Pursuing parity: Genetic tests for psychiatric conditions in the UK National Health Service

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Pursuing parity: genetic tests for psychiatric conditions in the UK National Health Service

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Summary:

Schizophrenia and anorexia nervosa were recently added to the list of conditions for which whole genome sequencing might be indicated as part of the 100,000 Genomes Project, reflecting the remarkable recent progress in findings emerging from psychiatric genetics research. Genetic testing methods may offer increased opportunities for diagnosis and estimation of familial risk and could have implications for management and treatment options. They also present ethical and philosophical questions about the role of testing and storage of genetic information. Mental health professionals will need to have a good understanding of this area in order for patients to fully realise the benefits of these advances.

At the end of September 2018 recruitment finished for the 100,000 Genomes Project, a pilot diagnostic service implemented by the UK National Health Service (NHS) which offered whole genome sequencing to patients with rare diseases or cancer through a separate company established by the UK government called Genomics England. Eligible rare diseases

included mental disorders such as intellectual disability and early onset dementia and, following new research findings, schizophrenia and anorexia nervosa were added from January 2018. This addition reflected the real and remarkable progress that has been made in identifying genetic risk factors for these diseases. For schizophrenia, it has been shown that certain copy number variants (CNVs) and sequence variants that damage a small number of genes have major effects on risk; additionally some variants already known to cause intellectual disability may have schizophrenia as a phenotype (1,2). For anorexia nervosa, a recent genome wide association study has shown that genetic risk is shared not only with schizophrenia but also with risks associated with markers of metabolic disorders such as high-density lipoprotein cholesterol and body mass index (3). For both diagnoses, inclusion criteria were specified with the aim of making it more likely that an identifiable genetic cause would be found – for schizophrenia that additional features such as early onset, neurological signs or dysmorphism were present; for anorexia that the condition was severe and familial.

Although recruitment to the 100,000 Genomes Project has now finished, the results from sequencing these subjects are awaited and these results will inform decisions regarding which genetic tests which will be provided by the newly established NHS Genomic Medicine Service. These tests are listed in National Genomic Test Directories and, of relevance to psychiatrists, the first versions of these already provide for microarray testing for autism or mild intellectual disability and whole genome sequencing for more severe forms of intellectual disability and for dysmorphism syndromes thought likely to be monogenic (*https://www.england.nhs.uk/publication/national-genomic-test-directories*). It is expected that further indications for testing, such as microarray testing for schizophrenia CNVs, will be added as new evidence is evaluated.

With the current state of knowledge, the proportion of patients with mental illness in whom a "probable genetic diagnosis" will be made is likely to be low. A recent study found that it was possible to detect a pathogenic CNV in 2.8% of participants with schizophrenia without intellectual disability , though this figure rose to 24.2% with co-morbid intellectual disability (4). In the future, when further genetic risk variants are characterised, it will be possible to re-examine stored DNA sequence and identify the patients carrying them and make retrospective diagnoses. Thus, it is reasonable to expect that over time the diagnostic yield will increase. Even for those patients in whom a diagnosis relevant to the psychiatric condition cannot be made there may still be benefits from "secondary findings" of genomic

sequencing, consisting of the detection of important genetic variants having actionable medical consequences such as increasing risk of cancer. Again, as genetic knowledge increases it is likely that the overall benefit from such findings will also grow. However, it will be important that patients are aware of such possible outcomes and that appropriate processes of gaining valid consent are developed.

Although the future looks promising, it would currently be over-optimistic to expect that identification of specific genetic variants would at this stage guide, for example, choices around which antipsychotic to use. However concrete benefit could certainly come in terms of a clearer understanding of familial risk. Where a *de novo* variant is identified one may be able to reassure relatives that nobody else in the family is at increased risk of developing the illness. Alternatively, if a variant is inherited then it will become possible to provide clear information about risk to patients and their families and offer genetic testing to, for example, siblings. Sometimes a variant may be associated with other potential health problems, for example, a finding of a 22q11 deletion (DiGeorge syndrome) could lead to screening for cardiac abnormalities and registration with the National Congenital Anomaly and Rare Disease Registration Service.

The more important benefits of genetic testing for psychiatric disorders may be less tangible. For some patients, presently a minority, a clear genetic diagnosis will be made that allows the patient and those around them to ascribe their illness to a specific, physical cause. Even if this might not have material effects on the management plan we argue that, for some patients, there is an intrinsic value in "having a diagnosis". For some physical illnesses the diagnosis can have little in the way of practical implications but may still provide an explanation and validation of the sick role. In the context of psychiatric illness, where lack of insight and poor compliance can be problematic, there may be a special benefit in being able to provide the patient and those around them with information about a concrete medical explanation which has led them to experience frightening symptoms. Potentially, ascribing illness to a more clearly defined physical cause could reduce stigma. Here, we see that the attempt to provide a diagnosis represents a manifestation of "parity of esteem" between mental and physical illness. People with mental illness are entitled to all appropriate and available tests to investigate the cause of their condition, just as those presenting with a physical health condition would be. We might anticipate that when a clear molecular genetic diagnosis can be made for a condition such as schizophrenia, which often attracts diagnostic uncertainty,

then this may lead to improved engagement and shared decision making. This may extend to refining the care process and precision in prescribing effective medication. Arguably, even when no genetic diagnosis is achieved then the very act of testing can send a clear message that the clinician believes that biological factors are important, that the illness is "real" and that devising a management plan which includes medical treatment is as appropriate as it would be for a "physical" illness such as asthma or diabetes. Although it is argued by some that a biological causal explanation could actually increase stigma, ultimately having clear evidence for a particular aetiology for certain patients might prove preferable to simply having a variety of optional explanatory models on offer.

Till now, few psychiatric patients have been offered genetic testing or been given much information about genetic risks. Clinicians themselves may have little awareness that for some patients such testing can give them helpful explanations about causation, and may also support them to manage other health issues. However this situation will inevitably change, as indeed is the case for a range of physical diseases. Such change will necessitate making use of innovative techniques for data gathering, storage and sharing between primary and secondary care. Thus this also bodes well for the integration of care systems to improve physical and mental health.

There are ethical and philosophical issues that need exploration and further research is needed to explore the role for testing and appropriate forms of information sharing. How will these new practices be implemented in culturally diverse settings, with contrasting levels of resource, health literacy and access to basic care systems? A study of the effects of genetic counselling for severe mental illness showed benefits in terms of increased knowledge but not stigma or perceived control (5). As genetic testing is rolled out it will be important to formally evaluate outcomes so that its advantages and disadvantages can be properly characterised. It will also be helpful to assess attitudes of patients and clinicians to testing, particularly when these may act as potential barriers, or indeed involve patients in the design and development of genetic testing pathways. Will patients have concerns about their DNA sequence being stored and contributing to a wider understanding of how genetic variation impacts on health? Will clinicians feel confident about the level of information they are providing and with justifications for referral to clinical genetics services? Do they have concerns about their ability to work alongside clinical genetics services in assisting the

patient and those around them to correctly understand, interpret and share the results of testing? Will the attribution of mental illness to a genetic cause reduce stigma or increase it? How will genetic information be routinely incorporated into the care plan approach and electronic data with all the concerns around information governance and commercial exploitation? A robust programme of research will be required to address these questions.

Psychiatrists in the NHS now have an opportunity to take advantage of the latest medical technology and refer appropriate patients for genetic testing. In doing so, they can send the clear message that they believe that psychiatric disorders can at least sometimes be due to genetic abnormalities and that there is value in identifying them. Patients have the right to be given the opportunity to access the best science, technology and clinical information systems, in order to understand as much as is currently possible about the nature of their own health problems. Although clinical genetics services will have a role, it seems certain that both medical and non-medical mental health professionals will need to improve their understanding of medical genetics and the ethical considerations around sharing genetic information. Training in this area is an issue which the Royal College of Psychiatrists should address as a high priority if psychiatric patients are to fully share the benefits of scientific progress.

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Declaration of Interests

DC - no relevant interests to declare

KA – no relevant interests to declare

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