific skill acquisition in incremental phases with a step on, step off curriculum with several exit points in training[83] (sometimes referred to as micro-credentialing).[417] Programmes such as Increasing Access to Psychological Therapies in the UK have been able to teach core skills and recruit practitioners from a range of backgrounds.[418] In all contexts, sustainability requires ongoing supportive supervision, ideally with a local implementation champion, and ensuring local ownership of the programme[409] and appreciation of the fact that more expectations cannot just be added to the roles of non-specialists without recognition and allocation of resources. Systems improvement, active engagement of health-care managers and users, and consideration of performance-based financing are all necessary to improve the application of knowledge to delivery.[419] In neurodevelopmental conditions such as autism, proactive, developmentally phased life-span system models of management that recognise periods of increased or decreased need in the individual or their family are appropriate.[48] The worldwide skilled workforce with expertise in working with autistic adults across all levels of identification, diagnosis, intervention, and support is very small. Therefore, systems are needed to support more skilled workers at both the non-specialty and specialty levels.

Conclusions

Autism spectrum disorder is a heterogeneous condition that affects how autistic people interact with others and with the world throughout their life span. It is both relatively specific in some of its characteristics (eg, particular repetitive movements and interests, aspects of communication, and effects on relationships) and general in its association with cognitive strengths and limitations and difficulties in self-regulation, mood, and attention. It is a prototype of a neurodevelopmental disorder, in that it arises from early emerging differences in brain development that affect many aspects of behavioural, social, and cognitive development and functioning across time. The experiences (and absence thereof) associated with autism affect brain and behavioural development. Autism affects both the people who receive the diagnosis and their families; and yet, individuals and their families can show extraordinary strengths in persistence, patience, and perception that, in turn, can change their development as well. Continued

respect for this diversity and heterogeneity is vital. Regarding autism as a specific disorder is important at times, whereas at others, recognition of the overlaps with neurodevelopmental disorders is insufficient and needs to be more carefully considered.

The goal of this Commission was to identify what can be done to improve and support the quality of life for children and adults with autism and their families worldwide. We built on what is already known to identify strategies and goals for future research and clinical practice, and to promote more equitable and broader dissemination and implementation of resources and services. We are aware that the evidence base that informed our recommendations is not perfect. However, one of the major premises underlying our recommendations is that much more than what is currently being done is possible, noting the need for social justice and a responsibility to those living now and to future generations. Individuals with autism should be a valued part of society. We urge commitment to greater investments in what can be done for them and their families now, with a focus on how to build on existing information to answer specific practical questions that will then better inform interventions and services to help autistic individuals achieve their fullest potential.

Now is a time for optimism, with acknowledgment of the potential for change that is present in different ways at different times for autistic people and for the communities in which they live. However, this is also a time for realism about what can be done across contexts, including HICs and LMICs, and across the life span. In this context, we have proposed the use of the term profound autism to describe individuals who are very likely to need substantial support throughout their lives, but still have opportunities for improved quality of life through positive daily activities, supported independence in everyday actions, and social contacts. Realism about the scarcity of resources, inequities, social justice, and the kinds of system developments that will be required to make these changes happen is also needed.

Autism is a neurobiological disorder. We have not dwelt much on biology in this Commission, not because it is unimportant, but because the likely benefits of basic science and even translational science to autism, for the most part, are limited to very particular populations (eg, those with rare genetic disorders), or are still somewhat too distant to be impactful now. We recognise the importance and future promise of basic science, but argue that deliberate investment in clinical research now is equally important to achieve improvements in quality of life for autistic people and their families.

Social justice is a theme we embrace beyond heterogeneity, the potential for change, and the need for systems change. The proportion of autistic people and families who receive adequate support is small even in HICs and very small in LMICs. This inadequate support happens because of a scarcity of knowledge about what is necessary for whom and when, and insufficient prioritisation of autism in social and health-care systems and research funding. If relatively obvious questions can be answered about which interventions are efficacious, for whom, at what intensity, and when, together with insights about the active components underlying any effects, resources in HICs could be allocated more appropriately and effectively. In much of the world, however, problems stem not only from a scarcity of resources but also even greater knowledge gaps, stigma, and systems that do not value sufficiently human life and people with disabilities. In general, our recommendations for both clinical practice and systems change are based on beginning with an individual's needs and methods of change, considered within models of stepped care and personalised health for intervention and assessment, and with continual involvement of stakeholders, including autistic individuals, families, supportive community members, and providers, at each step of the way. Capacity building is essential to strengthening care systems, particularly in LMICs, and for under-resourced populations in HICs. In the contexts of cultural and regional diversity, research and service strategies that use dimensional approaches to factors that influence development, yielding personalised, dynamic models of intervention and services, will be the key to a better future for individuals with autism and other neurodevelopmental conditions.

Contributors

All authors made contributions towards the scope, structure, and key messages of this Commission. CL and TCh oversaw the drafting of the initial and final report. CL, JBMcC, AHa, and ES analysed the data presented in the profound autism section. AHa analysed data from the Autism Birth Cohort Study and MoBa study for the section on assessment. PC led the subcommittee on medical needs. APi created figures 2 and 4. Other authors made contributions to specific sections of the Commission and various tables, figures, and panels. All authors reviewed the drafts of the Commission and approved the final version for submission.

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