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The role of genetic testing in mental health settings

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COLLEGE REPORT

Contents

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Conflicts of interests

Professor Walters and Professor Jones have received research grant funding from Takeda Pharmaceuticals and Akrivia Health for work identifying genomic risk factors and new molecular targets for psychiatric illnesses.

None of the other working group members has any conflicts of interests.

No member of the working group would have any financial gain from the recommendations made in this College Report.

Scope of the report

This report has been compiled by reviewing existing guidance documents and position statements from international and national organisations, and by undertaking a focussed literature review of research relevant to clinical practice. Experts from genetic research institutions, academic psychiatrists, clinical genetics services and clinical psychiatrists provided context and advice on the clinical relevance of research findings.

Objectives of the report

The working group identified the need for clinicians to have access to guidance on the role of genetic testing in clinical practice. Research into mental health and neurodevelopmental conditions has generated vast amounts of information, and it can be difficult for clinicians to navigate the available evidence in order to understand the clinical implications of research findings for patients receiving care in mental health services.

This report aims to provide clinically relevant summaries of the current evidence base for genetic testing across a range of mental health conditions. Where there is evidence to support it, service standards have been recommended.

Methodology

A series of meetings of the working group was convened, with written and oral contributions from its members. The working group consisted of a range of experts across faculties and disciplines, with representation from researchers, academic psychiatrists, the Mental Health Foundation, clinical genetics, genetic counselling and clinicians. A focussed literature review was undertaken, guided by the experts on the working group, to identify key research findings relevant to clinical practice.

The content and recommendations for each section were discussed and agreed by the working group.

Service user involvement

Dr Crepaz-Keay, Head of Research and Applied Learning at the Mental Health Foundation, was a member of the working group and contributed, in particular, to Chapter 2: Patient engagement in psychiatric genetic testing.

The Mental Health Foundation has conducted peer-discussion groups on genetic testing in psychiatric conditions. Resources, including videos, have been developed to provide accessible information on genetic testing in psychiatric services (see the resources section at the end of Chapter 2).

In addition to his professional contribution to this report, Dr Crepaz-Keay has led discussions on patient involvement in psychiatric genetics as co-chair of the International Society of Psychiatric Genetics Ethics, Policy and Position committee and has extensive personal experience of mental illness and use of mental health services.

Executive summary

Current context

Genetic testing technology is developing rapidly and significant progress has been made over recent years in identifying genetic contributions to major psychiatric conditions. The vast amount of information that has been generated from research into the genetic contribution to mental health and neurodevelopmental conditions makes it difficult for clinicians to assess the implications of research findings for patients receiving care in mental health services.

Aim of this report

This College Report aims to provide psychiatrists with clinically relevant summaries of the current evidence base for genetic testing across a range of mental health and neurodevelopmental conditions. It is not intended to be a comprehensive textbook of the genetic factors relevant to psychiatric conditions. The purpose of this report is to assist mental health services to incorporate genetic testing into service provision, where the research evidence base supports clinical utility.

This report does not comment on the complex area of prenatal genetic diagnosis. The technical and ethical issues which arise in the context of prenatal testing are relevant across genomic medicine and are not specific to genetic factors relevant to mental health conditions. The Joint Committee on Genomics in Medicine published guidance on these issues in November 2022 (see reference in Chapter 2).

What this report provides

This report:

- reviews and synthesises research evidence (which forms the basis of this report's guidance), including reference to existing guidance documents and position statements from international and national organisations
- provides key messages about, and recommendations for, genetic testing for a range of psychiatric conditions
- calls for genomic testing being embedded into clinical care pathways.

Summary of recommendations

1. **Patient discussion and informed consent:**
   Genetic testing is a significant clinical investigation and needs to be undertaken within an appropriate framework. It provides an opportunity for conversations about genetic risk, for both patients and their families. A record of discussion with the patient is necessary to demonstrate that important features of genetic tests have been discussed and considered, before proceeding. A range of resources available to support these discussions. For individuals unable to consent, legal authorisation for testing is required as per the relevant capacity legislation in each legal jurisdiction.

2. **Schizophrenia:**
   At least 2.5% of patients with schizophrenia will have an identifiable rare neurodevelopmental copy number variant (CNV) and this yield is likely to be higher in patients with lower IQ and/or other neurodevelopmental features. We recommend that testing for these CNVs should be considered and available for those diagnosed with schizophrenia who have co-occurring conditions (such as neurodevelopmental disorders, marked cognitive impairment or congenital anomalies) or if there are important implications because of specific aspects of the patients' situation, or that of their family.

3. **Intellectual disability:**
   Chromosomal microarray (CMA) and whole genome sequencing provides a genetic diagnosis in at least 25% of patients with intellectual disability (ID), with higher rates of diagnosis in those with more severe ID and in those with co-occurring conditions (such as schizophrenia, other neurodevelopmental disorders or congenital anomalies). We recommend that Fragile X testing, CMA and whole genome sequencing should be available for children and adults with intellectual disability as part of routine clinical care.

4. **Children and young people:**
   For child and adolescent mental health services (CAMHS), we recommend consideration of genetic testing in children/young people with dysmorphic features, developmental delay/developmental intellectual disorder or unusual medical presentations. In addition, for early onset schizophrenia, we recommend testing for rare neurodevelopmental CNVs given an anticipated greater yield for identifiable CNVs than in adult-onset schizophrenia. Testing should be considered, in particular, if other clinical features are present or if there are important implications because of specific aspects of the patient's situation, or that of their family. Clinical pathways should be established between CAMHS, community paediatric and genomic medicine services.

5. **Autism and ADHD:**
   We do not recommend routine genetic testing for adults with autism spectrum disorder (ASD) or attention-deficit hyperactivity disorder (ADHD), without any additional co-occurring conditions.

6. **Dementia:**
   We recommend that genetic testing be considered for all suspected frontotemporal dementia OR dementia with onset <55 years of age OR a

family history compatible with a dementia causing variant OR clinical features suggestive of Down Syndrome (mosaic cases) OR clinical features compatible with rare single gene forms of dementia. Current research evidence suggests that genetic investigation would identify a causative genetic variant in approximately 10% of selected dementia cases. We do not recommend APOE4 genotyping in assessment of dementia or for establishing the likely future risk of developing dementia in an individual.

7. **Clinical pathways for genetic testing:**
   We recommend the development of clinical pathways for genetic testing across the range of mental health services, with the establishment of multidisciplinary team meetings with input from clinical genetics and genetic counselling services (see Appendix for example of service provision).

8. **Psychotropic medication:**
   There is currently insufficient evidence of clinical benefit to recommend pharmacogenomic testing for CYP2D6 and CYP2C19 (or other genes) in routine prescription of psychotropic medication. Projects examining the use of pharmacogenetic testing in clinical practice are currently taking place and their outcomes may impact on future recommendations regarding clinical benefit.

9. **Mood stabilisers:**
   Screening for HLA-A and HLA-B alleles before prescribing certain mood stabilisers (e.g., carbamazepine) is indicated for particular ethnic groups (e.g., East Asian ancestry), but may have limited clinical utility within the wider UK population.

10. **Clozapine:**
    Testing to identify the Duffy-null genotype in individuals of African and Middle Eastern ancestry should be considered in those starting or already taking clozapine, particularly where neutropenia may otherwise limit access to clozapine treatment. Duffy-null genotype testing does not circumvent the need to follow mandated blood monitoring protocols and haematology consultation, which is required for the diagnosis of Benign Ethnic Neutropenia.

11. **Polygenic risk scores:**
    Polygenic risk scores are not recommended for use in clinical practice, as there is only a weak association between polygenic risk score and the absolute risk to an individual of developing a specific condition. Furthermore, there is currently no evidence of clinical benefit in using polygenic risk scores to predict treatment outcome.

12. **Epigenetic testing:**
    There are no clinical indications for the use of tests based on epigenetic mechanisms.

Introduction

Advances in genetics research (particularly the development of new molecular technologies and large international collaborations) have led to significant progress in identifying genetic contributions to major psychiatric conditions. These findings have added to our understanding that many mental disorders are multifactorial, whereby the interaction of multiple genetic and environmental factors influence an individual's risk of developing mental health disorder, the progression of that disorder and potential treatment responses.

A range of guidelines and position statements related to genetic testing in mental health settings has been published internationally, demonstrating significant variation in practice globally. Genetic testing technology is developing rapidly. Clinicians need to be aware of these developments and their relevance to clinical practice.

It is helpful to consider that there are several potential applications for genetic testing in psychiatry. One is to aid understanding of a patient's diagnosis, either in terms of their current illness or in terms of their, or their family's, risk of developing illness in the future. In addition, genetic testing results can inform clinicians of the presence, or future risk, of physical illnesses and the need for monitoring. A further application is to predict response to possible treatment approaches to assist in choosing treatments with higher likelihood of success or lower risk of harm.

Variations in an individual's DNA code can influence their risk of developing illnesses, including psychiatric illnesses, and of presenting with other conditions relevant to psychiatric practice, such as neurodevelopmental conditions.

Some genetic variants have very large deterministic effects on risk, such as the changes to the HD gene which causes Huntington's disease, while others have intermediate or small effects. Variants with large effect sizes are very rare, whereas common variants individually have very small effect sizes which can be detected when case-control association studies are carried out in very large samples. Some copy number variants (CNVs) increase the risk of specific conditions, whereas most others are associated with increased risk for a number of different diagnoses. Thus, to some extent there is an overlap in the genetic contributions that increase the risk of psychiatric illnesses and/or neurodevelopmental conditions for rare and common variants, and this needs to be borne in mind when interpreting the results of genetic testing.

Although genetic investigations may be useful for research purposes in order to better understand the aetiology of mental illness, when carrying out genetic testing for clinical purposes it is important to consider whether or not a test has utility and potential risks or harm, as well as advantages. As with any medical investigation, before carrying out genetic testing one needs to ask whether learning the results will have any influence on management or will helpfully predict prognosis. In particular, a test which reports a small or moderate effect on risk of developing an illness may not have clinical utility if there are no steps which can be taken to address these risks.

That said, it is generally recognised in medicine that there can be utility in identifying possible causes of a patient's presentation, such as a genetic test result, as an explanation for a patient's symptoms even if doing so does not lead to any changes in management. Sometimes, a genetic test result can give useful information about prognosis, as in the case with Huntington's disease. Additionally, identification of a genetic risk variant can have wider implications for assessment of risk of physical illness, such as when a CNV is discovered in a patient with schizophrenia, as will be discussed further below. However, it is possible to argue that detection of a genetic risk variant has value in its own right and that, for example, patients with psychiatric conditions that could be a consequence of a pathogenic CNV, are entitled to be informed of this even if there are no implications for treatment or prognosis.

For these reasons, it is helpful to distinguish genetic test results that are essentially diagnostic from those that simply report that a patient may be at higher or lower risk of a particular condition. We take the view that in the clinical situation, testing to estimate disease risk, rather than to obtain a definitive diagnosis, should only be undertaken if the results will in some way have a useful impact.

In clinical practice, different localities will have referral pathways to access specific genetic tests. The range of tests available, and the criteria by which clinicians can request them, are updated on an ongoing basis as research findings and technology evolve.

For the purposes of this report, we recommend specific tests for which there is an evidence base for their use. In a UK context, not all of these tests may yet be available on the NHS and, for some tests, referral pathways may not yet include psychiatrists as clinicians who can directly request the test(s). Where there is a discrepancy between recommendations for testing and genetic tests available for clinical use, it is hoped that this report will be a catalyst for service development and adjustments to referral pathways.

This report aims to provide a clinically useful summary of the current evidence relevant to genetic testing in a range of mental health conditions and to delineate the role of genetic testing as a component of comprehensive high-quality mental health services.

1. Genetic testing technologies

There are hundreds of individually rare – but collectively common – single gene or copy number variants (CNVs) that can cause mental disorders. In genetic variants with major effects, the alteration is sufficient to cause the condition, though the clinical features may vary significantly from one affected individual to the next. Single-gene disorders and/or CNVs can be highly heritable; for example, with an autosomal dominant (such as Huntington's disease) or recessive mode of inheritance.

In addition, chromosomal aneuploidies (having an atypical number of chromosomes, i.e., the total number does not equal 46) are associated with genetic syndromes, such as Down Syndrome (in which individuals have an additional Chromosome 21). Sex chromosome aneuploidies (having an atypical number of sex chromosomes) result in a variety of genetic syndromes (including Triple X syndrome, Klinefelter's Syndrome and Turner Syndrome) with a wide range of psychiatric, neuropsychological and physical presentations. (For more information, the Society for the Study of Behavioural Phenotypes has provided syndrome-specific information sheets.)

In clinical practice, genomic diagnostics is currently focussed on identifying specific genetic syndromes and causal (or 'pathogenic', as per the American College of Medical Genetics criteria) genetic variants, but not polygenic variants associated with multifactorial disease. Broadly speaking, there are diagnostic techniques, which can identify structural chromosomal abnormalities (aneuploidies), causal deletions or duplications of chromosomal regions (comparative genomic hybridisation [CGH] or chromosomal microarray [CMA]) or changes to the DNA code (gene sequencing through exome or genome sequencing platforms).

DNA and genetics recap

At this point, a brief refresher regarding genes and DNA may be useful. DNA is a double helix molecule with each of the two strands bound together by pairs of four 'bases' – adenine (A), cytosine (C), guanine (G) and thymine (T). A binds with T, and C binds with G. The sequence of the base pairs is sometimes referred to as the genetic code and genes are simply portions of this which act as an instruction manual for producing proteins.

The human genome was sequenced in the early 2000s, producing a reference against which the DNA of a particular person can be compared. There are many caveats to this, in particular, the fact that it is now clear that everybody carries millions of different single base pair changes (variants) meaning that each of us has a slightly different genome. It is also the case that the human genome sequencing data has, to date, been obtained mainly from individuals of European ancestry and therefore does not represent the diversity in the genetic code across different races and ethnic groups (Manrai, 2016).

DNA is transcribed into a primary RNA transcript, which contains introns and exons. The introns are then spliced out to form messenger RNA (mRNA). This mRNA molecule is translated at the ribosome to produce the functional protein. The nucleotide sequence of mRNA is read in triplets by the ribosome. A sequence of three nucleotides, sometimes called a codon, encodes a single amino acid.

DNA variants can increase risk and cause genetic conditions in several ways. Deletion of a chromosome segment can remove a whole gene and prevent synthesis of the protein. Alteration to a single nucleotide can result in the naturally occurring amino acid being swapped for a different amino acid. This can alter the structure and function of the protein and is called a missense variant.

DNA variants can also alter the splicing of RNA, and result in mRNA that encodes a faulty or non-functional protein. A single nucleotide change can also convert a normal codon into a stop codon, which signals that translation of mRNA should be terminated. If a single nucleotide is inserted or deleted, this will disrupt the reading frame, so that reading three nucleotides at a time will no longer produce a meaningful sequence of amino acids. Variants that are expected to completely disrupt the functioning of the gene so that it produces no useful protein are collectively known as loss-of-function (LOF) variants. There are three types: splice site, stop-gained and frameshift variants.

Genetic variations of large effect

The most commonly used genetic testing techniques at the present time are chromosomal microarray (CMA), whole exome sequencing (WES), gene panels and whole genome sequencing (WGS). These are best done on DNA extracted from a blood sample, but in theory can use any nucleated cell (e.g., cheek swab). If there are challenges in obtaining a blood sample, clinical genetics can advise on suitable alternative sample types. In clinical practice, the first line test in many instances (when dealing with complex heterogeneous conditions) would be CMA. Depending on the clinical scenario, a gene panel, exome or genome sequencing could then be requested if the CMA did not identify a cause. Other disorders have a set testing panel.

In CMA, the whole genome is examined for deletions or duplications (collectively called copy number variants [CNVs]). This is done by engineering DNA probes which are short portions of DNA that will bind to the genetic sequence of parts of the genome. Many thousands of different DNA probes, which cover the whole genome, are then immobilised on a silicon chip. A patient's DNA sample is fluorescently tagged with one colour and a reference sample is tagged with a different colour, and they are both applied to the silicon chip. Specialised computer software then calculates the ratio of the two colours to identify the areas of difference, which indicate which of the samples is binding more strongly with the probe at that point. If one sample is binding less strongly to a DNA probe(s) in a certain area, this implies a difference in DNA copy number. Modern CMA uses SNP probes and can detect deletions and duplications that may be so small that they affect only a single exon. If CMA does not identify a diagnostic CNV, then further testing could be considered depending on the clinical features.

Some mental disorders are caused by trinucleotide repeat expansions. For example, Fragile X is associated with an expansion of the number of (CGG) repeats in the FMR1 gene. At present, these repeat expansions cannot be reliably detected by WGS and need to be tested for separately.

Polygenic contributions to risk

Multiple common variants, each of small effect, can contribute to the genetic landscape of a clinical condition as well as rare variants of large effect. Environmental factors can influence the risk too, which adds to the complexity.

Common variants with small effects on risk are identified using Genome Wide Association Studies (GWAS). These typically compare the DNA from large numbers of people with a particular condition to an unaffected control group, allowing identification of the variants more likely to be found in the people with the condition. Common variants explain much greater variance (heritability) of common neuropsychiatric conditions than rare variants, but whilst these findings are of interest at a population level and for research purposes, they do not, at present, have relevance for clinical practice.

Epigenetics

Epigenetics refers to the mechanisms by which cells control gene activity without changing the DNA sequence. These mechanisms include DNA methylation, histone modifications and additional mechanisms such as non-coding RNAs. Clinical and animal studies have shown epigenetic changes within key genes regulating neurotransmission, neurodevelopment and immune function in psychiatric diseases. It has been postulated that epigenetic mechanisms may be one biological pathway via which the environment mediates risk in many highly heritable disorders. However, as yet, there is no clinical indication for tests based on epigenetic mechanisms.

Clinical interpretation of genetic testing results

If a specific genetic syndrome is identified, a range of resources is available to provide additional information for professionals, the individual affected and their family. Clinical genetics services can advise on the need for further familial investigation and genetic counselling should be offered to the individual and their family.

For other genetic variants, interpreting the results can be more complex. When whole genome sequencing is carried out, every nucleotide that differs from the reference sequence is identified and for each individual this will consist of a list of millions of variants, thousands of which will be extremely rare or unique. Hence, the task of identifying a variant that may be involved in the aetiology of any given condition is

extremely challenging. Typically, the process of attempting to identify pathogenic variants involves focusing on those which affect genes of interest and which, through their predicted impact on gene and protein function, are expected to have the most severe effects.

As no two individual human genomes are identical, deciding the contribution of any given variant is complex. Variants involving a change to a single nucleotide in the DNA sequence, termed single nucleotide variants (SNVs), can be classified according to the American College of Medical Genetics Criteria (ACMG criteria). Variants are classified on a 5-point scale: 1 (benign), 2 (likely benign), 3 (variant of uncertain significance), 4 (likely pathogenic) and 5 (pathogenic). (In this context, the term 'pathogenic' is intended to mean 'having some direct causal effect' on a clinical condition.)

Given the harms associated with variant misclassification, the ACMG criteria are justifiably conservative, and a large proportion of variants are classified as 3 (variant of uncertain significance, for which there is not enough evidence to classify as benign or pathogenic). CNVs are classified in a similar way.

Population (variant) databases include different cohorts, for example the general population or a cohort of people with the condition of interest. They can also vary in factors such as the age of people involved and the numbers from one family included, adding to the complexity of comparing variants against them (Richards et al., 2015).

The Genome Aggregation Database is a widely used database of the general population. Hence, with certain caveats, if a variant is found above a certain frequency in this database it is not likely to be pathological as it is carried by unaffected persons. Databases such as DECIPHER and ClinVar) are repositories for variants found in affected individuals.

Clinical laboratories can cross-check variants they identify, and also contribute to the available evidence by uploading information to these types of database.

Retention of DNA samples by genetic services, with the consent of the individual, is commonplace. This allows re-testing of samples at a later date as technology becomes more sensitive and as understanding of the relevance of specific variants (particularly those currently described as 'of uncertain significance') develops.

Discussing clinical genetics test results with patients

Clinicians are increasingly being presented with genetic test results, at present mostly from people with single-gene disorders. This can be potentially daunting. However, it is unreasonable for anyone to expect a psychiatrist (or a geneticist for that matter) to be familiar with every genetic condition relevant to psychiatry. Instead, when faced with a new, unfamiliar genetic diagnosis, reference to one of the resources listed at the end of this chapter is recommended. In many cases, the patient or family may have already researched it themselves and know much about it already.

A genetic test result should be carefully read, especially by clinicians who do not routinely use such tests. For this reason, close liaison between mental health and clinical genomics services is beneficial, ideally at a pre-testing stage. For single gene or copy number variant results, the report should state what testing platform was used (CMA, exome, genome) and where relevant, what panel of genes was applied (there will be a reference number which can be searched for using, for example, PanelApp, to check which genes have been analysed). The report will state a gene name or chromosome locus and describe the variant at the nucleotide level and the consequence (for example, amino acid change or splice variant). The variant will be classified according to ACMG criteria.

If a benign variant, or no variant, is identified you should consider if further diagnostic testing is necessary. For example, were the genes for the condition you suspect clinically found on the gene panel?

If a variant of uncertain significance is found, then the report may suggest further actions, for example, testing affected relatives. In such circumstances, seeking advice via a Clinical Genomics multidisciplinary team meeting or formal referral to Clinical Genetics is likely the best course of action.

If a likely pathogenic or pathogenic variant is found, then if the clinical features are in keeping with the described phenotype, this will help to establish a diagnosis.

There are various internet resources that can then be used to better understand diagnosed conditions. Good starting places are databases, such as DECIPHER and ClinVar which have a lot of detail on each known variant. Others to be aware of are the Online Mendelian Inheritance in Man database and GeneReviews, an inherited conditions resource in journal-style format Resources such as the genetics section of MedlinePlus (a service of the US's National Library of Medicine, which is part of the National Institute of Health) distil the information so it is more accessible for clinicians.

For many people, having a genetic diagnosis that explains or partially explains their condition is of psychological benefit. Therefore, patients may not look for anything more from their psychiatrist than to recognise this. However, other people may be keen to have more information, sources of which include:

- Clinical genetics services
- Support groups specific to that condition (typically easily found on the internet)
- More general support groups, e.g., Genetic Alliance UK and Unique.

Please see Appendix for a description of the All Wales Psychiatric Genomics Service that has been set up to support patients, their families and clinicians to address questions, offer guidance and potentially genetic testing to those with psychiatric conditions and developmental disorders.

Polygenic risk scores

For many human traits, including psychiatric conditions, it is possible to obtain a polygenic risk score by summing the contribution to risk of very large numbers of common variants, each individually having a very small effect. People with the highest polygenic risk scores may have a risk several times higher than those with the lowest scores, but most people will have an intermediate score with minimal effect on risk. There have been suggestions that for some conditions, such as heart disease or breast cancer, polygenic risk scores could be used to identify people, who are at high risk, for targeted preventative strategies. However, the topic remains controversial. The low predictive value of polygenic risk scores for psychiatric conditions and the lack of available preventative interventions means that they do not have a role in clinical practice at present, although they are being used extensively for research, including their potential to predict various outcomes in psychiatric conditions. Nonetheless, there is no current clinical indication for the use of polygenic risks score testing for psychiatric disorders.

Direct-to-consumer genetic testing kits

Nowadays, it is not just clinical genetics laboratories that offer genetic testing. Various kits are available that members of the public can buy directly. Some are more well known than others (e.g., 23andMe) and some are marketed for non-clinical purposes, such as ancestry analysis. However, many do claim to offer genetic testing and polygenic risk scores for health conditions.

It is vital that clinicians understand that these kits have significant limitations and potential for harm when their results are incorrectly interpreted or misunderstood. They use a variety of different methods and their accuracy is variable, which leads to the possibility of high false positive or false negative results and misleading polygenic risk score information. They are often based on SNP arrays (without any standardisation across kits), with the variants being tested for based on findings from people of largely European ancestry. Furthermore, their clinical implications are not necessarily well described to consumers and many companies either do not offer or do not insist on genetic counselling in advance of testing.

Perhaps the most important thing to be aware of is that there is only a weak association between polygenic risk score and risk itself, meaning that somebody may be told that they have a high polygenic risk score for a particular condition, but in reality their absolute risk of developing this condition may be increased only very slightly from that for the general population.

Genetic testing available in the NHS

With regard to genomic testing in the NHS, the situation differs between the nations of the United Kingdom.

In England, eligibility for genomic testing is set by the NHS England Genomic Test Directory. Intellectual disability, epilepsy and structural brain malformations are listed as conditions eligible for genomic testing.

The test involves whole genome sequencing, followed by analysis of a panel of relevant genes. The genes on a given panel have been selected by a consensus-setting exercise run by Genomics England and made available via PanelApp. Only genetic variants from the panel of genes will be reported. If no variants are found, then the patient can consent to their whole genome sequencing data being placed in a research database where university research groups and commercial companies can apply to analyse the data. In NHS England, psychiatry is now included as a requesting specialty for adult neurodegeneration (including dementia) and intellectual disability genomic investigation.

For Scotland, the eligibility is set by NHS Scotland Genetics and Molecular Pathology Consortium Test Lists. Northern Ireland has equivalent processes and a directory. In Wales, eligibility for genomic testing and the tests made available are determined by the partnership between the All Wales Medical Genomics Service and Genomics Partnership Wales (see Appendix).

Resources

Information:

- **ClinVar**
  ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence.
  https://www.ncbi.nlm.nih.gov/clinvar/

- **DECIPHER**
  DatabasE of genomiC variation and Phenotype in **H**umans using Ensembl Resources is an interactive web-based database which incorporates a suite of tools designed to aid the interpretation of genomic variants.
  https://www.deciphergenomics.org/

- **GeneReviews**
  Provides information about inherited conditions in a standardised journal-style format, covering diagnosis, management, and genetic counselling for patients and their families.
  https://www.ncbi.nlm.nih.gov/books/NBK1116

- **MedlinePlus**
  Provides information about the effects of genetic variation on human health
  https://medlineplus.gov/genetics

- **Online Mendelian Inheritance in Man database (OMIM)**
  A catalogue of human genes and genetic disorders
  https://omim.org/

Support groups:

- **Genetic Alliance UK**
  A national charity working to ensure that the needs and preferences of all people affected by genetic, rare and undiagnosed conditions are recognised, understood and met.
  https://geneticalliance.org.uk/

- **Rare Disease UK**
  A campaign by Genetic Alliance UK, working to raise the profile of rare diseases across the UK.
  http://www.raredisease.org.uk/

- **Unique**
  Support, information and networking for families affected by rare chromosome and gene disorders.
  http://www.rarechromo.org/

2. Patient engagement in psychiatric genetic testing

Psychiatric genetic testing has the potential to raise a vast range of concerns, and it would be unlikely that most people would consider these in all detail. For many, the topic can be intimidating or, at least, highly technical.

With this in mind, many of the considerations identified below would benefit from collective discussion in supportive environments, such as peer-support groups and self-help groups, or as part of broader patient and public engagement activities by trusts, health boards and the College.

Before testing

Discussion of genetic testing will result in highly individual responses, and it will be important to allow sufficient time for a measured discussion to take place.

In stark contrast to many decisions in mental health services, there is not likely to be critical time pressure on a decision around testing. The space and time this offers the process should be used wisely. The specialist skills of clinical genomics services and genetic counsellors can be helpful for patients and, more broadly, for clinicians making decisions regarding genetic testing.

The Mental Health Foundation has run peer-discussion groups on this topic and found that both patients and informal carers are interested in finding out more about the genetics of mental health and its treatment. This type of discussion could be introduced to help people to start thinking about what genetic testing might mean for individuals and help them to formulate questions.

Understanding patient needs

Why might someone want to be tested?

In order to frame a discussion about psychiatric genetic testing in the most productive way, it is helpful to understand why someone would want to be tested. Understanding the motivation for testing will help to identify whether people have realistic expectations of what a test can achieve.

Purpose of testing

It is particularly important to be clear that psychiatric genetic testing, for the most part, cannot either confirm or rule out any psychiatric diagnosis. If the motivation behind testing is clarification of diagnosis, it is important that this limitation is clearly understood to avoid disappointment. A distinction between diagnostic genetic testing and predictive genetic testing is important to note. For example, genetic testing may confirm a genetic cause for dementia, with implications for the wider family. At present, the role of predictive testing is limited, generally impacting family members where a causative genetic abnormality has been identified in an individual. Genetic counselling should be provided for wider family members, to help clarify the risk that they may develop the condition and the implications.

More detailed analysis of what testing can and cannot achieve is covered elsewhere in this report.

Understanding values and articulating risk

Everyone will attribute different values to different outcomes and people are not always good at understanding likelihood and risk. Part of any discussion should encourage people to think about and articulate their own values and the relative importance they place on aspects of their life that may be affected by testing.

There may be particular issues that relate to someone's family circumstances; these may be different for people who were adopted, fostered or who grew up in care.

People may also want family-planning decisions to be informed by genetic risk and it is important that the genetic contributions of any potential diagnosis are accurately communicated.

Informed consent

As with any significant clinical investigation, informed consent needs to be considered. This requires people to have a good understanding of the consequences of both testing and not testing. The information needs to be clear and appropriate for everyone. Making complicated technical information accessible is no easy task, but there is a range of existing resources that might help, some of these are listed in the resources section at the end of this chapter.

Genetic testing has unique features that impact on the type and nature of information that needs to be provided. Accessible information on genetic testing is available and can help individuals and their families come to a decision (Adlington et al., 2019). If, despite the provision of accessible information, an individual is unable to consent to the investigation, legal authorisation for testing needs to be in place, as per the relevant legislative jurisdiction for individuals lacking capacity.

People will need to be aware of what is being tested for and what may become apparent as a result of any genetic test. This may include family history and health risks beyond

those directly related to the reason for testing. This, in turn, raises the issue of broader family engagement.

Family history is a key factor in trying to establish whether psychiatric genetic testing will be of value. Individuals may not be aware of family history and its importance, so this will need to be explained clearly. Family engagement may offer a valuable contribution to understanding family history, but it could also introduce complications or conflict, if not managed well. It will be important to understand that family history is not limited to the diagnosis under consideration and any, or all, of the following diagnoses in family members may need to be considered: intellectual disability, congenital abnormalities (such as cardiac malformations), schizophrenia, autism spectrum disorder, ADHD or epilepsy (see appropriate chapters for more details).

One of the advantages of collective discussions is that questions may be raised that individuals may not previously have considered, and people may be able to explain to each other, particularly with experts on hand to clarify or check details.

Discussions about consent will also need to include clarity about who owns, holds and controls the information that follows any test. People may take a different view on whether to agree to psychiatric genetic testing on the basis of who will have access to the results. This should include discussion about future disclosures (for example to employers, insurance companies, banks and so on). A record of discussion needs to be completed to confirm that the relevant information about genetic testing has been provided and considered. This includes discussion of family implications, uncertainty, unexpected information, DNA storage and data storage.

Screening or predictive testing raises particular challenges, for example, presymptomatic testing in individuals with a family history of Huntington disease. Genetic centres across the United Kingdom have developed a programme with the help of the Huntington's Disease Association to ensure individuals receive the information and support required when considering undertaking this test (resources are given at the end of this chapter).

Psychiatric genetic counselling

Genetic counselling is the process by which people are helped to understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. It involves integration of family and medical histories to assess the chance of the occurrence or recurrence of a condition, and includes information on testing, management and resources. Genetic counselling has a key role in promoting informed choices.

Although psychiatric genetic counselling is not yet widely available across the UK, it is a growing profession. International evidence suggests that it can make psychiatric genetic testing decision-making an empowering experience. Even if not routinely available, psychiatric genetic counsellors would be very useful contributors to any group discussions or engagement events on psychiatric genetic testing.

After testing

People may experience a degree of anxiety in the period between taking a test and receiving results, both in terms of what the results would show and any corresponding changes in their care or treatment. It is important to ensure that an accurate timescale is given for receiving results, and that appropriate support is available in the period after testing.

Treatment decisions

One of the areas that people living with a psychiatric diagnosis are particularly interested in is the role of genetics in informing treatment decisions. Pharmacogenomics, and its current place in clinical practice, is covered in detail in Chapter 8 of this report. In many situations, genetic testing may be helpful diagnostically, but may, in practice, offer little in terms of implications for treatment, and it may be appropriate to ensure that patients are made aware of this.

Biobank inclusion

In addition to the standard issues regarding data sharing, there may be particular decisions regarding inclusion in research projects such as Biobank. People may be happy to contribute their anonymised information to academic research, but may have questions regarding whether genetic information can be anonymised. Discussions about data sharing should form part of obtaining informed consent for genetic testing.

Involving families

Seeking broader engagement by involving the family, as well as the patient, must also be considered as part of good practice. In addition, there are two aspects of psychiatric genetics that may increase the value of family engagement: the importance of family history and the broader family impact of both history and genetic test results.

Clinicians and patients will need to consider the risks and benefits of sharing information and family involvement, to inform the decision whether to undertake genetic testing, with particular consideration of patient confidentiality. Depending on the individual circumstances, psychiatric genetic counselling may have an important role to play in supporting the entire family through the testing decision and, if appropriate, testing process and results.

As for genomic medicine in general, complex ethical issues can arise in contexts where families may be considering prenatal diagnosis. These may be particularly relevant when genetic variants have a broad potential phenotype or increase the risk of adult-onset conditions. The Human Fertilisation and Embryology Authority permits embryo testing for almost any genetic condition if legal criteria related to the risk of transmission and the seriousness of symptoms in somebody affected by the genetic abnormality are met: Pre-implantation genetic testing for monogenic disorders (PGT-M) and Pre-implantation.

The Royal College of Physicians, Royal College of Pathologists and the British Society for Genetic Medicine have published guidance on ethical issues in prenatal diagnosis for clinical practice: Ethical issues in prenatal genetic diagnosis: Guidance for clinical practice

Resources

Ethics

The following publications explore some of the ethical issues raised by genetic testing in psychiatric settings:

Crepaz-Keay D, Austin, J, Weeks L (2021) Journey into Genes: Cultural Values and the (Near) Future of Genetic Counselling in Mental Health. In: Stoyanov D, Fulford B, Stanghellini G, Van Staden W, Wong MT (eds) *International Perspectives in Values-Based Mental Health Practice*. Springer, Cham https://link.springer.com/content/pdf/10.1007/978-3-030-47852-0.pdf)

Lázaro-Muñoz G, Sabatello M, Huckins L, Peay H, Degenhardt F, Meiser B, Lencz T, Soda T, Docherty A, Crepaz-Keay D, Austin J, Peterson RE, Davis LK (2019) ISPG Ethics Committee. *International Society of Psychiatric Genetics Ethics Committee: Issues facing us. Am J Med Genet B Neuropsychiatr Genet*, **180(8)**:543–54. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861601/pdf/nihms-1029837.pdf

Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine (2022) Ethical issues in prenatal genetic diagnosis. *Guidance for clinical practice. Report of the Joint Committee on Genomics in Medicine*

Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine (2019) *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic. 3rd edition. Report of the Joint Committee on Genomics in Medicine*

Videos

These videos by the National Collaborating Centre for Values-based Practice in Health and Social Care offer an accessible explanation of what psychiatric genetics can and cannot offer now and how this might be useful in a (public) mental health setting: Seminar 4: The benefits and risks of genetics in public mental health

Explaining genetic testing to people with learning disability:

The following publication provides material designed to help explain genetic testing to people with learning disability in the 'supporting information' section:

Adlington K, Smith, J, Crabtree J et al (2019) Improving access to genetic testing for adults with intellectual disability: A literature review and lessons from a quality improvement project in East London. *Am J Med Genet Part B. 2019*, **180B**: 566–75

Huntington's Disease Association
Genetic testing:
http://www.hda.org.uk/getting-help/if-youre-at-risk/genetic-testing

Human Fertilisation and Embryology Authority
Pre-implantation genetic testing
https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/pre-implantation-genetic-testing-for-monogenic-disorders-pgt-m-and-pre-implantation-genetic-testing-for-chromosomal-structural-rearrangements-pgt-sr/

3. Adult patients with mental illness

Research has demonstrated that, as for practically all human traits, there is some genetic contribution to the susceptibility to develop mental illness. This contribution is substantial for schizophrenia and bipolar disorder, and is smaller, though still present, for conditions such as anxiety and depression. Genetic variation even has an effect on predisposition to conditions with a clear environmental precipitant, such as post-traumatic stress disorder.

Characterising the relationship between DNA variation and susceptibility to mental illness will improve understanding of aetiology and could lead to the development of improved treatments. In principle, there might be potential to use genetic information to guide treatment choices but research findings to date are inconclusive. So, there are no current clinical applications of such genetic testing (see Chapter 8: Pharmacogenomics). Rarely, the identification of a specific genetic abnormality could have clinical implications in terms of possible co-occurring conditions and could have important implications for the patient and their relatives.

It is helpful to distinguish between the contributions of common variants, rare sequence variants and rare copy number variants.

Relevant research evidence

The extent to which research has been successful in identifying specific genes and variants differs between diagnoses, but in general we can say that there are common variants which individually have minimal effects, but collectively contribute substantially to heritability, while some very rare variants can have quite large effects on risk, but collectively explain a smaller amount of heritability of most psychiatric conditions.

The common variants can be identified by genome-wide association studies (GWAS) and, although this research may be helpful in terms of leading to a better understanding of the aetiology of mental illness, the effects of these variants are too small for there to be any clinical value in testing for them individually.

The cumulative effects of thousands or millions of such variants may be summarised as a polygenic risk score (PRS). Across the population, the PRS for susceptibility to each disease will be slightly higher for people with that diagnosis, although still statistically significant (Trubetskoy et al., 2022). People with very high PRS only have moderately increased risk and there is currently no clinical situation in which there seems to be value in identifying that a given person has a somewhat higher or lower risk of developing a mental illness.

Ongoing research seeks to determine whether a PRS may be of value, along with other variables, in predicting poor outcomes or transition to more severe conditions in high-risk groups, or physical health outcomes, but none of this research has, to date, indicated clinical utility of such testing.

Two types of rare genetic variation can impact on susceptibility to disease. Changes in the sequence of DNA bases can affect a gene by changing one of the amino acids in the protein it codes for or can disrupt the function of the gene completely, for example, by introducing a new stop codon near the start of the gene. To date, a few such sequence variants in 10 specific genes have been identified as having large effects on the risk of developing schizophrenia, but they are only found in such a small proportion of cases that, at present, there is no clinical justification to test for them (Singh and The Schizophrenia Exome Meta-Analysis (SCHEMA) Consortium, 2022).

Another kind of rare variant consists of the deletion or duplication of a small section of a chromosome and is called a copy number variant (CNV), because it changes the number of copies of that chromosomal segment from the normal number of two (as there are two copies of each chromosome) to either one (for a deletion) or three (for a duplication). Although the chromosomal segments are small, each will typically contain a number of different genes. There have been 11 chromosomal locations identified where occurrence of a CNV can dramatically increase the risk of developing schizophrenia and at least 2.5% of people with schizophrenia will, if tested, be found to carry one of these CNVs (Kirov et al., 2015). It is important to appreciate that not everyone who has one of these CNVs will develop schizophrenia (i.e., CNVs are not fully penetrant). Indeed, as well as increasing risk of schizophrenia, all these CNVs are also associated with an increased risk of other neurodevelopmental conditions including intellectual disability, ADHD, autism and epilepsy.

The identification of a pathogenic CNV in a patient with schizophrenia has several implications which mean that there may be a clinical benefit in testing for them (Curtis et al., 2019). Firstly, it may be helpful for the patient and those around them to simply have an explanation of why they have developed schizophrenia. The magnitude of excess risk produced by one of these CNVs, for some as much as a 10-fold increase or higher, is such that if one is found, it is likely to have been a key factor in the development of the patient's illness in the sense that if the patient did not carry the CNV, they would have been unlikely to have developed schizophrenia.

For some, having a clear explanation of why they have become unwell may reduce stigma and may support engagement with treatment efforts. A secondary benefit for the patient is that some CNVs increase the risk of specific physical health problems. Therefore, the identification of a CNV may lead to targeted screening and monitoring, followed by appropriate interventions. For example, identifying a 22q11 deletion (1 in 4000 in the population) indicates that cardiac abnormalities may be present (40% of cases), and that there may be implications if treatment with clozapine is being considered (see Chapter 8: Pharmacogenomics).

The identification of a pathogenic CNV may have implications, not only for the patient but also for their relatives. The CNV may occur as a *de novo* mutation, meaning that it occurs as a result of copying errors during meiosis and that neither of the patient's parents carries it. If this is the case, then the patient's siblings will be unlikely to carry it and will not themselves be at substantially

increased risk of developing schizophrenia. On the other hand, if the CNV is inherited from a parent then each of the patient's siblings would have had a 50% chance of also inheriting it. Equivalent risks potentially extend to the children of those patients identified as having a CNV. The implications for the wider family can thus be significant and reinforce the value of involving specialist genetic counsellors and clinical genomics services early in the testing process, given their experience and expertise in guiding patients and their families in decision-making.

Clinical practice points

Given that at least 2.5% of patients with schizophrenia have a pathogenic CNV and that this can have clinical implications, testing for such CNVs may be indicated in some situations. Two sets of factors might influence this decision – how important it is to know the result and how likely it is that the result will be positive. The shared decision-making around genomic testing that should happen between health professionals and patients will be context specific, dependent on individual circumstances, needs and potential benefits.

It could be argued that the results of testing might have a greater impact for a young, newly diagnosed patient who may be contemplating parenthood or may have younger sibling worried about their own risk, compared with an older patient who is stable, well-established on treatment and is not contemplating having (more) children. A number of factors influence the probability that a pathogenic CNV will be detected and may inform testing policies where the yield (percentage of positive tests of all those tested) is a consideration. CNVs are more prevalent in patients with schizophrenia who have a lower IQ than those with average or above average IQ (Hubbard et al., 2021). Also, because CNVs typically have multiple manifestations, including increasing risk of a range of neurodevelopmental disorders, they are more likely to be detected in patients who have additional features suggesting some developmental condition such as dysmorphism, cardiovascular malformation or neurological symptomatology.

Rarely, psychosis can be the presenting feature of a genetic disorder such as Huntington's disease or fronto-temporal dementia. If family history or unusual aspects of a clinical presentation suggest the presence of a rare genetic disorder, further discussion in a multidisciplinary meeting including neuropsychiatry or neurology, clinical genetics and genetic counselling services would be advised.

Recommendations

1 **Polygenic risk scores:**
There is currently no clinical role for seeking to interpret effects of common variants, whether considered individually or combined into a polygenic risk score, for any mental illness.

2 **Rare sequence variant testing for schizophrenia:**
Although some rare sequence variants can substantially affect risk of schizophrenia, they are so rare that, at present, there does not seem be a role for testing for them in the clinical situation.

3 **Testing for rare CNVs in people with schizophrenia with co-occurring conditions:**
At least 2.5% of patients with schizophrenia will have an identifiable rare neurodevelopmental copy number variant (CNV) and this yield is likely to be higher in patients with lower IQ and/or other neurodevelopmental features. We recommend that testing for these CNVs be considered and made available for those diagnosed with schizophrenia who have co-occurring conditions (such as neurodevelopmental disorders, marked cognitive impairment or congenital anomalies), or if there are important implications because of specific aspects of the patient's situation, or that of their family.

4 **Establishing clinical pathways:**
Clinical pathways should be established between adult psychiatric services, clinical genomics and genetic counselling services as part of multidisciplinary working.

Resources

- **International Society of Psychiatric Genetics:**
  - Statement on genetic testing: https://ispg.net/genetic-testing-statement/
  - Educational resources: https://ispg.net/resources/educational-presentations/

- **British Society of Genomic Medicine**
  Guidance on taking and recording a family history: www.bsgm.org.uk/healthcare-professionals/taking-and-recording-a-family-history/

4. Children and adults with intellectual disability

Intellectual disability (ID) is a significant impairment in global cognitive ability, present during the developmental period, and having a significant impairing impact on adaptive functioning. With the latest techniques, a genetic aetiology may be able to be identified in 40–50% of all cases (Wright et al., 2018), with higher rates being seen in those with a more significant degree of intellectual disability.

Relevant research evidence

Historically, only chromosomal abnormalities (e.g. Down syndrome, William's syndrome), and, later, the triplet-repeat disorder Fragile X syndrome, could be identified as giving rise to ID. However, with increasing sophistication of diagnostic technology, it is now possible to identify genetic changes caused by variations in copy number (CNVs), i.e., microdeletions or microduplications, as well as pathogenic variants at a single nucleotide level (SNPs).

Several hundred genes have now been identified in which variants with large effects on brain function can cause both syndromic or non-syndromic ID (Vissers et al., 2016). The classification of these is complex, however. They are generally considered to be causative and thus classified as pathogenic or likely pathogenic when there is a disruption of genes known to be important for neurodevelopmental functions, such as neurotransmission.

Chromosomal microarray analysis (CMA) can identify clinically-relevant variants in 15–20% of people with unexplained intellectual disability (Thygesen, 2018; Utine, 2014). Diagnostic yields are higher, at 30–40%, with whole exome sequencing (WES), which is becoming increasingly available in clinical services as the costs of doing the sequencing reduce. Where parental samples are also available, the diagnostic yield can be even higher, at over 50% (Srivastava et al., 2020).

Overall, a genetic diagnosis can be made in at least 25% of patients with ID (Wright et al, 2018), with higher rates in those with more severe levels of ID and in those with co-occurring conditions (such as schizophrenia, other neurodevelopmental conditions and/or congenital anomalies).

Clinical practice points

Identifying a genetic aetiology is principally important as there may be clinical implications for both mental health and general medical care. For example, Cornelia de Lange syndrome (CdLS), which is caused by a variety of different genetic mutations, is associated with very high rates of gastro-oesophageal reflux caused by congenital

diaphragmatic hernia. The pain associated with this appears to be a key cause of distress for affected individuals, and treatment of this can significantly alleviate this distress. Similarly, deletion of chromosome 22q11.2 can confer a significant risk of developing adult-onset psychosis and/or epilepsy, and affected individuals are also at substantially increased risk (75%) of cardiac abnormalities, and of developing rheumatoid arthritis. Similarly, duplication at 16p11.2 is associated with a fourteen-fold increase in the risk of psychosis.

Armed with this knowledge, clinicians can ensure they are vigilant in looking out for the early signs of onset of these conditions, allowing for prompt treatment, as well as considering likely physical comorbidity that may impact on, or even cause, the patient's clinical presentation (particularly in someone who cannot explain their distress) and its effect on selection, dosing and monitoring of psychiatric medication, when it is indicated.

As well as having implications for the individual, genetic diagnosis may have implications for the broader family. For example, in Fragile X syndrome, the diagnosis of the individual can also lead to the diagnosis of the Fragile X premutation in other family members. As the premutation itself is associated with premature ovarian insufficiency (Fragile X-related Premature Ovarian Insufficiency, FXPOI) and Fragile X-associated Tremor & Ataxia Syndrome (FXTAS) and higher rates of mood and anxiety disorders, knowledge of this can be helpful for families and aid early diagnosis and/or treatment.

Identifying a genetic aetiology in individuals with ID ensures that monitoring for known co-morbidities is part of the ongoing management to allow early diagnosis and treatment, as well as providing information to the patient and family regarding prognosis and implications for the family.

A second, often-overlooked, benefit of genetic diagnosis can be the impact on families of 'just knowing'. For some, this is by way providing an explanation that may allow the family to move forward. This may be particularly true for parents with feelings of guilt due to believing their actions could in some way be responsible for their child's intellectual disability, e.g., not following the dietary advice during pregnancy which was available at the time. For others, the genetic diagnosis will allow the family to connect with other similarly affected families and access support groups, such as Unique. With the increasing sophistication of testing available and, thus, the identification of rarer variants, it is of growing importance for families to able to connect with each other, wherever they are in the world, to share their experiences and learn from each other.

In most centres, Fragile X molecular testing alongside chromosomal microarray analysis (CMA) is considered as part of the routine investigation of significant childhood developmental delay. This is because CMA on its own, is not able to identify the nucleotide repeats seen in Fragile X, and because Fragile X is relatively common, with significant impacts on wider family members. Whole exome sequencing is also being increasingly used for those with the most severe phenotypes, e.g., in epileptic encephalopathies. Thus, looking to the future, many more individuals with an intellectual disability will have a genetic diagnosis than has historically been the case.

However, when considering adults with an intellectual disability, and in particular older adults, far fewer have a genetic diagnosis. Thus, services need to consider how to address the need for genetic testing in adults with an intellectual disability, and how

to best meet this need. International guidance recommends that adults with ID, who either have never had genetic testing or who were tested much further back in time when testing was only available for a much smaller number of conditions, be offered genetic investigation (Frueh et al., 2021).

Whilst most genetic centres should be routinely checking for Fragile X when screening individuals with ID, it should be noted that tests that did not specifically look for Fragile X (either by using older tests or relying on array tests alone) do not exclude the diagnosis. Thus, it is advised for clinicians to determine whether it is included routinely by their local genetic services, and whether previous negative results examined the possibility sufficiently.

Diagnostic yield from genetic testing in people with ID (and, in particular, for people with moderate/severe ID or other co-occurring conditions, such as other neurodevelopmental disorders or major mental illness) supports these investigations being undertaken as part of routine clinical care. Developing routine assessment pathways (including the provision of accessible information to patients and families and the establishment of multidisciplinary team meetings) should be prioritised as part of quality improvement processes for ID services (Adlington et al., 2019)

Recommendations

1 **Consulting clinical genetics services:**
Clinicians should consult with clinical genetics services if patients present with features suggestive of a particular genetic syndrome.

2 **Fragile X, CMA and whole genome sequencing for children and adults with ID:**
Chromosomal microarray (CMA) and whole genome sequencing provides a genetic diagnosis in at least 25% of patients with ID, with higher rates of diagnosis in those with more severe ID and in those with co-occurring conditions (such as schizophrenia, other neurodevelopmental disorders or congenital anomalies). We recommend that Fragile X testing, and CMA and whole genome sequencing be made available for children and adults with intellectual disability as part of routine clinical care.

3 **Genetic testing for adults with ID:**
Services should consider how best to support genetic diagnosis of adults with ID who have not previously been offered testing, as well as considering re-testing for those who have not had whole genome sequencing or whose CMA was conducted prior to the availability of the most recent panels. Particular attention should be paid to whether prior testing included Fragile X testing.

4 **Establishing routine assessment pathways for people with ID:**
We recommend that routine assessment pathways for genetic testing in people with ID be developed, including the establishment of multidisciplinary team meetings with input from clinical genetics and genetic counselling services.

Resources

Guidance and information:

- **British Society of Genomic Medicine**
  Guidance on taking and recording a family history:
  www.bsgm.org.uk/healthcare-professionals/taking-and-recording-a-family-history/

- **Society for the Study of Behavioural Phenotypes**
  Syndrome information sheets:
  https://ssbp.org.uk/syndrome-sheets/

Support:

- **National Fragile X Foundation**
  Support for families living with Fragile X through community, awareness and education and research:
  www.fragilex.org

- **Unique**
  Support, information and networking for families affected by rare chromosome and gene disorders:
  www.rarechromo.org

- **Downs Syndrome Association**
  Support for families affected by Downs syndrome:
  www.downs-syndrome.org.uk/

- **Contact**
  Support for families with disabled children:
  www.contact.org.uk

5. Adults with other neurodevelopmental disorders

ICD 11 defines neurodevelopmental disorders as involving significant difficulties in the acquisition and execution of specific intellectual, motor, language or social functions with onset during the developmental period. The developmental period encompasses the time between birth and adulthood, with adulthood assumed to have been reached by age 18.

Neurodevelopmental disorders causing significant levels of impairment are generally identified well before the end of adolescence, subsequently persisting into adulthood. Some development continues beyond the age of 18, with limited data on the long-term stability of diagnostic criteria for neurodevelopmental disorders with less severe associated functional impairments. There is no significant divergence in classification of neurodevelopmental disorders between ICD 11 and DSM-5 (Reed, et al., 2019).

Conditions included under this overarching category include intellectual disability (ID), autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), tic disorders and specific learning disorders.

Relevant research evidence

Intellectual disability

See the previous chapter, Chapter 4, for genetic testing recommendations for children and adults with intellectual disability.

Autism spectrum disorder

Autism spectrum disorder (ASD) as defined in the ICD 11 is a heterogenous condition with a wide range of elements contributing to its presentation, including both common and rare genetic variants, as well as environmental and developmental factors. In rare instances, ASD is associated with known syndromes such as tuberous sclerosis, 22q11 microdeletion or Down syndrome.

Current research evidence suggests that the clinical utility of CMA testing in children with autism is greater when there is co-occurring intellectual disability, congenital anomalies or dysmorphic features (Ho et al., 2016; Tammimies et al., 2015). NICE guidelines for the

assessment of ASD (without co-occurring conditions) do not recommend routine genetic testing. There is a lack of research evidence on ASD diagnosed in adulthood.

ADHD

The genetics of ADHD follow a similar pattern to that observed for ID and ASD: heritability seems to be largely attributable to common variants and CNVs, with rare genetic syndromes observed in some cases. This genetic liability is not specific to ADHD, conferring increased risk for a range of other disorders.

Equally, ADHD is a common, co-occurring condition in a number of rare genetic disorders (Faraone and Larsson, 2019). Recent family and twin studies have shown a strong familial and genetic overlap between ADHD and ASD (particularly in individuals with ASD without significant support needs). In common with other mental health conditions, relatives of someone with ADHD are at elevated risk of a range of other neurodevelopmental disorders and well as psychiatric illness (most commonly major depression). ADHD with childhood onset and which persists into adulthood is recognised to have a higher genetic loading. There is a lack of research evidence on ADHD diagnosed in adulthood (Thapar, 2019).

Clinical practice points

Any decision around genetic testing in adults with ASD or ADHD must be based on the likelihood of benefit to the person being tested.

Some genetic changes which confer an increased likelihood of ASD also increase the likelihood for developing physical or mental health conditions (e.g., in 22q11 deletion syndrome). Identifying recognised genetic syndromes associated with ASD (for example, PTEN, MECP 2 or tuberous tclerosis) allows for assessment and monitoring of known additional health conditions. As previously indicated, these cases will usually be highlighted by the presence of other relevant features indicating that genetic testing should be considered.

It is common for individuals to have more than one neurodevelopmental disorder. Any given neurodevelopmental disorder that occurs in isolation is less likely to have an identifiable causal CNV. However, the higher the number of co-occurring conditions present, the more likely it is that an underlying genetic variant can be identified. Relevant co-occurring conditions include mental illness, other neurodevelopmental disorders, congenital anomalies or dysmorphic features.

See Chapter 7 for further information and guidance on genetic testing in Child and Adolescent Mental Health Services (CAMHS).

Recommendations

A genetic diagnosis is significantly more likely to be made in, and provide benefit to, individuals who have co-occurring conditions alongside their neurodevelopmental condition (particularly intellectual disability, mental illness, congenital anomalies or dysmorphic features suggestive of a genetic syndrome).

For ASD or ADHD associated with intellectual disability:

- Guidelines for genetic testing in intellectual disabilities should be followed (see previous chapter).

For ASD or ADHD without co-occurring intellectual disability:

- Routine genetic testing in adults is not recommended.
- Testing for CNVs should be considered and available for individuals with ASD who have other co-occurring neurodevelopmental disorders, mental illness, congenital anomalies or dysmorphic features, or if there are important implications because of specific aspects of the person's situation or that of their family.
- For recommendations on genetic testing in child and adolescent mental health services, please refer to the next chapter.

Resources

NICE
Autism assessment guidance:
https://www.nice.org.uk/guidance/cg142/chapter/Recommendations#identification-and-assessment-2

6. Child and adolescent mental health services

Since the importance of genetic factors in autism were illuminated in a publication by Folstein and Rutter in 1977, many twin, family and adoption studies have consistently supported the importance of genetic factors in childhood neurodevelopmental and psychiatric disorders.

The strength of genetic liability can be quantified by:

- twin studies, which typically show higher concordances (or correlations if behaviours are measured dimensionally) in monozygotic twins (sharing 100% genes) compared with dizygotic twins (sharing 50% genes) for genetically influenced disorders
- family studies, where risks for familial disorders are proportionate to degree of relatedness with first-degree relatives having highest risk
- adoption studies, in which genetic liability is separated from rearing effects.

Research studies have illuminated the inheritance patterns and we now understand that most childhood onset disorders show complex (thousands of genes) rather than Mendelian (single-gene) inheritance and are multifactorial in origin meaning that they are not determined by any single risk factor. Rather, there is interplay between many different genetic ('constitutional') and non-genetic factors (biological, interpersonal and social environment and stochastic effects). Genetic risks are not deterministic and many other factors, including environmental factors, contribute to the expression, course and outcome of a particular condition.

Families in receipt of Child and Adolescent Mental Health Services (CAMHS) where there is a history of psychiatric disorder (e.g., a parent with schizophrenia) may wish to seek information from a CAMHS clinician about the risks of the same disorder in their child.

Whilst it is important to know familial risks of disorder, it is also important for the CAMHS clinician to inform families that genetic risks:

- cross diagnostic boundaries (e.g., the offspring of a parent with schizophrenia may have increased risk of depression or autism, rather than only of schizophrenia)
- are non-specific, as well as being non-deterministic.

A genetic contribution also does not necessarily mean a disorder needs to be treated with medication.

Relevant research evidence

The most highly heritable conditions in CAMHS are autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD) and Tourette's syndrome (neurodevelopmental disorders), as well as early presentations of schizophrenia and bipolar disorder. These disorders have a complex genetic architecture comprising thousands of common genetic variants of small effect size, as well as rare structural

genetic variants (e.g., chromosomal deletions and duplications) of moderate effect size and rare/single gene variants of moderate-large effect size. Large research collaborations are developing methods to add the small-effect common genetic variants together to produce a polygenic risk score (PRS), which may in time be used as a biomarker and aid clinical decision-making and treatment. Currently, there is no evidence of clinical utility for these but clinicians should be aware that families could obtain them from commercial providers and present requesting clarification regarding the interpretation of the results. (See the previous discussion of polygenic risk scores in chapters 1 and 4.)

The moderate and large effect size rare genetic variants account for a small percentage of the total number of people presenting to clinicians, enriched in those with ASD, ADHD, schizophrenia and are more commonly, but not exclusively, found in those patients with co-occurring disorders of intellectual development (DID), dysmorphic features and medical comorbidities. Within this subgroup are a number of recognisable syndromic genetic conditions associated with DID, for example, Fragile X, Rett's, Tuberous Sclerosis, Smith-Magenis syndrome. However, some rare genetic syndromes are not always accompanied by ID and can present in CAMHS, for example with ADHD, ASD or psychosis (e.g., 22q11 microdeletion syndrome). Rare variants can be transmitted from parents or arise *de novo* in the offspring which has implications for risk and genetic counselling. In addition, chromosomal (including sex chromosome) disorders can lead to a wide variety of clinical presentations and testing for these should be considered where clinical features are consistent with such syndromes.

See Chapter 3 for more detailed discussion of genetic testing recommendations for mental illness (in particular, schizophrenia). A genetic aetiology is more likely in early-onset schizophrenia or in psychotic illnesses that develop in adolescence.

Clinical practice points

In the CAMHS setting, a genogram of first- and (possibly also) second-degree relatives showing, in particular, ASD, ADHD, intellectual disability/developmental delay and other neurodevelopmental disorders, bipolar disorder and schizophrenia may indicate a complex genetic inheritance or, alternatively, highlight a potentially *de novo* genetic variant where a condition is presenting in a family for the first time. A history of bipolar disorder in a first-degree relative of a young person presenting with depression may suggest the desirability for increased monitoring of a switch to mania/hypomania if SSRIs are prescribed.

Referral to genetics services is neither practical nor necessary for most patients. However, CAMHS clinicians are advised to make contact with their local genetics service to discuss guidelines for referral.

NICE guidelines do not recommend genetic testing in the assessment of ASD in the absence of other co-occurring conditions. Please see Chapter 5 and 6 for recommendations for genetic testing in intellectual disability or other neurodevelopmental disorders.

Testing needs to be accompanied by genetic counselling to ensure the wishes of the young person are properly considered.

Recommendations

1 **Genetic testing for children/young people with dysmorphic features; developmental delay/intellectual disorder or unusual medical presentations** :
Consider genetic testing in children/young people with dysmorphic features; developmental delay/developmental intellectual disorder or unusual medical presentations (e.g., central hypopituitarism, skeletal anomalies, congenital heart conditions, epilepsy, neurocutaneous lesions, such as, adenoma sebaceum, ash leaf macules, café-au-lait spots). Your local service may be interested in seeing other young people (e.g., familial clustering of neurodevelopmental and/or psychiatric disorders and/or epilepsy).

2 **Early-onset schizophrenia:**
For early onset schizophrenia, we recommend testing for rare neurodevelopmental CNVs given an anticipated greater yield for identifiable CNVs than in adult-onset schizophrenia. At least 2.5% of patients with schizophrenia will have an identifiable CNV and this yield is higher in patients with lower IQ and/or other developmental conditions, and with earlier onset of psychosis. We recommend that testing for these CNVs should be available for any young person with schizophrenia and that it should especially be considered if other clinical features are present or if there are important implications because of specific aspects of the patient's situation, or that of their family.

3 **Establishing clinical pathways:**
Clinical pathways should be established between CAMHS, community paediatric and genomic medicine services.

Resources

The Association of Child and Adolescent Mental Health
Newsletter summarising the role of genetics in CAMHS clinical practice:
https://www.acamh.org/expert-perspectives/genetics-informing-care/

British Society of Genomic Medicine
Guidance on taking and recording a family history:
https://www.bsgm.org.uk/healthcare-professionals/taking-and-recording-a-family-history/

7. Dementia

Dementia is a clinical syndrome characterised by progressive impairment of higher cortical functioning. Many diseases can cause dementia. The syndrome may be the central feature of the disease, as in Alzheimer's disease, or part of a broader phenotype, as in Huntington's disease. Consequently, the role of genetic testing in the assessment of dementia depends on the overall clinical presentation.

As with most psychiatric diagnoses, genetic risk variants for dementia range from the common (each conferring a small additional risk) to the extremely rare (causing dementia). Common variants identified through large-scale genome wide association studies (GWAS) of Alzheimer's disease only increase an individual's risk by 5–30% (Van Cauwenberghe *et al.*, 2016). By contrast, there are extremely rare Presenilin 1 gene (*PSEN1*) variants which will almost inevitably result in the development of Alzheimer's disease by the age of 60 (Pilotto *et al.,* 2013). Few people with dementia have such causative variants and monogenic forms of dementia only account for a very small proportion of the overall burden of the disease.

Relevant research evidence

It is beyond the scope of this report to discuss comprehensively the genetic architecture of the very long list of diseases that cause dementia. Therefore, this section will focus on subtypes of dementia commonly seen in memory clinics and for which genetic testing is currently available in the NHS – namely frontotemporal dementia (FTD), Alzheimer's disease,and vascular dementia.

Frontotemporal dementia

In approximately 30–50% of people presenting with FTD, an autosomal dominant pattern of inheritance can be identified in their family. Variants in multiple different genes have been identified as being causative of FTD.

An important feature of the genetics of FTD is genetic pleiotropy (where a single gene variant has multiple effects). The outcome of variation in the 'FTD genes' is not only FTD – other phenotypes are observed. These phenotypes include atypical parkinsonian syndromes (corticobasal syndrome and progressive supranuclear palsy) and motor neurone disease. A combination of clinical diagnostic phenotypes (for example, FTD and motor neurone disease) can occur in one individual, and members of the same family (possessing the exact same aetiological variant) can present with different phenotypes. Furthermore, dementia genetics do not entirely respect clinical diagnostic boundaries. There are (rare) instances of people presenting with FTD being found to have 'Alzheimer's causing variants', and vice versa.

Alzheimer's disease

The first variant causal of autosomal dominant Alzheimer's disease was identified over 30 years ago – a single guanine to adenine base change in exon 17 of the amyloid precursor protein (APP) gene. Duplication of APP gene on chromosome 21 (i.e. having 3 copies of APP instead of two), occurs in Down syndrome (DS), as well as in rare families with a copy number variant involving the APP region. These individuals and those with Down syndrome are all at exceptionally high risk for developing Alzheimer's pathology due to amyloid overproduction (Wiseman et al., 2015). Subsequently, variants causative of autosomal dominant Alzheimer's disease were found in the Presenilin 1 (PSEN1) gene (Sherrington et al., 1995) and the Presenilin 2 (PSEN2) gene (Rogaev et al., 1995). However, it should be emphasised that genetic forms of Alzheimer's disease are rare. Individual causative variants may be extremely rare and have only been identified in a handful of families worldwide.

GWAS has shown that risk of late onset Alzheimer's disease has a polygenic component – in other words, many variants impact an individual's risk and most of these each has a small effect on risk. The notable exception is the apolipoprotein E (APOE) gene located on chromosome 19. Variation in the APOE gene determines which apolipoprotein E protein isoform is produced by that gene, labelled as APOE2, APOE3 and APOE4. Presence of the APOE4 isoform results in a medium to large increase in the risk of Alzheimer's disease (up to ten-fold if an individual has two copies of the APOE4 isoform). At the population level, these variants account for most of the genetic risk for Alzheimer's disease, with approximately 30% of the population attributable fraction relating to APOE. GWAS results can be used to calculate a polygenic risk score (PRS) but at present this is not considered to have clinical utility (see Chapter 1 on genetic testing technologies).

Vascular dementia

Consideration of vascular dementia is complicated as it can arise from separate or partially separate aetiologies (acute stroke, multiple infarcts and small vessel disease). The majority of vascular dementia seen in memory clinics is related to white matter damage consequent of small vessel disease.

Two rare genetic forms of vascular dementia are recognised: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL).

Clinical practice points

It should be noted that, notwithstanding the advances in our understanding of the genetic architecture of Alzheimer's disease, non-genetic factors (e.g., lifestyle and social environment) impact significantly on the risk of developing dementia in later life, and many of these are modifiable. For the majority of the population, genetic risk factors are not determinative.

However, people undergoing memory assessments are entitled to access the full range of appropriate investigations depending on their availability in a given locale. For some people, knowing the underlying cause of their dementia may be important and genetic investigation will answer the "why me/my family?" question.

Genetic investigation can potentially reduce the time from presentation to diagnosis, reduce the number/burden of investigations for the individual and improve diagnostic accuracy. This is particularly the case for younger people presenting with cognitive problems – a population that is enriched for genetic forms of dementia – since they are known to experience diagnostic delay compared with those presenting after the age of 65.

Subtype diagnosis is important for individualised post-diagnostic care, informing psychoeducation/support, social interventions and pharmacological treatments. A genetic diagnosis may give additional prognostic information. Furthermore, there are a number of ongoing genetic variant specific therapeutic trials and it is possible that the efficacy of future disease modifying therapies will be variant dependent.

Genetic diagnosis of the affected individual provides the opportunity for cascade testing of at-risk relatives and the provision of recurrence risk information. Diagnostic testing needs to be clearly differentiated from predictive testing of asymptomatic individuals at risk due to their family history. Individuals/families at such risk should be referred to a clinical geneticist/genetic counsellor. However, predictive testing will only be an option if the proband has a genomic diagnosis – i.e., a causative variant has been identified by testing. Predictive testing should only be undertaken by clinical geneticists/genetic counsellors.

A proportion of at-risk family members will, after counselling, opt for predictive testing. Without a genetic diagnosis, very limited counselling can be offered to family members who are worried about their risk of inheriting dementia. Prenatal testing for adult-onset disorders is a complicated area, but it is possible to carry out pre-implantation genetic diagnosis for dementia. This raises the question as to whether there is a duty for clinicians to inform individuals that their dementia might have an identifiable genetic cause.

Diagnostic genetic testing is undertaken to make or confirm a specific dementia diagnosis. In the UK context, dementia is included in adult-onset neurodegenerative disorders (R58) in NHS England's national genomic test directory. Psychiatrists are listed as one of the specialties permitted to routinely request the genetic testing panel for dementia/neurodegeneration.

The genetic testing panel for dementia is based on the MRC dementia gene panel, which for selected patients gave a yield of pathological variants of just over 10% (Koriath *et al.*, 2018).

The appropriate tests to request will, of course, depend on the clinical context, but often a combination of tests will be indicated.

The current NHS England criteria for genetic investigation of unexplained dementia are **either** of the following:

- Age at onset <55 years where acquired causes (e.g., stroke, tumour) have been excluded
- Family history of dementia of the same type in a first- or second-degree relative

Assessment for a possible genetic aetiology

Taking a careful family history is fundamental to the identification of individuals who may have a dementia-causing genetic variant. Classically a three-generation pedigree diagram is constructed. However, taking a family history is not a 100% sensitive method of identifying patients for which offering genetic investigation may be appropriate. There are some generic problems associated with obtaining an informative family history, as well as some issues that are dementia- or dementia-subtype-specific.

Given the pleiotropic effects of some of the causative variants – most notably for FTD associated variants – it is important to go beyond memory/dementia phenotypes when taking the family history. For example, it would be important to ask about parkinsonian-like illness and motor neurone disease in the family for someone presenting with FTD.

Information that family history informants might have about their relatives' medical conditions naturally declines as the report goes further back in their family history. However, there is also a cohort effect in the likelihood of positive diagnosis of dementia and subtyping of dementia – with the older generation less likely to receive a diagnosis. Furthermore, rates of diagnosis and subtyping vary by country – with lower rates in low- and middle-income countries (LMIC). In the UK, people from Black and South Asian minority ethnic groups are less likely to report a family history of dementia. There is the potential for this to impact equity in genetic investigation for dementia.

Clinical features suggestive of Down syndrome should trigger consideration of genetic investigation as there are cases in the literature of people with mosaic cases for trisomy 21 being identified in memory/cognitive disorder clinics. As such, cases are likely due to mosaicism, discussion with clinical genetics services is advised.

If the individual does not meet the criteria, but a genetic form of dementia is still suspected, we would advise discussion with clinical genetics/genomics laboratory colleagues.

The British Society of Genomic Medicine provides general guidance on taking of a family history and generating pedigree diagrams

Recommendations

1 **Genetic investigation**
Consider genetic investigation for people with any the following: suspected frontotemporal dementia onset <55 years of age, a family history compatible with a dementia-causing genetic variant, clinical features suggestive of Down Syndrome (mosaic cases), clinical features compatible with rare single-gene forms of dementia. Current research evidence suggests that genetic investigation would identify a causative genetic variant in approximately 10% of selected dementia cases (Koriath et al., 2020).

2 **Risk variants and polygenic risk scores**
We do not recommend genetic testing for dementia risk variants (notably APOE4) or dementia polygenic risk scores.

3 **Establishing local pathways**
Develop local pathways for genetic investigation of dementia to ensure equitable access to appropriate genetic testing. We recommend the establishment of multidisciplinary meetings that include clinical genetics and genetic counselling.

Resources

NHS England

- National genomic test directory: https://www.england.nhs.uk/publication/national-genomic-test-directories/
- Dementia panel: https://panelapp.genomicsengland.co.uk/panels/474/

The British Society of Genomic Medicine

General guidance on the taking of a family history and generating pedigree diagrams: https://www.bsgm.org.uk/healthcare-professionals/taking-and-recording-a-family-history/

Alzheimer's Society

Genetics of dementia factsheet 405LP June 2021: https://www.alzheimers.org.uk/sites/default/files/2019-09/factsheet_genetics_of_dementia.pdf

8: Pharmacogenomics

Pharmacogenomics refers to genetic variation that leads to variability in medication response. This variability relates to both therapeutic effect and adverse reactions. At present, there is a lack of consensus on the effectiveness of pre-therapeutic genotyping in improving clinical outcomes and on the cost-effectiveness of pharmacogenomic testing, with no convincing evidence supporting its use from large-scale clinical trials.

There are a number of existing guidelines related to pharmacogenomics. The International Society of Psychiatric Genetics reviewed the published literature, prescribing guidelines and product labels of psychotropic medications in 2021. Its consensus statement made a number of recommendations for genotyping, but also acknowledged that no robust guidance can yet be made on when or to whom this testing should be offered. The Dutch Pharmacogenetics Working Group also published guidelines for CYP2C29 genotyping before starting escitalopram, citalopram or sertraline, and CYP2D6 genotyping before starting paroxetine.

Two cytochrome P450 genes (*CYP2D6* and *CYP2C19*) are implicated in the metabolism of most psychotropic medications. Genomic characterisation of these pharmacokinetic genes can be used to categorise individuals' enzyme activities, ranging from ultrarapid to poor metabolisers on a scale defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

These enzyme activities reflect the rate at which drugs that are metabolised by these enzymes are cleared from the blood. An inability or failure to account for drug metabolism during treatment can lead to significantly increased rates of adverse reactions. For instance, if standard doses are used in poor metabolisers or a lack of therapeutic effect in the case of ultrarapid metabolisers. Pharmagenomics resource PharmGKB provides a database identifying genotypes associated with differential metabolism and response for many psychiatric drugs, and its guidelines may be helpful to clinicians in terms of dosing in situations where genetic information from the individual to be treated is available. The resource also provides an annotated database of pharmacogenomic drug labelling.

Whilst there is evidence that pharmacogenomic variation in these metabolic enzymes influences rates of response and adverse reactions, there is currently a lack of evidence demonstrating a beneficial impact of pharmacokinetic genomic testing on patient outcomes. Therefore, there is no substantive support for the routine use of such pharmacogenomic testing in clinical care. Although not specific to psychiatric medication, a recent open label implementation study of genotype-guided treatment reported a reduced incidence of clinically relevant adverse drug reactions using a 12-gene pharmacogenetic panel (Swen *et al.*, 2023). Further research on the clinical utility of actionable pharmacogenetic test results is needed before a clear determination on clinical utility can be made.

Research in this area shows promise but significant gaps in research evidence for clinical utility remain. The importance of non-genetic factors in pharmacological metabolism

should also be noted, in particular the impact of other prescribed medications and conditions that may affect metabolism.

Nonetheless, there are specific medications and indications when pharmacogenomic testing is recommended. Such testing aims to prevent severe idiosyncratic adverse reactions (such as Stevens-Johnson syndrome) and is the purpose of testing for human leukocyte antigen genes before prescribing certain mood stabilisers: carbamazepine (HLA-A and HLA-B), oxcarbazepine (HLA-B) and phenytoin (CYP2C9 and HLA-B).

For valproate, screening for certain variants is recommended when a mitochondrial disorder or a urea cycle disorder is suspected (POLG, OTC, CSP1). However, it should be noted that variations in allele (genetic variant) frequencies in a population may have an impact on the utility of the genetic testing in clinical practice. For example, HLA-B alleles present in Han Chinese and other ethnic groups from East Asia confer significantly higher risk of serious cutaneous adverse events when anticonvulsants are prescribed (Cheung et al., 2013). However, a Dutch impact analysis in 2021 concluded that genotyping before prescribing anticonvulsants in predominantly European populations is not cost-effective (Manson et al., 2022).

There has been particular interest in the potential of pharmacogenomic testing for prescription of clozapine, perhaps given it is the only licensed treatment for treatment-resistant schizophrenia and is associated with several serious, although mostly rare, adverse reactions. Whilst recent research has outlined the important part genomic variation plays in clozapine metabolism, the clinical utility of such pharmacogenomic testing has not been adequately examined. Clozapine blood-level monitoring can be effective in guiding clinicians on dosing requirements in individual patients, and whilst additional pharmacogenomic testing could supplement blood-level monitoring, perhaps particularly during dose titration, no additional clinical benefit has yet been demonstrated.

Agranulocytosis is one of the most serious adverse reactions to clozapine and genetic variation contributes to its risk. However, at present there does not appear to be additional benefit beyond mandated regular full blood-count monitoring in identifying these particular genetic variants. The exception is the Duffy-null genotype (ACKR1 gene), which is not associated with agranulocytosis on clozapine, but has been robustly associated with benign ethnic neutropenia (BEN) in people of African and Middle Eastern ancestries (it is vanishingly rare outside of those ancestries) (Legge et al., 2019). Being aware of the presence of this variant may aid diagnosis of BEN and avoid unnecessary exclusion or cessation of clozapine therapy due to low neutrophil levels in this particular patient group.

A further consideration relates to how genetic conditions associated with neuropsychiatric disorders can influence medication response and place individuals at increased risk of adverse reactions from psychotropic medications. Individuals with 22q11 deletion syndrome and schizophrenia respond as well to clozapine as those with schizophrenia due to other causes. However, there is evidence that they disproportionately experience serious adverse events, in particular seizures. This serious adverse event can be avoided by using lower doses of clozapine and prophylactic anticonvulsant medication. This provides an example of how the provision of genetic testing for individuals with

schizophrenia (as recommended in this College Report) has the potential to improve prescribing practice and limit adverse outcomes.

Within the United Kingdom, pharmacogenomic testing is not currently routinely available to NHS mental health services. This is likely to be an area of further development within mental health that will benefit from collaboration and joint working with pharmacists and medical genomics services. At present, clinical genetics tests undergo an NHS test evaluation and validation process. For example, for a genomic test to be funded by NHS England, an application is submitted to the test directory and is then considered by the test evaluation committee. The aim of this process is to promote equity of access and standardisation. All genetics laboratories should be accredited to ISO15189 standards. Clinicians are advised to only use tests that have been through this process, where clinically indicated.

A number of pharmacogenetic tests of relevance to psychiatry are available commercially, with many marketed directly to 'consumers' (patients) and to clinicians. There is a lack of standardisation for these tests, with limited if any evidence for clinical validity or utility.

Recommendations

1 **Pharmocogenomic testing:**
There is currently insufficient evidence of clinical benefit to recommend pharmacogenomic testing for *CYP2D6* and *CYP2C19* (or other genes) in routine prescription of psychotropic medication. A number of guidelines highlight the potential utility of such testing, particularly when prescribing SSRIs, tricyclic antidepressants and some antipsychotics. However, it is not clear when or to whom this testing should be offered in order to achieve therapeutic benefit. In practice, testing should be considered if an individual has had inadequate responses to previous medications, or has experienced marked, dose-associated adverse reactions to similar medications.

2 **Genetic variant testing:**
There is insufficient evidence to currently recommend testing of any genetic variant to predict response to psychiatric medications.

3 **Prescribing mood stabilisers for people of East Asian ancestry:**
Screening for *HLA-A* and *HLA-B* alleles before prescribing certain mood stabilisers (e.g. carbamazepine) is indicated for particular ethnic groups (e.g. East Asian ancestry), but may have limited clinical utility within the wider UK population.

4 **Prescribing clozapine for people of African ancestry:**
Testing to identify the Duffy-null genotype in individuals of African ancestry should be considered in those starting or already taking clozapine, particularly where neutropenia may otherwise limit access to clozapine treatment. Duffy-null genotype testing does not circumvent the need to follow mandated blood monitoring protocols and haematology consultation, which is required for the diagnosis of benign ethnic neutropenia.

Resources

Information for clinicians:

- **Association for Clinical Genomic Science**
  Best practice guidelines
  https://www.acgs.uk.com/quality/best-practice-guidelines/
- **Clinical Pharmacogenetics Implementation Consortium (CPIC)**
  Creates, curates, and posts freely available, peer-reviewed, evidence-based and detailed gene/drug clinical practice guidelines
  https://cpicpgx.org/
- **GeneReviews**
  Provides information about inherited conditions in a standardised journal-style format, covering diagnosis, management, and genetic counselling for patients and their families
  https://www.ncbi.nlm.nih.gov/books/NBK1116
- **International Society of Psychiatric Genetics**
  Statement on Genetic testing and psychiatric disorders
  https://ispg.net/genetic-testing-statement/
- **MedlinePlus**
  A service of the US's National Library of Medicine, which is part of the National Institute of Health) provides information about the effects of genetic variation on human health
  https://medlineplus.gov/genetics
- **Online Mendelian Inheritance in Man database (OMIM):**
  A catalogue of human genes and genetic disorders
  https://omim.org/
- **PharmGKB**
  Provides a database identifying genotypes associated with differential metabolism and response for many psychiatric drugs, and an annotated database of pharmacogenomic drug labelling
  https://www.pharmgkb.org/
- **Society for the Study of Behavioural Phenotypes**
  Syndrome information sheets
  https://ssbp.org.uk/syndrome-sheets/

Support groups:

- **Genetic Alliance UK**
  A national charity working to ensure that the needs and preferences of all people affected by genetic, rare and undiagnosed conditions are recognised, understood and met
  https://geneticalliance.org.uk/
- **Rare Disease UK**
  A campaign by Genetic Alliance UK, working to raise the profile of rare diseases across the UK
  http://www.raredisease.org.uk/
- **Unique**
  Support, information and networking for families affected by rare chromosome and gene disorders
  http://www.rarechromo.org/

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Appendix

Exemplar service design and delivery of genetic testing

The All Wales Psychiatric Genomics Service (AWPGS)

Background

Our service has been developed over the last five years, building on expertise and synergies between the Welsh NHS (Cardiff and Vale UHB Mental Health Services, All Wales Medical Genomics Service) and local clinical academic expertise (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University).

The service began with a regular multidisciplinary team (MDT) meeting with representatives from psychiatry (adult, learning disability, CAMHS), medicine and medical genomics (clinical geneticists, community paediatrics, genetic counsellors, laboratory clinical scientists, pharmacists) and academic researchers (psychiatric genetics and social scientists).

The MDT carried out case discussions, as well as wider considerations of gaps in service provision of genetic counselling and testing for those with psychiatric disorders, as well as a lack of support for psychiatric assessment and mental healthcare provision for those with relevant genetic diagnoses, informed through discussion and consultation of patients and families with lived experience.

Based on these discussions, the group developed a business case that was supported by Genomics Partnership Wales (GPW). In 2021, funding was provided to set up and pilot a new psychiatric genomics clinical service aligned with the Welsh Government's Genomics for Precision Medicine Strategy. Funding was fixed term for 18 months, and extensive support was provided through Cardiff University.

Our funding provided support for:

- a principal genetic counsellor (full time)
- administrative support (full time)
- Support for service set up including patient and public outreach and website development
- academic consultant psychiatrist (2 sessions)
- consultant geneticist (2 sessions)
- copy number variant (CNV) genetic testing and bioinformatics support for test result interpretation

GPW has recently agreed to a further 12 months of funding, and we are drawing up a business case for permanent financing from the Welsh Government.

Aims

The AWPGS aims to provide:

- access to genomic advice and information for individuals, families and healthcare professionals who have questions about genomic susceptibility to mental ill health
- a safe, high-quality service through a framework of co-production, multi-disciplinary working, education and training.

The AWPGS multidisciplinary team

The AWPGS is set on a foundation of partnership working between clinical, academic and scientific partners. The service benefits from dedicated input from clinical academic psychiatry through the Centre for Neuropsychiatric Genetics and Genomics and the National Centre for Mental Health at Cardiff University, and clinical and laboratory genetics via the All Wales Medical Genomics Service.

The service is underpinned by a monthly MDT meeting, which provides a forum for clinical discussion, laboratory testing options and test results. In addition, meetings act as education settings – both for clinical and laboratory trainees and for stakeholders across Wales via an 'open-door' policy.

Services outside of Wales, namely in Scotland and England, have consulted us for specialist advice, and we have supported requests from clinical genetics colleagues in England to attend our MDT meetings.

The service we provide

The AWPGS transforms genomic knowledge into personalised care for individuals and families with questions about genetic susceptibility to mental illness and neurodevelopmental conditions. Our referral criteria and forms are on our website.

Our clinics are run every two weeks, with access to a genetic counsellor, clinical geneticist and psychiatrist. The team also offers consultations with mental health teams to support mainstreaming genomic testing as appropriate. We have also engaged with mental health services throughout Wales to provide education on psychiatric genomics and the AWPGS and shared our learning internationally, providing updates on the service via conference presentations and posters.

Future plans

We plan to:

- secure long-term funding for the AWPGS
- extend our service to support young people with questions about genetic susceptibility to mental illness and neurodevelopmental conditions, with the support of child and adolescent mental health services
- conduct a clinical feasibility study of whole genome sequencing in individuals with psychiatric disorders