SCIENCE AND SOCIETY

In search of biomarkers for autism: scientific, social and ethical challenges

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Abstract | There is widespread hope that the discovery of valid biomarkers for autism will both reveal the causes of autism and enable earlier and more targeted methods for diagnosis and intervention. However, growing enthusiasm about recent advances in this area of autism research needs to be tempered by an awareness of the major scientific challenges and the important social and ethical concerns arising from the development of biomarkers and their clinical application. Collaborative approaches involving scientists and other stakeholders must combine the search for valid, clinically useful autism biomarkers with efforts to ensure that individuals with autism and their families are treated with respect and understanding.

Autism spectrum disorder is the term used for a diverse group of developmental conditions that affect a person's ability to relate to and communicate with others (BOX 1). These conditions (henceforth referred to as 'autism') are characterized by impairments in social skills and communication, narrow and intense interests, and repetitive behaviour. An increase in recognition of the symptoms of autism among professionals and a heightened societal awareness of the condition has resulted in a substantial growth in research in the past few decades. However, despite some major advances in the understanding of the genetic[1], neurobiological[2] and developmental[3] underpinnings of autism, many aspects of the condition are still poorly understood.

Recent epidemiological studies, conducted in different regions of the world, have indicated that at least one in every 100 people has some form of autism[4,5]. This is a much higher prevalence than previously estimated and may reflect an increase in the number of diagnoses owing to improved methods of detection and to a shift away from understanding autism as a narrowly defined, categorical disorder to understanding it as a spectrum of conditions that affect individuals differently[6] (BOX 1). As such, the impact of autism varies; some individuals can lead independent and fulfilling lives, but many develop substantial medical, educational and social difficulties that have a serious negative effect on their quality of life[7]. The heterogeneity of the condition has led some scientists to suggest that instead of one unique phenomenon, there are probably many 'autisms' with different underlying biological processes and developmental pathways (BOX 1).

Against this background of complexity, there is an intensive search for biological markers for autism. Such biomarkers could not only reveal causes of the condition but could also be clinically useful in complementing or improving the behavioural diagnosis of autism and in enabling earlier detection of the condition. Biomarkers would thereby assist in the validation of very early, targeted and individualized intervention programmes (BOX 2). In this Perspective we examine key scientific and methodological challenges that currently impede the development of biomarkers for autism. In addition, we discuss some of the most fundamental social and ethical issues that are raised by the search for autism biomarkers, and consider how these issues might be addressed and best resolved.

Autism biomarkers: the state of the science

The development of biomarkers in some areas of medicine has had important beneficial effects on health policy and culture. For example, lipoprotein and cholesterol screens for cardiovascular disease risk have led to dramatic changes in the medicines that are prescribed for preventing or reducing the risk of cardiovascular disease and have had strong effects on lifestyle choices. There is widespread hope that valid biological markers for autism (BOX 2), a condition currently defined on the basis of behavioural criteria, will similarly substantially advance research and be readily translated into clinical applications. This hope has been fuelled by recent progress in our understanding of the pathogenetic mechanisms involved in several neurodevelopmental disorders that are associated with an increased risk for autism (for example, Rett syndrome, fragile X syndrome, tuberous sclerosis and neurofibromatosis). These developments have revealed that potential new treatments that are identified for these conditions may have wider applications in other cases of autism. However, a number of key scientific challenges have yet to be overcome. First, experience in other areas of biomedical research highlights how challenging it can be to translate biomarker discovery into clinical applications, and very few clinically useful biomarkers have as yet been identified for neuropsychiatric conditions. Second, the identification of autism biomarkers has so far proved elusive, partly because definitions of the condition itself have changed considerably over time and are still developing (BOX 1). Researchers have primarily focused on mapping biomarkers onto clinically defined categories, but such categories do not capture the current understanding of the increasingly multidimensional and complex clinical, cognitive and behavioural phenotype that is associated with autism and its overlap with other disorders. Third, developmentally invariant biomarkers for autism are particularly challenging because the phenotypic manifestations unfold as

development progresses, especially during infancy and early childhood, reflecting dynamic developmental interactions among multiple risk factors[3]. Fourth, several proposed biomarkers (TABLE 1) were found not to be universal, and none has indexed the presence of autism in a majority of cases (poor sensitivity). Candidate biomarkers tend also to be associated with a range of other neurodevelopmental conditions and not only with autism (poor specificity). Finally, measuring some putative biomarkers is currently expensive, laborious and reliant on a high degree of technical expertise, restricting the possibility of their application in most clinical settings.

Using examples from three current lines of enquiry, we will demonstrate these interlinked challenges and consider recent scientific developments that are already underway to address those challenges. The examples include potential biomarkers that reflect genetic or environmental factors that increase susceptibility to autism, that may confirm or assist the diagnosis of autism, or that may reflect precursors and early signs of autism before the full clinical manifestation of the syndrome.

Biomarkers for susceptibility. A specific cause of autism is only identified in a small proportion of cases, but twin and family studies have implicated yet-to-be-identified genetic and non-genetic risk factors in the remaining cases (BOX 3). The clear implication of genetic factors in the aetiology of autism has instigated a major search for 'autism genes' over the past decades. The evidence for some genetic risk factors is stronger than for others, with no single causal pathway indicated (BOX 3).

Currently, the prevalence, penetrance and variability in phenotypic expression of most genetic risk factors have not been established, and large-scale studies are ongoing to ascertain the extent to which each genetic risk factor is implicated in the aetiology of the disorder. Hence, none of the genetic variants that have been identified so far can be considered clinically useful for the identification of autism in the general population[8]. Nevertheless, the testing for genetic variants of individuals diagnosed with a developmental disorder, including autism, aims to improve medical care by identifying variants that may give rise to co-morbid medical problems (for example, the medical complications associated with tuberous sclerosis and micro-deletion and -duplication syndromes, such as epilepsy, and renal and gastrointestinal problems) and by establishing the risks of potential recurrence in future offspring of parents who already have a child with the condition.

Recently, molecular genetic techniques (for example, chromosomal microarray (CMA)) have been developed for detecting submicroscopic deletions and duplications. Several scientific-industry consensus reports have advocated the use of these more powerful techniques as a first-tier test for genomic abnormalities for individuals with a range of developmental conditions, including autism[9]. Studies using CMA to test very large samples of individuals who are already diagnosed with a developmental disorder have shown some form of genetic anomaly in 5–10% of individuals[9]. In addition to indicating co-morbid medical problems and recurrence risk, it is suggested that CMA testing may help families to understand the genetic contribution to the condition. There are currently no scientific or industry guidelines for how CMA results should be reported to participants, but first steps towards such guidelines are underway[9].

Attempts to translate new genomic findings into clinical applications have resulted in mixed reactions from the scientific community and the public[9,10]. Difficulties often arise in cases in which genetic variants are identified but their clinical significance is currently unclear. The limited information regarding specificity, sensitivity, penetrance and phenotypic expression of these variants means that accurate prediction of recurrence risk and developmental outcomes is not yet possible in most cases. In the future, a key scientific challenge will be to develop sufficiently large databases of genetic variants to ascertain their clinical utility in isolation or in combination with other genetic and non-genetic risk factors.

Diagnostic biomarkers. Although autism is defined on the basis of behavioural criteria, the condition is associated with a wide range of other biological phenomena (TABLE 1). It is hoped that translating markers of these phenomena into clinically useful biomarkers will improve the validity and efficiency of existing diagnostic methods. There is a growing need for efficiency in diagnostic procedures because wider awareness of the condition in the community has led to a much larger number of referrals to specialist clinical teams, including services for adolescents as well as adults[11]. Currently, the diagnostic process typically includes a clinical developmental history, assessments of speech, language and intellectual abilities, and of educational or vocational attainment. Additional medical assessments, such as genetic tests and brain scans, are sometimes used to exclude other neurological conditions or to assess for co-morbid conditions[12]. Standardized and semi-standardized procedures for conducting developmental interviews with caregivers and for observing and assessing social, communicative and repetitive behaviours that are characteristic of autism have been developed to aid and improve clinical diagnosis[12]. This comprehensive evaluation, conducted by multidisciplinary expert clinical teams, is viewed as necessary not only to establish or to confirm a clinical diagnosis of autism but also to inform and tailor the service provisions that are required for different individuals. However, these so-called 'gold-standard diagnostic tools' have not been widely adopted in community services because they are laborious, expensive and

Box 1 | **The changing concept of autism**

Although autism has almost certainly always existed, it was only recognized as a distinct condition in the mid-twentieth century. At that time it was thought to be a categorical condition that affected a relatively small number of people and was characterized by a distinctive set of behavioural abnormalities, such as severe delays in language, impaired cognitive skills and a profound lack of emotional contact with others. This understanding of autism was challenged in the 1980s with the introduction of the concept of an autistic spectrum, which recognized that autism affects people with no language or learning difficulties as well as those who do have those difficulties but nevertheless share 'core' diagnostic features in social and communication difficulties. The current *Diagnostic and Statistical Manual of Mental Disorders*[51] includes 'autistic disorder', 'Asperger's disorder' and 'pervasive developmental disorder not otherwise specified' (PDD-NOS) as types of autism. Research has thus far failed to map these clinical subgroups onto a specific aetiology or developmental pathway leading to each disorder. Today, there is increasing appreciation of the heterogeneity in the expression of the condition along numerous phenotypic dimensions, which overlap with those found in other conditions and in the general population[52,53]. As a result, the next edition of the *Diagnostic and Statistical Manual of Mental Disorders*, to be released in 2013, will replace current categorical 'subtypes' with a single category labelled 'autism spectrum disorder'.

resource intensive. In fact, in many communities, autism-specific services have yet to be developed.

It has been suggested that biomarkers may aid and/or improve the efficiency of the diagnostic process, and recent studies[13–16] have attempted to build diagnostic algorithms for autism on the basis of composite features of brain structure that have been associated with the condition. In these studies, multiple MRI measures — in addition to diagnostic classification of participants (into those with autism, with other clinical diagnoses or with no diagnosis) — were used to train machine learning algorithms. Established methods for checking the accuracy of classification (which involve training on a subset of the data and testing on the remaining data) suggest that, depending on the study, such algorithms reach an accuracy of 80–90% when there are 20–30 participants in each diagnostic category.

There is wide consensus that the use of machine learning algorithms in brain imaging studies is an exciting scientific development. It builds on the large body of previous findings in this area, and is an important preliminary step towards testing the proposed brain imaging methods as useful aids in behavioural diagnosis. However, some media reports have promoted the findings from the studies[13–16] as discoveries of new low-cost diagnostic methods that could replace current diagnosis based on behavioural measures. These claims provoked much criticism and debate[10,17]. The main criticism of the approach of using machine learning algorithms on MRI data is that applying such classification methods to small selected samples inaccurately estimates the sensitivity and specificity of the proposed methods as diagnostic biomarkers. It is generally agreed that the utility of proposed predictors in aiding diagnosis can only be established in large studies of unselected population samples, in which participants are drawn from the community rather than being identified on the basis of having a pre-existing diagnosis.

Other scientific and practical limitations of the proposed predictors have yet to be overcome. First, the accuracy of the proposed biomarkers in distinguishing autism from phenotypically overlapping conditions, such as language, attention and motor disorders, has not yet been sufficiently established. Second, although some of the studies included children[15,16], it is unclear whether the proposed method should be used with children and with low-functioning individuals, because obtaining good quality brain scans from these groups can be very difficult — brain imaging may require sedation, which carries risks and substantial costs. Third, this method alone could not replace the multidisciplinary assessment approach that provides important additional information necessary to tailor service provision. So, despite claims to the contrary, the translation of brain structure findings into biomarkers is still in its early days. In a similar way to approaches that are currently underway for attention deficit hyperactivity disorder (ADHD; see The ADHD-200 Sample website), larger and more representative samples, obtained by pooling brain scans from different research groups, will simultaneously inform neurobiological models of autism and accelerate the development of diagnostic biomarkers. Nevertheless, despite its intellectual and scientific appeal, structural brain imaging is unlikely to be of clinical utility in general community practice in the foreseeable future.

Box 2 | **In search of autism biomarkers**

A biological marker (biomarker) is an indicator of a biological state. Biomarkers need to be measurable, associated with the particular condition and stable or predictable across and within individuals. Biomarkers can be measured using various biological samples, including blood, urine or saliva. There is increased interest among researchers in so-called neuromarkers, which are biomarkers based on measures of neurochemicals in the cerebrospinal fluid, brain structure measured using MRI, and/or brain function (TABLE 1). Biomarkers have several applications. First, they can be viewed as risk factors that increase an individual's susceptibility for a condition, and as such can be used to identify individuals who are at high risk for the condition. Biomarkers that can be detected before disease symptoms occur could be used to improve early detection of a condition. Second, they can be used to improve diagnosis, as they may enable better prediction of the nature and severity of disease outcomes in an individual. Third, they may be used to develop personalized treatments and, if monitored over time, can be used to evaluate treatment outcomes. A wide range of autism biomarkers has been proposed (TABLE 1), but as of yet none has been validated for clinical use.

Predictive (presymptomatic) biomarkers. The behaviours that are characteristic of autism first emerge and then evolve over the first few years of postnatal development. Atypical behaviours can be observed in some children as early as 12 months, but in the majority of cases such characteristics are not sufficient to pass the clinical threshold for an autism diagnosis[3,18]. In many cases, it is difficult within this early period to distinguish autism symptoms from normal variations in development, or from transient delays or difficulties that resolve over time without any need for intervention. As a result, families often experience what is commonly known as a 'diagnostic odyssey', in which substantial delays occur between the time when they express concerns about their child and when diagnosis is confirmed and intervention can be accessed. This situation is frustrating for families and clinicians alike, given the increased recognition of the importance of early intervention, before symptoms become more pronounced and their treatment becomes more difficult and costly[19].

Recently, large-scale prospective studies of infants at risk for autism — by virtue of a family history of the condition or parent or clinician concerns — have begun to investigate precursors of autism symptoms in infancy[18]. It is hoped that valid biomarkers that are identified before the onset of clear symptoms will help in the early detection of emerging autism[19]. In general, recent evidence suggests that before the expression of overt behavioural symptoms at around the end of the first year, measures of brain function distinguish infants at risk for autism from low-risk controls[3]. These findings have been valuable in identifying the correlates of early functional brain development in this risk group, and have inspired the hope of translating these findings into predictive biomarkers of the condition.

Using similar classification algorithms to those described above, a recent proof-of-concept study showed that measures of spontaneous electroencephalography (EEG) predicted risk status for autism in a group of infants with approximately 80% accuracy[20]. Despite the novelty and promise of their approach, the authors of this study cautiously qualified their findings by the need to ascertain diagnostic outcomes in these infants in toddlerhood. Another study reported that eye-tracking measures of social preference are 100% accurate in predicting provisional and confirmed diagnoses of autism in a group of infants aged between 14 and 42 months[21]. Although diagnostic outcomes in those infants younger than 3 years in the sample are yet to be confirmed, this latter study suggested that eye tracking may yield "a novel easily detectable signature of

Table 1 | **Examples of proposed biomarkers for autism**

Biomarker type	Sample/measure	Refs
Gene expression profile	Blood samples	9
Proteomic profile	Serum samples	62
Metabolomic profile	Urine samples	63
Head size	Head circumference trajectory	64
Brain size and structure	MRI, DTI	13
Brain function	Functional MRI, EEG, ERPs	20
Eye movement	Looking measures, saccadic reaction time	21

DTI, diffusion tensor imaging; EEG, electroencephalography; ERPs, event-related potentials.

autism early in life," and that eye tracking could conceivably assist diagnosis in primary care settings[21].

The classification approach has attracted criticism, particularly because the media reported some findings inaccurately as discoveries of new autism biomarkers in infants[22,23]. As in the case of machine learning algorithms for diagnostic biomarkers, a major limitation of this kind of study is that the sensitivity and specificity of the proposed candidates as predictors of autism will probably be very different when applied to the general population. Second, previous studies that used laboratory measures similar to the proposed biomarkers suggest that these measures are highly sensitive to age[24]. To accurately evaluate the utility of these measures as predictors of autism, the developmental course of these candidate measures within the period of infancy and toddlerhood needs to be determined in large samples of participants. Last, the value of the proposed biomarkers as predictors of autism is based on the assumption that observed differences in infants who are at risk for autism necessarily reflect later symptomatology in the subgroup who will go on to develop autism. This assumption has been challenged by findings that suggest that the neurodevelopmental process in infants who are at risk is atypical. In those infants who do not develop the disorder, observed neural differences may reflect the brain's resilience and adaptation in the face of genetic risk[3].

Despite the promise of these recent findings regarding how autism develops in infancy and the insights that they provide for models of complex multifactorial aetiology, premature claims of the clinical utility of predictive biomarkers may only serve to undermine the value of these scientific advances. Indeed, the challenges outlined above have already been recognized in the broader field of developmental psychopathology, and new concepts have been adopted. One idea that has been adopted in autism studies[25] and that has more recently been applied to studies of infants at risk[3] is the concept of using more proximal endophenotypes (or intermediate phenotypes) in the path towards biomarker development[26]. Such endophenotypes are considered to reflect the genotype better than does complex clinical characterization. Intermediate phenotypes index susceptibility and are expected to be present in both diagnosed individuals and in their unaffected family members. Some intermediate phenotypes will also be associated with other conditions that share genetic, environmental and neurobiological risk pathways. Given their intermediate status, endophenotypes may have limited clinical significance but may be found to be clinically valuable when combined with other measures and/or when they are evaluated over a long developmental period. In general, the promise of predictive biomarkers is more likely to be fulfilled if the scientific community continues to focus on building the understanding of autism as a complex condition that is probably determined by multiple, yet to be understood pathways that lead to heterogeneous outcomes.

Ethical issues

Heterogeneity. The difficulties in the search for biomarkers for autism underscore the biological heterogeneity of the condition. This heterogeneity contributes to a complex phenotypic picture of autism, and it is this picture that most provokes ethical reflection on the therapeutic interventions that biomarkers could introduce. People with autism are located somewhere on a broad spectrum from low to high functioning. This is reflected, for example, in the range in IQ (from severe intellectual impairment to extremely high IQ) and communication styles (from no speech or language use to highly articulate, if eccentric, speech and language) that are associated with the condition. The concept of a spectrum is also used to capture the variability in health, in developmental difficulties and in sensory problems that contribute to the different profiles of people who are affected by autism. The general public, however, rarely appreciate this level of complexity and the broad spectrum of functioning that characterizes the condition. The quirky savantism of the person with autism depicted in the film *Rain Man* remains for many people the iconic representation of autism, whereas in reality the majority of diagnosed individuals are placed somewhere along the spectrum rather than at or near its extreme ends. Furthermore, in any given period, an individual with autism can fit descriptions of both high and low functioning in different respects and even in different settings. Hence, a diagnosis of autism can represent a person who is extremely disabled but has unique strengths in some areas (such as art, music or mathematics), or someone who functions effectively when he or she can work in solitude and engage with colleagues in virtual discussions but who is profoundly disabled by social difficulties in real-time encounters with them[27]. Moreover, the position of an individual on the spectrum is not fixed through the course of life, if only because environmental inputs may help them to learn social communication behaviours and to adjust to their surroundings and, more generally, may minimize (or exacerbate) their symptoms. For example, a young withdrawn and nonverbal child with autism may grow into a high-functioning adult.

Given the relatively plastic nature of autism symptoms (particularly early in life) and the possibility of movement within a broad spectrum from low to high functioning through the course of a life, it is important that biomarker discovery in autism does not result in children being given a biological label that fixes and defines their potential and treatments. Ideally, biomarker discovery should lead to an increased understanding of the complex nature of the autistic spectrum, rather than to deterministic or reductive thinking about autism.

Difference versus disability. The prospect of autism biomarkers sharpens the fundamental question of what value to place on autism as a condition, and on different aspects of the condition. Autism is generally described in a negative way by listing its core attributes as impairments in social communication, narrow but deep interests and stereotyped behaviour, but emphasis could also be placed

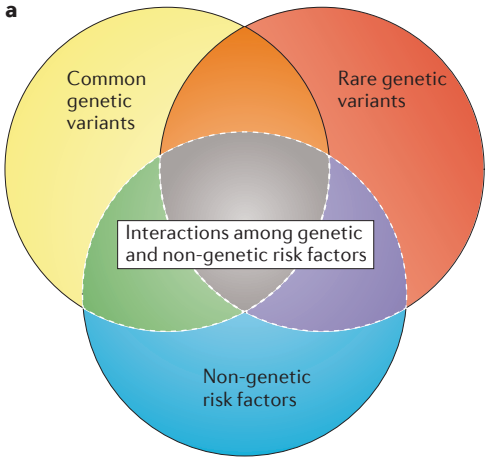
on the more positive aspects of the condition, such as "strong persistent interests, attention to detail, unusual memory, fascination with systems and patterns, and ability to concentrate for long periods that may be conducive to creativity and originality"[27]. In addition to these more generic attributes, heightened skills (such as superior visual functioning[28] or musical processing[29]) are associated with some forms of autism. Forms of giftedness (for example, in mathematics) are also found in some individuals. The degree to which the positive (or positively described) features and the negative (or negatively described) features are independent of each other is a very important question. Hans Asperger, who first identified the form of autism that came to be called Asperger's syndrome, understood them to be two sides of the same coin. With regard to one of his patients, he wrote: "this boy's positive and negative features are two naturally necessary, connected aspects of one really homogenously laid out personality. We can also express it like this: the difficulties this boy has with himself as well as his relationship to the world, are the price he has to pay for his special gifts."[30] Clearly, a better understanding of the relationship and interplay between the positive and negative traits that are associated with autism is relevant to the development and eventual use of biomarkers for autism, and to the question of whether research should focus on those forms of prevention, cure and amelioration that protect the positive while working against the negative.

The question of value — of whether to focus on the positive or the negative aspects of autism symptoms and profiles — has current political, as well as ethical, implications. A debate about whether autism is a disability extends outwards from the autism community. On one side of the debate is a group that includes proponents of 'neurodiversity', who claim that autism is best understood as 'cognitive difference' that requires no treatment or intervention but rather social acceptance and support (BOX 4). From the neurodiversity perspective, the classification of, and the treatment strategies for, conditions like autism are influenced by societal factors such as tolerance and acceptance of different styles of social behaviour and cognitive ability, the availability of treatments and the resources that are in place to support those with different learning styles[31]. On the other side of the debate are those who regard autism as a serious disability and those who fund scientific research into the condition with the hope that it will

Box 3 | **Known risk factors for autism**

Twin and family studies have demonstrated that both genetic and non-genetic factors contribute to an increased susceptibility to autism[1]. The involvement of some genetic factors is stronger than others and so far a heterogeneous mix of signalling pathways, rather than a single causal pathway, has been indicated. There is, however, growing evidence for the involvement of genetic risk factors that interfere with synaptic development and plasticity. Risk factors (illustrated in part **a** of the figure) include common and rare genetic risk variants, as well as non-genetic risk factors. Common genetic variants[9] are associated with low odds ratios of risk for autism, but replication and confirmation of the role of these variants, for example MACRO domain containing 2 (*MACROD2*)[54] and 5p14.1 (REF. 55), in autism risk is still awaited. Among the clearer associations with autism are rare (defined as occurring in <1% of the general population[1,9]) copy number variants (see the figure, part **b**) and genetic syndromes (part **c**). Non-genetic factors that increase the risk of autism are still poorly understood, and could include stochastic, epigenetic and environmental factors[56]. As illustrated in the figure (part **a**), interactions between genetic and non-genetic factors can further contribute to autism risk[3].

a



b **Copy number variants**

Location	Type	Size (kb)	Frequency in autism
16p11.2	Deletion	422	0.37%
7q11.23	Duplication	1,371	0.09%
15q11.2	Duplication	161	0.18%
15q11.2–13.1	Duplication	4,856	0.16%
15q13.2–13.3	Duplication	1,508	0.13%
16p11.2	Duplication	521	0.13%
15q13.2–13.3	Duplication and deletion	1,508	0.16%
16p11.2	Duplication and deletion	521	0.50%
22q11.21	Duplication and deletion	2,521	0.13%

Frequencies are based on a meta-analysis of studies with a combined sample of 3,816 cases with autism[57].

c **Genetic syndromes**

Genetic condition	Gene	Frequency in autism
Established association		
Fragile X syndrome	*FMR1*	1–2%
Tuberous sclerosis	*TSC1* and *TSC2*	~1%
Rett syndrome	*MECP2*	~0.5%
Emerging evidence		
Neurofibromatosis type 1	*NF1*	Rare
Timothy syndrome	*CACNA1C*	Rare
Smith–Lemli–Optiz syndrome	*DHCR7*	Rare
Prader–Willi and Angelman syndrome	*UBE3A* (and others)	Rare

Information is adapted from REF. 1. *CACNA1C*, calcium channel, voltage-dependent, L type, alpha1C subunit; *DHCR7*, 7-dehydrocholesterol reductase; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; *NF1*, neurofibromin 1; *TSC*, tuberous sclerosis; *UBE3A*, ubiquitin protein ligase E3A.

lead to a cure for autism or to a means of preventing autism. It should be noted that these objectives are shared by many carers of autistic people and many autistic people themselves[32,33]. However, it also seems likely that differences of opinion about the value of autism exist within families, with the views of carers charged with providing life-long support being at odds with those of family members with a diagnosis of autism.

The current research emphasis on the desirability of early identification and (potentially) prevention of autism has further stimulated this debate. Although official mission statements of relevant governmental and research funding organizations identify the need for increasing support for individuals on the autistic spectrum[34,35], the search for prodromal biomarkers of autism and the development of strategies aimed at reducing the disabilities and challenges resulting from autism remain current research priorities[34,36]. However, from the perspective of neurodiversity proponents, the search for biomarkers designed to identify, treat or prevent autism is fundamentally misguided from a moral point of view[37]. Of course, people who support early identification of autism and resultant interventions are not necessarily opposed to respecting cognitive difference. Nevertheless, the two perspectives seem to be polarized on the issue of preventing autism.

It is possible that ambiguities in the term 'prevention' have contributed to this polarization of opinions. Some people in the autism community assume that preventing autism would mean that it would be totally eradicated[38]. Perhaps some researchers do aim to prevent autism in this sense, but the goal of most research is to prevent the severe cognitive, behavioural and social challenges that are associated with autism, and their negative impact on individuals and their families. A distinction between primary, secondary and tertiary forms of prevention is useful in this context: primary prevention strategies aim to avoid the development of a condition through health-promotion activities that target the general population or that focus specifically on the population at risk; secondary prevention strategies attempt to diagnose and treat the condition in its early stages before it results in substantial morbidity; and tertiary prevention strategies involve interventions aimed at reducing the negative effects of the condition by restoring function and reducing condition-related complications as far as possible. Notably, in the case of autism, even the relatively radical 'secondary prevention' would target the resulting morbidity rather than autism itself.

It seems undeniable, however, that each category of preventative intervention and study of preventative intervention, assumes that autism is problematic. This may be the core objection of proponents of neurodiversity. More specifically, with regard to secondary prevention, they may question what counts as 'morbidity' and who is to decide this. With regard to tertiary prevention — arguably the least controversial category — research and interventions that are directed at preventing or ameliorating suffering, difficulty and distress in people with autism (which attract near universal support) occur in parallel — and may sometimes overlap — with research and interventions aimed at 'normalizing' autistic behaviours. Certain behavioural interventions, for example, aim to reinforce approved behaviour (such as making more prolonged eye contact) while reducing behaviour that is perceived as problematic (such as the repetitive and stereotyped behaviours sometimes known as 'stimming'), but the value of such activities is regarded by many as highly debatable. More controversially, a recent study reported the effects of administering the hormone oxytocin to a group of high-functioning people with autism in a context that was designed to measure their social interactions and improve their understanding of the intentions of others and of social cues[39]. According to the researchers, the behavioural changes in these individuals — such as stronger interaction with, and preference for, the partner most favourable to them — showed that oxytocin induced "more appropriate social behaviour and affect" in people with autism. However, the study was interpreted by some in the autism community as an experiment in which autistic people had instead "learned and displayed selfishness and hypocrisy and us-versus-them thinking. Their objectivity, fairness and altruism were — temporarily — 'cured.'" (see The Autism Crisis website). Clearly, the challenge is to achieve and communicate as much clarity as possible on the goals and rationale of a particular research and intervention strategy, and on the crucial question of whether the perceived desirability of the outcome is based on something more objectively important than 'fitting in' with contemporary cultural norms.

Uncertainty and reproductive choice. The issue that probably causes the most concern to some parts of the autism community (and, indeed, to members of the general public with particular cultural, religious or personal views on reproductive decision making) are the twin prospects of prenatal diagnostics leading to large-scale elective abortion of fetuses deemed to be at risk and, perhaps also, an avoidance of having children by those identified as at risk of conceiving autistic offspring — which might be classified, somewhat awkwardly, as forms of primary prevention. To those major concerns might be added the prospect of eventual secondary prevention strategies aimed at diagnosis and treatment of autism *in utero*.

Some people fear the development of a biomarker for autism that could identify risk of autism pre-implantation or *in utero*,

Box 4 | **Neurodiversity**

Proponents of neurodiversity claim that the atypical neurological development seen in autism is, in fact, a normal human variation that should be recognized as an acceptable difference. They therefore reject the conceptually problematic classifications of 'normal' and 'abnormal' functioning and insist on a distinction between 'neuro-diverse' and 'neuro-typical' functioning[58]. As a result, we are encouraged to broaden our understanding of health, disease and disability and to reconceptualize autism in such a way that we no longer think of it as a condition that needs treatment, correction and prevention.

The neurodiversity movement presents an important challenge to our usual perspectives on autism by forcing us to attend to the contested nature of the concept of 'normality' and its attendant complexities, by drawing our attention to the positive aspects of autistic spectrum conditions and by insisting on respect for cognitive differences. In all of these ways, it resembles the campaigns for recognition by other disadvantaged groups who eventually succeeded in changing public perceptions of their condition. The positive side of this standpoint is that it enables people with autism to celebrate their distinctive strengths. However, it has also been suggested[59] that accepting neurodiversity may reinforce the unhelpful and potentially dangerous idea that there are differences between autistic and non-autistic people at a fundamental biological and ontological level that affect, for instance, how we conceive of their moral agency and membership of the moral community[60]. It may also lead to a tendency to underestimate the severe effects autism has on the lives of those with serious cognitive impairments and the acute isolation and loneliness experienced by even high-functioning individuals[61].

as this could lead to embryo selection and elective termination (to avoid having a child with autism) becoming the norm[40] — as seems to have happened in the case of prenatal testing for some genetic disorders. As mentioned above, given the complexity and heterogeneity of autism, it is unlikely that a single biological test or biomarker will be able to establish the risk of autism in an embryo or fetus with a high degree of certainty in the vast majority of cases. However, despite the challenges outlined above, it is possible that biomarker discovery may help to identify different typologies within the autism spectrum, and this could provide both prospective parents and parents of infants who are at risk with a probabilistic estimation of the symptoms and course of autism if the condition were to manifest itself in the child. Therefore, it is appropriate and timely to consider the impact of autism biomarkers in relation to reproductive choice.

Supporting the fears of proponents of neurodiversity, there is evidence to suggest that preventing the birth of individuals with disabilities that can be diagnosed prenatally seems to many people to be an obvious step to take, and is encouraged by some medical professionals and bioethicists[41,42]. Indeed, some have argued that there is a moral obligation to prevent the births of disabled individuals where possible[43], regardless of the level and kind of disability[44]. Recent abortion statistics indicate that, between 2002 and 2010, almost 18,000 abortions were performed in England and Wales on the grounds that the fetus was at risk of handicap or deformity (see UK Department of Health website). A small number of parents chose to abort a fetus with a relatively mild or a correctable disability. This suggests that a biomarker that indicates some level of risk of autism would lead some parents to abort, even if the test was a lot less than 100% accurate. Conversely, the availability of successful (secondary) prevention strategies, if and when they are developed, may reduce the number of terminations because parents will be assured that treatments are available for a child who is diagnosed with autism. As parental decision making is likely to be influenced by future biomarker information regarding the treatment of autism, it will be crucial to offer parents counselling about genetic and non-genetic risk factors, potential social, educational and developmental outcomes, and treatment options. In the United States, the provision of support services, counselling and evidence-based information to parents about "the range of outcomes for individuals living with a (prenatally) diagnosed condition" has been legally mandated since 2008 by the The Prenatally and Postnatally Diagnosed Conditions Awareness Act. The Act was introduced partly because of evidence suggesting that physicians were failing to provide positive information about children with disabilities such as Down's syndrome to parents with a prenatal diagnosis of possible disability[45].

However, legal mandates to provide fair, supportive, evidence-based information to prospective parents are not the heart of the matter. The final moral decision appropriately lies with the individuals who choose among the available options — the parents of the child, or potential child, at risk of autism — and ethical considerations regarding, for example, the morality of abortion or how we should think about disability and disabled lives will no doubt continue to weigh heavily on the choices people make.

Translating biomarker information into clinical practice. If there is a natural reluctance on the part of many people to bring children with disabilities into the world (which would mean a high likelihood that fetuses identified as at risk will be aborted), then it is imperative that biomarker-based information on risk of autism — a condition that some argue is not even a disability — is translated into clinical practice with great caution and care. Thresholds for clinical utility of biomarker information (that is, acceptable levels of sensitivity and specificity of biomarkers in the clinical setting) have thus far been decided by scientists. Given the debate about whether autism is best thought of as a disability or a difference, it is necessary that the clinical utility of biomarkers is established with involvement from people with autism and from their families, whose lives will be affected by such decisions.

High thresholds for clinical sensitivity and specificity will help genetic counsellors to face the challenge of conveying a complex and uncertain picture of autism risk to anxious parents, enabling more informed reproductive decision making. Published scientific agreement about the threshold for clinical utility of biomarkers may also help to better inform decision making by parents who receive results of genetic tests for autism. *In utero* testing for autism is already available through genetics laboratories. In the United States, genetics laboratories report that they receive an increasing number of requests for *in utero* CMA tests for autism from parents who have no obvious risk factors themselves. As discussed earlier, such tests may identify known genetic abnormalities that are associated with autism, but CMA testing also identifies many novel copy number variants as well as recurrent variants of unknown clinical significance[46]. More research is needed before these can be linked to autism.

How genetic counsellors communicate to parents the probabilistic and therefore uncertain picture derived from autism biomarkers, and the complex and contested nature of the autism spectrum itself, is likely to have an enormous impact on parental decision making. Clinical and laboratory geneticists have acknowledged the importance of this communication in a consensus statement calling for CMA to be used as the first-tier clinical genetic test for individuals with developmental disabilities[65]. The consensus statement emphasizes the need for geneticists to work closely with genetic counsellors to ensure that accurate, consistent and updated information is provided to families along with the test results.

Although more research is needed to better understand parental needs and attitudes in the context of genetic counselling for autism, it is clear from current research that when parents access counselling, this plays an important educational and supportive part in their decision making[47]. Study outcomes suggest that parents have a generally poor understanding of genetics; in particular, they overestimate the chances of recurrence of disorders, and this substantially affects family planning decisions[48,49]. Parents also express that they want to be given biomarker results only when these can point to the causes of autism (which most parents believe are genetic) and when the results of genetic tests can be said to be 'true'[50]. The need of parents for aetiological explanations (and for truth) shows that the establishment of thresholds for the clinical utility of biomarkers for autism is crucial. Although it should be possible to develop guidelines for public communication about autism biomarkers on a national level, it will be more difficult to produce guidance that could be used to inform clinical practice globally, given the need to take into account specific societal and cultural norms.

Conclusions

Against a background of great hope and promise, and an abundance of studies using elaborate methodologies, it may seem surprising that despite huge advances in the basic scientific understanding of autism,

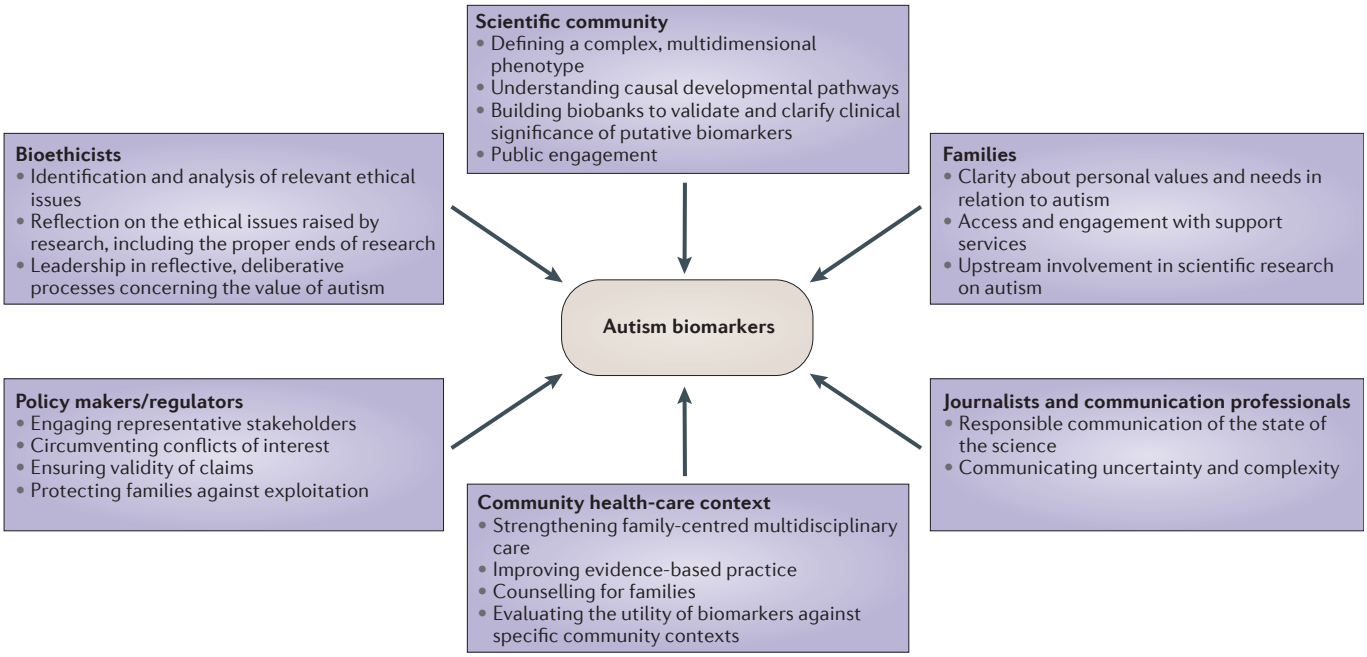


Figure 1 | **Towards autism biomarkers.** Meeting the challenge of valid, ethically sound and clinically useful autism biomarkers may be achieved through collaborative approaches representing multiple interested parties willing to engage in open discussion of complex scientific, social and ethical issues.

comparatively little has been achieved to date with regard to translating the resulting evidence into clinically useful biomarkers. We have considered some of the key challenges that the field has yet to overcome. Several new approaches have emerged that promise to meet these challenges and to advance the development of biomarkers in the near future. First, autism research has recently witnessed a growth in collaborative approaches that rely on pooled data sets (biobanks), which allow for much larger studies than were previously possible. In the long run, biobanks of genetic samples or brain scans will allow for testing more specific hypotheses about causal pathways of the disorder. Second, improved understanding of complex gene–environment interactions that lead to autism will accelerate biomarker discovery. Accordingly, autism research should make more use of theoretical advances in other areas: for example, in modelling gene–environment interactions in typical development and in other neurodevelopmental conditions. Last, biomarker development is increasingly reliant on combining different markers and accounting for the relationships among them. Improved analysis techniques that can be used to model multimodal biomarker data and evaluate their sensitivity and specificity will be required.

New approaches in biomarker development for autism are unlikely to be met with unqualified approval and support unless certain important ethical issues are also addressed. We have suggested that crucial among these concerns is the possibility of the prevention or cure of autism. Autism presents a unique challenge to biomedical research precisely because it cannot be classified simply as a 'harm', in light of the richness and value that some individuals with autism claim as part of the autistic experience. The diverse views on the question of prevention and cure of autism should inform the scientific agenda. Key to this will be to ensure that members of the autism community and their carers are involved in the biomarker research process (and the autism research process generally). This involvement may motivate more diversity and equality in scientific research funding for autism, with programmes that research biomarkers to aid early identification and intervention running alongside research programmes that focus on education, training and interventions that improve the lives of people living with a diagnosis of autism. The current absence of systematic input from the community affected by autism and of research about what determines the perspectives of various stakeholders are major challenges to be overcome. Clearly, a failure to contextualize the use of biomarkers within the unique needs of diverse communities would only serve to undermine their potential value.

The involvement of families and other representative stakeholders in informed dialogue with researchers regarding scientific advances would also circumvent the miscommunication of findings by the media. The dangers of such miscommunication include increased social, and possibly funder, pressure on scientists to move away from key questions about autism aetiology. Such pressure may already have tempted a minority of scientists to exaggerate claims about the clinical utility of their research well before the science is sufficiently ready for translation into clinical or community practice. By contextualizing existing and new research knowledge within the real-life experiences of affected families, science communication regarding autism biomarkers can serve its primary purpose of informing the public and contributing to ethically informed knowledge translation.

In the above discussion we do not assume that the question of whether autism should be understood as difference or disability is just a matter of opinion. We do not claim that there is no right or wrong answer to that question. Rather than settling for a relativist solution to the debate, our approach acknowledges some force in both sides of the argument and aims to encourage discussions about the correct balance between rightful acceptance and rightful intervention in this context. Some may see it as an added advantage of this approach that it increases

the range of decisions open to those at risk of conceiving a child with autism. In the particularly difficult context of reproductive decisions, for example, parental decisions and preparations will be improved by knowing which of the many autisms on the spectrum could develop in their child. Biomarker information in the future will hopefully help to make this prediction, although this remains to be established. At the same time, parental choice will be facilitated through the knowledge that should a child with autism be born, that child and its family will receive scientifically grounded, evidence-based services, including education and interventions that enable the individual to flourish over the course of their life.

In our view, the issues that we have addressed should lead to continuing discussions that are conducted openly and that are not restricted by one-dimensional scientific research agendas or through governmental regulations. Only through this difficult process of discussion, debate and discovery (FIG. 1) can we gain clarity on which areas of autism should be accepted in principle, and which should be prevented or cured, if this becomes possible.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES

Pathway Interaction Database: http://pid.nci.nih.gov

FURTHER INFORMATION

Abortion statistics, England and Wales: 2010: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_126769
Autism Crisis — Science and Ethics in the Era of Autism Politics: http://autismcrisis.blogspot.com/2010/02/oxytocin-versus-autism-cure-for.html
The ADHD-200 Sample: http://fcon_1000.projects.nitrc.org/indi/adhd200/
The Prenatally and Postnatally Diagnosed Conditions Awareness Act: http://olpa.od.nih.gov/tracking/110/senate_bills/session1/s-1810.asp

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