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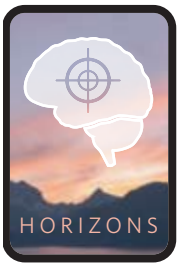
Are they tomorrow's criminals?

Biomarkers in psychiatry

Ilina Singh and Nikolas Rose

The use of biomarkers to predict human behaviour and psychiatric disorders raises social and ethical issues, which must be resolved by collaborative efforts.



Psychiatry has long been a second-class citizen in science and medicine. Despite much effort, the causes of many psychiatric disorders remain unclear, and it has been difficult even to categorize such disorders precisely. In the past decade, however, there has been a large shift towards incorporating biomarkers into psychiatry (Fig. 1), and there is hope that such biological indicators will improve psychiatric diagnoses by underpinning them with physiological evidence (Boxes 1 and 2). But biomarkers promise far more than a basis for better diagnoses. They could assist in predicting the course of an illness in an individual and in tailoring treatment. And they could be used to predict the development of not only psychiatric disorders but also certain behaviours, personality traits, and mental or emotional capacity.

Scientific innovations that will ultimately improve psychiatric outcomes and general well-being are to be welcomed. But they must be scrutinized to assess their value to the general public. Despite the wealth of research into biomarkers and the considerable interest in their use in clinical and non-clinical situations, there has been little discussion of the social, ethical and legal problems posed by their use in psychiatry. Here we set out the key challenges in this area. We focus on interventions in children and adolescents, particularly those aimed at preventing behavioural problems, because the identification of biomarkers in these age groups forms an important research agenda and the initial pathways through which this research is being translated from the laboratory to the clinic, as well as the classroom and other locations, can already be observed.

The promise of biomarkers

At present, psychiatric disorders are diagnosed on the basis of signs, symptoms and course of illness, according to the classifications in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). Finding a biological or physiological marker, rather than relying on behavioural symptoms and signs, might provide a more precise means of diagnosis, thereby aligning psychiatric classification with classification systems used in other areas of medicine[1]. Such methods might also go further and help to re-organize the DSM system of classification, offering a counter to the swelling catalogue of categories, each with its lengthening lists of behavioural symptoms and subclassifications that have no differentiated aetiology.

Moreover, biomarkers might be used to predict the potential for developing a particular disorder. This is of particular significance in child and adolescent psychiatry. Genetic screening and neuroimaging — the main techniques for identifying biomarkers — could be used to assess children before symptoms appear. And existing childhood disorders are now themselves being viewed as 'biomarkers' for the risk of developing more severe disorders.

In this sense, biomarkers promise to be the most powerful psychiatric tool since the discovery of antipsychotic drugs — a biological means of predicting not only the development of a disorder but also its course and outcome. Biomarkers could therefore inform the type, timing and course of interventions, and they could allow disorders to be subtyped based on physiological criteria, creating a more personalized approach to psychiatric treatments.

But the potential impact of psychiatric biomarkers extends beyond the clinic, to arenas responsible for the growth and development of children as productive citizens: the classroom and the courtroom. For example, in the United Kingdom, a new national agenda of ensuring 'mental capital and well-being' is grounded in new science that has transformed the understanding of child development and learning[2]. Enthusiasts for educational programmes based on neuroscience argue that neuroscientific evidence should be applied at an early age and with a broad remit, not only informing how children are taught and how classrooms are structured but also helping to identify developmental challenges — such as impulsiveness and learning difficulties — that are thought to be associated with later psychiatric, educational and social problems[3]. In the courtroom context, neuroscientific understanding of how the brain develops is being used to inform juvenile justice decisions. A landmark 2005 decision in the US Supreme Court that overturned the death penalty for juveniles (those under 18 years of age) is thought to have been strongly influenced by neuroscientific evidence about the capacities of the 'adolescent brain' to control impulsive and risk-taking behaviours[4]. In addition, research efforts are underway to identify brain-based biomarkers associated with juvenile delinquency so that neurodevelopmental risks can be built into models to predict youth antisocial behaviour[5]. These non-clinical applications of psychiatric biomarkers suggest the extent to which biomarkers could come to shape the lives of 'normal' individuals, especially children.

The challenges

The use of biomarkers in any of these contexts presents many challenges. A biomarker — for example, a certain pattern of brain activity — is not the cause of a disorder. So the current interest in biomarkers is a sign that psychiatry has undergone a methodological shift, away from searching for the causes of a condition towards estimating the probability that the condition is present or will develop. One challenge arising from this approach is that individual variables associated with an increased risk of developing a condition, for example information about a single biomarker, usually have small effect sizes: that is, when used alone, they are not robust predictors of the presence or absence of a condition. However, when bundled into an algorithm that incorporates other biomarker information, as well as social and environmental risk factors (such as prenatal exposure to alcohol, postnatal exposure to lead, family poverty and child abuse), biomarkers could be powerful predictors that a disorder will develop. However, biomarker information will always be a statement of the probability that a condition will develop: that is, a statement about the risk of developing that condition. Therefore, even risk algorithms that are powerful predictors will retain a degree of uncertainty. The hope is that this uncertainty will lessen over time, as highly predictive variables become easier to identify.

Many psychiatric researchers, however, have deep-seated doubts about whether the current methods for identifying biomarkers — such as genome-wide association studies (which search for genetic markers associated with disease risk) and imaging of the brain region of interest, which are based on studies of groups — can uncover biomarkers with strong predictive value for a specific individual. There are also doubts that biomarkers will have translational applications within the next decade in a manner that would allow biomarker information to guide clinical, educational and legal practices and policies substantively.

Outside specialist circles, these doubts are often minimized, and questionable biomarkers can begin to take on scientific and social importance. This process of overgeneralization and oversimplification has occurred on many occasions, for a long list of neuroscientific discoveries, including claims about the 'gene for aggression' in humans and about the implications of 'mirror neurons' in non-human primates (neurons that are active when an animal carries out a particular action or observes another animal carry out the same action), which have been equated with these animals having human-like empathy[6,7]. These kinds of overstated claim are even more evident when commercial enterprises have an interest in promoting the diagnostic value of a test.

Moreover, the translation of research from the laboratory to particular social practices, such as medicine or education, is not determined by the scientific innovation itself but by social and political decisions that are often shaped by many factors other than scientific evidence. These processes of translation, and the ethical dilemmas they raise, need to be analysed. And the analyses should not be viewed as merely the 'social work' adjunct to the 'hard science'. Research into the social and ethical processes of translation, and into the challenges that are often faced, should inform the work of researchers themselves and can help to ensure that this research does result in improvements in social practice. For example, challenges to the validity of psychiatric diagnoses have led to increasingly complex models of conditions such as attention deficit hyperactivity disorder (ADHD), as well as to efforts to validate and to standardize diagnoses for these conditions[8].

We have three main concerns about the potential use of psychiatric biomarkers. What is the best way to communicate the idea of a 'risk profile', and how might this affect personal identity? Given that human behaviour and psychiatric disorders arise from a complex set of factors, how can this complexity be retained when using information about biomarkers in the clinic and community? And what issues might arise from the commercialization of biomarkers, and how should they be addressed?

Personal identity and risk profiles

For children and adolescents, it has been common practice to identify those 'at risk' of psychiatric disorders, educational failure, or social and emotional difficulties, and to provide them with special resources as part of a social programme. However, identifying such children by using genetic and neurobiological biomarker information (potentially before symptoms develop) will be new. The lack of predictive power of biomarkers as risk factors for individuals, and the probabilistic nature of risk assessments based on them, raises specific issues. We are particularly concerned about biomarkers

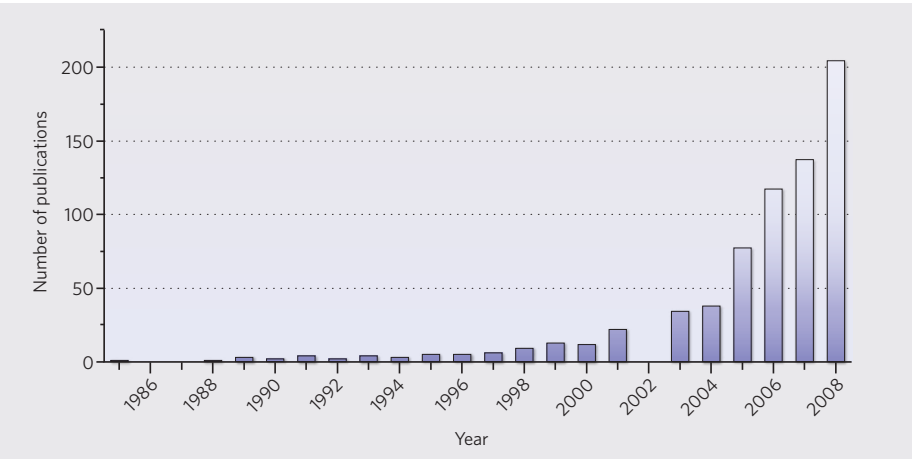


Figure 1 | Rising interest in biomarkers and psychiatry. In the past decade, psychiatric researchers, doctors and policymakers have become increasingly interested in finding objective biomarkers that will provide a more accurate and precise means of assessing actual and potential psychiatric conditions. This increased attention to biomarkers is reflected by the rise in the number of scientific articles on this topic. Data were obtained from a search of the ISI Web of Knowledge in May 2009 for articles with the term 'biomarker' and the word stem 'psy' in the topic field. No articles were indexed by ISI for the years 1986, 1987 and 2002. It should be noted that some early articles may have focused on non-psychiatric conditions and only tangentially addressed the psychiatric aspects. (Courtesy of J. Abi Rached, The London School of Economics and Political Science, UK.)

Box 1 | What are biomarkers?

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention[40].

Different markers can be used to make various assessments: to diagnose a condition, to predict the natural outcome for an individual with this condition, to predict whether the individual will benefit from a particular treatment and how aggressively to treat the individual, and to assess an individual's response to this treatment.

In a psychiatric context, biomarkers could be used to detect and assess, or predict the development of, not only psychiatric disorders but also personality or behavioural traits, and emotional or cognitive capacity. Biomarkers could also be used to inform treatment decisions. Examples of biomarkers are

- specific variations in skin conductivity;
- specific patterns of neural activity in particular brain regions, detected by imaging techniques, such as functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET);
- specific genetic sequences or single-nucleotide polymorphisms, identified by genetic screening;
- specific endophenotypes (intermediate traits in the chain of causality between genes and diseases), such as biochemical, neurophysiological or neuropsychological features.

that identify the risk of behavioural problems developing in children, as well as the risk of psychiatric diagnoses such as ADHD, conduct disorder and oppositional defiant disorder, all of which are directly or indirectly linked to delinquency, substance abuse, antisocial behaviour, personality disorder and/or criminality. Because antisocial behaviour by young people is a major social problem in many countries, if biomarkers for such behaviours are found to be present during early childhood screening, then children might be subject to intrusive medical interventions that focus on individual-level risk factors rather than on social and environmental risk factors[9]. Indeed, given the increasing use of psychotropic medication in very young children (3 to 5 years of age)[10], and the problem of inconsistently applied diagnostic thresholds in child psychiatry[11], it is possible that young children with a high risk profile for antisocial or criminal behaviour could be given drug treatments at a pre-symptomatic or subclinical stage.

The problems inherent in the probabilistic nature of risk assessment are not unique to psychiatry. But the consequences of psychiatric risk profiling for children and their families might differ qualitatively from those of profiling other medical conditions in childhood. At present, it is unclear what will happen when children are identified as being at risk of developing a psychiatric disorder or antisocial behaviour in societies that are suffused by anxiety about the adverse social consequences of such conditions. As risk profiling of children, using biomarkers, begins to replace efforts to identify biological or environmental causes, will ideas about the identity and the capacity of individuals begin to change? That is, how will people feel about themselves given their risk profile, and will others perceive them differently? Will 'risk' and 'potential' eventually dominate ideas of personal identity, health status and opportunity in rigid, coercive or stigmatizing ways? Will these ideas become institutionalized within education, law and policy? And how will such changes affect the life trajectories of children identified as at risk early in life?

There is a body of research on risk perception and stigma that addresses how people's judgements and beliefs about the genetic basis of psychiatric disorders affect their self-identity and their attitudes towards others with psychiatric diagnoses[12–14]. However, there has been little research on how these perceptions and attitudes might differ when they are shaped by information based on markers whose predictive value is probabilistic, although there are ongoing studies of these issues as they are arise in the context of personal genomics[15]. Such research needs to be expanded to examine issues involved in the screening of individuals for the presence of psychiatric biomarkers, in order to evaluate the potential for children developing a negative 'risk identity'. It is also important to assess how biomarker information might reshape the beliefs, practices and decision-making of the people in a child's environment, including parents, teachers and health providers. And, given that young people themselves discuss these issues and share information about psychiatric conditions and interventions, it is important to understand further how biomarker information might affect both young people's identities as individuals and as members of various groups and their relationships with their peers.

Discoveries in neuroscience can, however, have a positive effect, particularly when they converge with patient activism, resulting in broader conceptions of self and possibility. For example, there are strong claims by some autism researchers and autism patient groups that biomarkers associated with autism indicate a divergence from the norm that is a source of creativity and special cognitive capacities[16]. In this case, how does biomarker information motivate individuals instead of inducing a fatalistic attitude? And how can such resilience be promoted in varied contexts, such as families and classrooms, when there is challenging news regarding a child's risk profile?

Another important issue is the potential consequences of claims about differences in risk prevalence between population groups. As is the case for physical diseases, evidence that a certain condition is more prevalent in one ethnic group than another is a double-edged sword. On the one hand, such evidence supports the development of strategies to tackle those disorders. On the other hand, it can lead to discrimination on biological or genetic grounds[17,18]. Although some people claim that identifying a high level of risk among ethnic minorities, single parents or the very poor can help to direct more attention and resources to the problems encountered by such groups, there is evidence that people in these groups are also more likely to be, and to feel, stigmatized by at-risk labels and psychiatric labels[19]. It is also important to determine whether children from these or other populations are more likely to be ascribed harmful risk identities than children from majority or advantaged groups when biomarkers are used to identify those at risk. In particular, genetic biomarkers that identify children from ethnic minorities as being at risk of problem behaviours and/or psychiatric conditions might build on existing assumptions about links between race, genetics and behaviour. And they might have a self-reinforcing effect, leading to efforts to undertake risk screens that genetically profile young people who have first been classified by race or ethnicity.

The only way to explore the 'social life' of biomarker information is to carry out a programme of detailed qualitative research in which all groups of individuals who are affected participate, including children. Such a programme of research should accompany current scientific research on biomarkers, even if these studies are not yet seeking translational outcomes. Because the expectations around biomarkers are so high, it is possible that any translational applications will be quickly implemented, without time for deliberation over the social and ethical issues. Prospective research on these issues is needed to inform policies and practices that will maximize the positive potential of biomarker information and protect individuals and families from harm.

Retaining complexity

Issues around communicating and explaining risks link directly to our second major concern: that the many factors contributing to behaviour and psychiatric conditions need to be considered in addition to information about biomarkers. The techniques used to measure biomarkers (mainly neuroimaging and genetic screening) produce images and numbers. These results seem to be precise and objective and therefore have great persuasive power, often greater than is warranted by their predictive power. Indeed, recent criticism over the level of funding of genome-wide association studies has highlighted their failure to uncover genetic markers that account for

most of the genetic contribution to the risk of common disease[20,21]. Similarly, magnetic resonance imaging (MRI) studies have uncovered much about the basic science of brain function and structure, but the predictive utility of brain-based biomarkers does not match the hype surrounding their discovery[22]. Although research on biomarkers is of considerable scientific interest and importance, the persuasive power of biomarkers will be greater than their clinical or social utility for the foreseeable future. It is important to prevent such persuasiveness from leading to reductionist explanations for complex behaviours or conditions in children. Information about a biomarker can help to build a risk profile for a particular condition or set of behaviours. But biomarkers alone, taken out of context of environmental influences, are unlikely ever to provide complete explanations for children's behaviour or a forecast of how children's lives will unfold. Biology is not destiny: biology provides information about potentials. So how can this level of complexity be retained when biomarkers move from 'the bench to the bedside'?

First, systematic assessments of the explanatory power of biomarkers for particular behavioural conditions and psychiatric diagnoses are needed. These assessments must focus on two areas. The accuracy and reliability of the techniques themselves — particularly genetic screening and neuroimaging — must be tested. And the validity of the findings must be assessed, given the problems with the methods and with study design. To take functional MRI (fMRI) studies as an example, studies involving children are often significantly underpowered[23]. Moreover, applying different statistical methods to fMRI data has been shown to deliver markedly different estimates of the significance of associations between brain-based biomarkers and cognitive–emotional traits[24]. There is also a lack of normative fMRI data for children, partly as a result of ethical concerns about scanning healthy children; therefore, children's scans are frequently analysed by comparing them with adult brain scans. Finally, outcomes of fMRI research are relevant at the population level but are not yet relevant for individual diagnoses and treatments. Published studies should be scrutinized for problems of validity, by meta-analyses for example (such as the recent critique of fMRI data reported in social neuroscience studies, which describes many of the results as 'voodoo' correlations[24]), and the results of such scrutiny should be reported and debated in scientific journals.

The next task will be to disseminate the results of these assessments in a comprehensive programme of public engagement. Dissemination strategies could take various forms, including media appearances, teacher and student education, publication in the popular press, and artistic performances. Scientists must take up the challenge of collaboration with a variety of professionals from other disciplines, to build a better public understanding of behavioural conditions in children and the environmental and biological underpinnings of these conditions. Moreover, these activities should support the public's ability to think critically about current neuroscientific theories and the evidence that forms the basis of these theories, including the continuum of normal and abnormal behaviour, interactions between genes and the environment, causality and the direction of effects, and the probabilistic nature of genetic and neurobiological influences on behaviour and cognition. Given the public's lack of knowledge — indeed the misperceptions — about genetics, neurobiology and behaviour[25–27], one of the most important components of this public-engagement programme will be to study its outcome: to examine which modes of dissemination and education are most effective at building an accurate public understanding in this area, and for which populations; and which initiatives are most likely to inspire sustained public engagement with these issues.

In addition, the translational activities of scientists and scientific teams who carry out research on biomarkers in children need to be investigated. How do efforts to find applications for biomarkers in the clinic, the classroom or the juvenile courtroom accommodate complex models of behaviours, models that are probabilistic, multidirectional and incorporate a variety of causes. And to what extent do proposed treatments or interventions either reinforce or undermine such models? For example, the rise in childhood diagnoses such as ADHD, bipolar disorder and social anxiety disorder suggests that the availability of effective drug treatments (such as stimulants, antipsychotics and antidepressants) undermines multicausal explanations of childhood behaviours. If biomarkers are used to inform strategies for treatment with psychotropic drugs, and if such treatment is used preventively, then there is a substantial risk that biomarkers will be seen as the primary or ultimate cause of behavioural conditions in a child.

Finally, biomarker-based family and educational interventions for children should be monitored by a research team that includes professional educators, mental health professionals, ethicists and social scientists, working in collaboration with family representatives and teachers. Part of the remit of such research will be to identify the disadvantages and the advantages of policies that are informed by research on biomarkers, by evaluating the long-term educational, social and behavioural outcomes for particular groups of children. It will be especially important to carry out research that identifies and investigates the conditions under which genetic and neurobiological factors may come to define an individual's risk and potential without appropriate attention being paid to non-biological factors. At present, there is a strong emphasis on early identification and intervention programmes that assure children's long-term mental health and positive social contributions; therefore, a comprehensive system of monitoring the educational, social and ethical outcomes of such programmes for individuals and society is essential.

Commercial issues

Biomarkers are entering the public's awareness, through the activities of commercial enterprises such as 23andMe and other companies that offer genetic screening and brain scanning services directly to consumers. Such ventures promise to provide individuals with significant information about their risk profile for numerous diseases and disorders, as well as information on personality and behavioural types. Clearly, businesses need to attract customers and will therefore emphasize what they consider to be the benefits of their services to potential consumers. This is the case not only for genetic tests but also for tests available on

Box 2 | Status of psychiatric biomarker research

Evidence of biomarkers associated with psychiatric disorders is emerging from studies in experimental neuroscience and psychiatric genetics, and many of these studies are improving our understanding of the neural pathways and mechanisms underlying such disorders. But, at present, only a few biomarkers show promise as robust predictors of psychiatric disorders. One prominent example is a variant of the monoamine oxidase A gene, which several studies have found to be associated with risk of antisocial behaviour but only when there is a history of adversity in early childhood[41,42]. This discovery is the strongest indicator so far that biomarker information alone is unlikely to explain most of the variance in observed behaviours. Gene–environment interaction studies, rather than studies that search for single genetic polymorphisms, could deliver more robust results that have potential social and clinical applications.

In addition, researchers are identifying endophenotypes that can act as predictors of behavioural and psychiatric disorders. An example of a robust psychiatric endophenotype is abnormal eye-tracking movements in patients with schizophrenia[43]. In child psychiatry, a promising endophenotype is callous and unemotional traits[1]. Several studies have shown such traits to be strongly associated with the development of psychopathy in children. And although the neurobiological and genetic basis of these traits is not well understood, they are associated with a variety of biochemical, neuroendocrine and genetic markers.

At present, although neuropsychological testing is sometimes used to inform psychiatric diagnoses, biological information derived from brain scans or genetic screening is not yet used in clinical psychiatry.

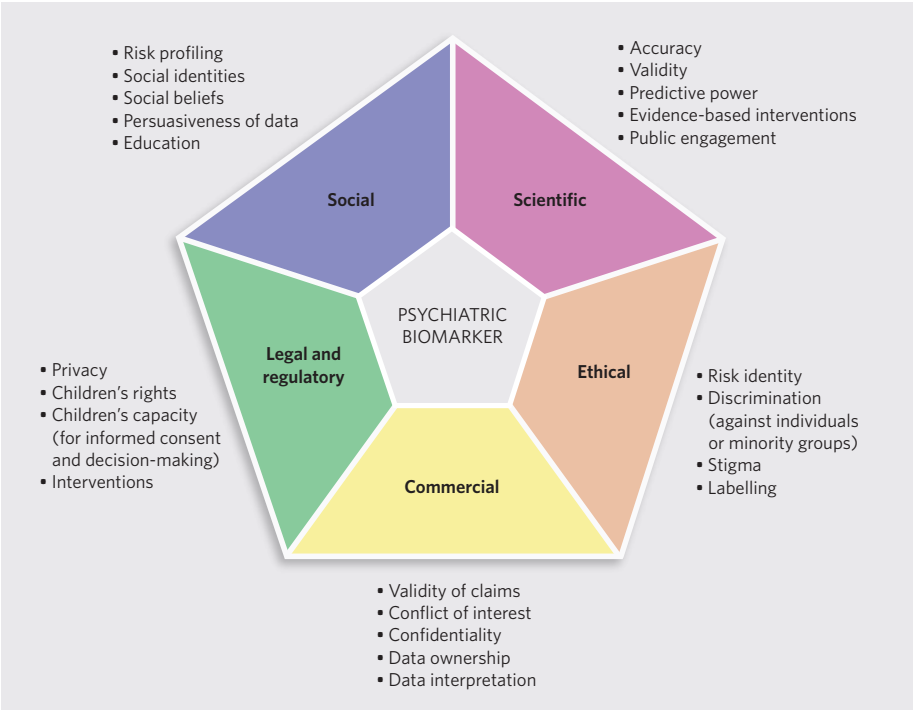


Figure 2 | Issues that influence the use of biomarkers in psychiatry and beyond. As the search for psychiatric biomarkers increasingly shapes research, as well as clinical and non-clinical settings such as classrooms and courtrooms, many issues need to be debated, studied and resolved. These include social, legal, ethical, commercial and scientific issues.

the Internet for everything from depression to osteoporosis and for home test kits such as those for measuring cholesterol levels and detecting signs of diabetes and bowel cancer. Many of these are a cause of concern to doctors and regulators, who consider that they provide information of dubious medical value and are sometimes dangerously misleading[28].

We are concerned that the commercialization and marketing of biomarker data about psychiatric conditions, personality traits, and emotional and cognitive capacities might have harmful consequences for the ways that families and children make vital decisions and view their future, and indeed how others make decisions on their behalf. The companies often argue that knowledge cannot be harmful and that they are making access to biomedical information more democratic[29]. They have also tended to resist regulation of their activities, branding this as paternalistic[30]. However, we think that social science research is required to examine the extent to which such commercialization of biomedical information, and its availability on a direct-to-consumer basis, may encourage individuals and families — and perhaps medical and non-medical professionals — to develop unrealistic ideas about the explanatory power of this information. For example, evidence from the United States shows that patients who mention an antidepressant by name to their doctor are more likely to receive a prescription for that drug[31]. So will doctors be more likely to diagnose a child as having a particular psychiatric condition — or to provide medical treatments — if families come into the clinic on the basis of biomarker information that they have obtained themselves?

Little is known about how those who take advantage of commercial screening and scanning interpret and use information about personal biomarkers. Social research on the use of personal genetic risk information suggests that individuals do not always reshape their lives or identities around such information, even when the probability of developing a severe disease is high[32–34]. But will this be the case when the personal biomarker information is obtained by a child or by a parent acting on behalf of a child, and when the targeted biomarkers ostensibly reveal information that is closely associated with personal identity (such as personality traits, behavioural traits, and/or predisposition to certain thoughts and feelings)? Why would parents initiate commercial genetic screening or brain scanning for their child? Will biomarker information that provides a cognitive–behavioural risk profile for a young child affect not only how parents think about their child but also how they act on behalf of the child? In what circumstances might this have positive consequences for the child, and when might this information do harm? Much more information is needed about the social and behavioural consequences of the availability of personal biomarker information for children before evidence-based judgements can be made about the ethical issues raised by such technologies.

One key ethical issue is the capacity of children to understand the consent processes involved in submitting to commercial screens and scans, as well as their capacity to make decisions about the complex issues that results often raise. To what extent, and at what age, do children have the right to know about their personal biomarker profiles? Do children have the right to refuse to submit to genetic screens and brain scans when these are not clinically indicated? Conversely, should children have the right to submit their own samples to such companies or to choose to undergo brain scans to learn more about their risk of displaying certain behaviours or traits? Research into this issue is needed so that thresholds can be set for the age at which children are competent to provide consent for screening and scanning and to make informed decisions about the findings. The regulation of children's rights, capacity and consent in analogous contexts, such as birth control and cosmetic surgery, could inform thinking about children's access to personal biomarker information.

A related area of concern is confidentiality and ownership of information. Who has the right to manage a child's 'potential' when that potential seems to be made evident by a genetic screen or a brain scan? Medical lawyers and ethicists need to identify the appropriate precedents for ownership of such information: for example, is legislation around blood and tissue data held in biobanks relevant to personal data derived from genetic screening and brain scans, or is such information more analogous to medical records, access to which is covered by data protection legislation in the United Kingdom and privacy legislation about access to health-related data in the United States.

To understand children's capacities, and to evaluate the potential risks and benefits of the availability of psychiatric biomarker information to them (as well as to their families, their doctors and other authorities), empirical research must involve children themselves. Questionnaires and surveys alone cannot adequately capture children's thought processes or their capacity for making complex decisions. These approaches need to be supplemented by detailed interviews with children are required. Only then will there be enough evidence to underpin the development of appropriate regulation for commercial organizations, in order to maximize the benefits of access to biomarker information for children while effectively protecting them from harm.

Towards the future

So how might biomarkers be applied in the future? To take one example, in the United States and the United Kingdom, there are several high-profile research programmes that seek to identify biomarkers associated with risk of delinquency, antisocial behaviour or criminality in children[35–37]. Some of this research is being carried out with children identified as having behavioural problems such as hyperactivity and impulsiveness. In other studies, the research subjects are children diagnosed with conduct disorder, oppositional defiant disor-

der or ADHD. Some researchers hope that such studies will establish biomarkers (for example, brain-based markers, cardiac markers or neuroendocrine system markers) that would allow at-risk children to be identified before they display serious behavioural problems. Children at high risk could then be treated before symptoms arise, to prevent the development of delinquent behaviours. For prevention to be successful in this high-risk group, interventions would need to take place very early, in the pre-school years (ages 3 to 5)[38].

The aim of this research is to develop programmes of identification and intervention that will reduce the individual and social burdens of severe antisocial behaviour in adults. However, we are of the view that, at present, the assumption that better understanding of the neurobiological risk of delinquency will facilitate early identification and prevention efforts is unfounded. Certainly, carrying out early interventions on the basis of this assumption would be premature. For example, we would be very concerned if a 4-year old boy displaying mild hyperactive behaviours were a candidate for treatment with stimulant drugs based on his hyperactivity being a predictor of future delinquency. Antisocial behaviour in adults arises from a complex course of neurological development in particular environmental and social contexts[39], and we do not think that there is enough evidence that biomarkers, at least as they are conceived and identified at present, provide a justifiable basis for intervention programmes of this type.

Moreover, the assumption that childhood diagnoses such as conduct disorder, oppositional defiant disorder and ADHD represent underlying biological impairments is problematic, given that these diagnoses have questionable validity, especially in the preschool population. Without ongoing social and ethical analysis, as well as careful thought by the researchers about their role in this process, the future use of psychiatric biomarkers could marginalize efforts to identify and address social and environmental factors associated with the development of antisocial and criminal behaviours in young people. It could also reinforce the use of problematic diagnoses and/or medical treatments to manage the current and anticipated behaviour of very young children. Such developments could lead to stigma and labels that affect children's psychological development, their social and educational opportunities, and their medical care and employment options.

Clearly, the aim of developing psychiatric biomarkers is to improve the well-being of children and of society in general. But given the many issues that need to be considered (Fig. 2), a comprehensive programme of research needs to be carried out before biomarkers can ethically and effectively be used in the clinic, courtroom, classroom and community. The programme that we have outlined here can be accomplished only through interdisciplinary interactions between neuroscience researchers, doctors, social scientists, ethicists, legal scholars, policymakers and those involved in commercializing biomarkers. We do not envisage one large research programme, however. Instead, we think that multiple smaller collaborations, built around a variety of clinical and non-clinical sites, will be most effective.

The involvement of social researchers and ethicists at such sites should not be ad hoc. Social, ethical and policy concerns should be integral to the design of each study. This will also help to ensure that multidisciplinary engagements are collaborative and constructive for all researchers involved. It is unclear whether mandating the inclusion of these concerns in all relevant scientific research programmes on biomarkers is an effective strategy. All genomics research programmes are required to include an ethical, legal and social issues component, and this has resulted in important research but has also created many problems, such as tensions among researchers from different disciplines, and a lack of integration of social and scientific research goals. It is probably more effective to identify which ethical issues are the most crucial and then to challenge the funders of such research programmes to encourage grant applicants (through higher ratings on proposals and direct feedback to applicants) to integrate ethical, legal and social issues research and the appropriate researchers into their grant proposals.

Non-scientific sites where collaborations need to take place include communities and schools that carry out early-intervention programmes for children, juvenile prisons and courtrooms, and corporations that commer cialize biomarker information. The development of research programmes will depend on access to these sites. Again, funding mechanisms can be used to encourage collaborative engagements between people working at these sites and researchers. As research information is gathered across all sites, workshops and conferences can be organized to share knowledge and specifically to guide ethically informed, clinically relevant and socially effective policymaking around the use of psychiatric biomarkers in children. ■

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