Genetic testing in dementia — utility and clinical strategies

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Abstract | Techniques for clinical genetic testing in dementia disorders have advanced rapidly but remain to be more widely implemented in practice. A positive genetic test offers a precise molecular diagnosis, can help members of an affected family to determine personal risk, provides a basis for reproductive choices and can offer options for clinical trials. The likelihood of identifying a specific genetic cause of dementia depends on the clinical condition, the age at onset and family history. Attempts to match phenotypes to single genes are mostly inadvisable owing to clinical overlap between the dementias, genetic heterogeneity, pleiotropy and concurrent mutations. Currently, the appropriate genetic test in most cases of dementia is a next-generation sequencing gene panel, though some conditions necessitate specific types of test such as repeat expansion testing. Whole-exome and whole-genome sequencing are becoming financially feasible but raise or exacerbate complex issues such as variants of uncertain significance, secondary findings and the potential for re-analysis in light of new information. However, the capacity for data analysis and counselling is already restricting the provision of genetic testing. Patients and their relatives need to be given reliable information to enable them to make informed choices about tests, treatments and data sharing; the ability of patients with dementia to make decisions must be considered when providing this information.

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Neurodegenerative diseases account for most cases of dementia worldwide. Some of these diseases are common, for example, Alzheimer disease (AD), whereas others are less common or rare, such as frontotemporal dementia (FTD) and prion diseases; however, they all involve progressive accumulation of abnormal forms of brain proteins, a process that can begin more than a decade before neuronal damage is detectable[1–3]. Biofluid and imaging biomarkers of these processes are available but use of these tests in clinical practice is currently prompted by the development of symptoms, by which time molecular pathologies are often already widespread in the brain. Similarly, clinical trials have largely involved patients with dementia who already have advanced pathologies, which could be a hindrance to the discovery of disease-modifying treatments — evidence from animal and clinical studies suggests that disease-modifying treatments, when discovered, will work better if given earlier in the disease course[3–5].

Sporadic neurodegenerative dementias generally occur in old age[6] and are highly polygenic[7]. However, a proportion of neurodegenerative dementias are Mendelian, providing an opportunity to make a precise diagnosis in the very early stages of disease and to identify pre-symptomatic carriers of causal mutations. These familial forms of dementia are being leveraged to study potential pharmacological therapies that have been developed based on the pathophysiological mechanisms revealed by the genetic causes. Trials of approaches such as amyloid-β antibody therapy in AD[8], *GRN* replacement in FTD[9] and gene-silencing in Huntington disease (HD)[4] offer hope to patients and could improve our understanding of disease mechanisms.

Genetic testing to identify individuals with causative mutations is essential for trials of therapies in Mendelian dementias. However, the justification for genetic testing in a clinical context is less obvious given the absence of proven disease-modifying therapies. Advances in testing technologies and changes in public awareness have created several areas of uncertainty around when to offer testing and how best to do so[10,11]. In this Review, we consider the currently available genetic technologies and their potential use in neurodegenerative dementias as well as the strengths and weaknesses of each. We discuss the clinical presentations of dementia and how their differences and pathological associations determine the most appropriate form of testing. We also explore the universal challenges of clinical genomics,

Key points

- For typical dementia, the most appropriate genetic test is usually a gene panel and *C9orf72* expansion testing, which balances the likelihood of discovery with costs and minimizes variants of uncertain significance.
- Single-gene tests are warranted in specific situations, including typical Huntington disease, prion disease or to confirm a known familial mutation; atypical syndromes can necessitate whole-exome sequencing (WES) or whole-genome sequencing (WGS) and *C9orf72* expansion testing.
- Discovery rates with WES and WGS are similar to those with gene panels, but WES and WGS data can be re-analysed when new information becomes available.
- The uptake of predictive testing is currently low but could increase as treatment options become available because patients with a genetic diagnosis are good candidates for disease-modifying drug trials.
- Additional tests are currently required to detect repeat expansions, but long-read sequencing will enable simultaneous testing for SNPs and repeat expansions once it becomes sufficiently reliable and accurate.
- Genetic testing requires counselling on variants of uncertain significance, secondary findings and implications for relatives; in dementia disorders, mental capacity is an important consideration.

including variants of uncertain significance and secondary findings, the duty to update findings based on new discoveries, the ethics of consent, and the rights of relatives. We focus on Mendelian forms of dementia because the use of common risk variants, either alone or in polygenic risk scores, is not yet established in clinical practice. Specifically, we focus on Mendelian forms of AD and FTD as the typical forms of dementia but also discuss atypical parkinsonian syndromes (which partially overlap with FTD) and rarer causes of dementia, including prion disease and HD, which warrant a different approach to testing; we have not expanded on vascular dementia and dementia with Lewy bodies, for which few specific genetic factors are known[12,13].

Sequencing technologies and their use

Genetic testing is currently underused in clinical practice and there is considerable geographical variability in its use, both internationally and within countries[14,15]. Nevertheless, the increasing availability of genetic testing and the growing knowledge about the genes and pathways implicated in dementia are transforming diagnostic genetic testing from a niche technique to a mainstream clinical tool.

Gene panel testing

The most important recent development in the methodology for gene testing is the capability to sequence multiple genes simultaneously using so-called next-generation sequencing (NGS). The most common application of NGS in diagnostic genetic testing is the use of gene panels — targeted sequencing of a set of genes with similar associated clinical phenotypes, often including rarer causes of disease (TABLE 1). Most laboratories use focused gene panels, either by sequencing amplicon-selected regions of interest or by performing whole-exome sequencing (WES)[16] or whole-genome sequencing (WGS) and subsequently restricting their analysis to genes that are selected on the basis of the referral diagnosis. A dementia gene panel includes most genes linked to the phenotype; that is, the AD genes *APP*, *PSEN1* and *PSEN2* and the canonical FTD genes *GRN* and *MAPT*, but also genes associated with rarer causes of familial dementia and leukoencephalopathy[17].

WES and WGS

NGS techniques include WES and WGS[18] (TABLE 1). The exome is the 1% of the genome that comprises all human exons, that is, the DNA that is transcribed to produce mature mRNA. The exome is thought to contain the vast majority of mutations that cause inherited human disease[19]. The costs of WES and WGS have been falling rapidly, making these techniques financially feasible clinical testing methods. WES and WGS are particularly useful for highly heterogeneous disorders[16,20]. Compared with the use of targeted gene panels, WES and particularly WGS can reduce bias and increase diagnostic capabilities; for example, these approaches can detect structural variations, such as duplications, deletions, insertions and inversions of DNA, and enable data re-analysis should new clinical information become available or a new gene–disease association be discovered. They also make novel gene discovery possible.

Despite their benefits, some problems exist with WES and WGS. Both are still substantially more expensive than gene panels, especially the analysis and storage of large amounts of data. They can also raise the issue of incidental findings in genes that are unrelated to the suspected disease[21,22]. These issues are exacerbated with WGS, which is more expensive than WES and generates ~100-fold more data. Nonetheless, WGS offers the advantage of interrogating not only the exome but also non-coding regions, such as splice sites, promoters and regulatory sequences, where an increasing number of pathogenic mutations are now being identified[20,23–25]. In addition, WGS provides more homogeneous coverage with more accurate genotyping, is less susceptible to allelic drop out and identifies more variants[26,27]. Reported rates of diagnosis with the use of WES are >25% for neurological disease[20,28–30]; this rate is likely to be higher with the use of WGS[31].

Overcoming the limitations of NGS

The existing NGS techniques excel at detecting SNPs and small insertions and deletions. However, as a result of sequence assembly by aligning overlapping fragments with a reference genome, the detection of larger deletions and insertions, copy number variants, and tandem repeat disorders is hampered by the achievable read length in standard WGS, as is the recognition of structural variants if their breakpoints are located in a repeat region[32,33] (BOX 1). Tools for the detection of copy number variants perform poorly with WES data and, therefore, other methods should be employed for the detection of these variants[34]. Bioinformatics analysis methods have been developed to overcome these difficulties with some success, especially with data from modern PCR-free WGS or from paired-read sequencing[35–37], but these methods are not yet reliable enough to be used on a larger scale or in a clinical setting[36]. Fragment analysis, repeat prime PCR and Southern blotting (TABLE 1) are still needed to confirm the presence of expansions and their size.

Allelic drop out
Failure to amplify one or both alleles during a sequencing reaction.

Breakpoints
Limits or borders of a structural variant where they link to the surrounding normal genomic sequence.

Paired-read sequencing
The process of sequencing a genomic fragment using adapters to both ends of the fragment, which improves reference sequence alignment and facilitates the analysis of repetitive regions.

Table 1 | **Methods of gene testing**

Method	Technology	Advantages	Disadvantages
Single-gene testing			
Sanger sequencing	PCR generates sequences of different lengths with terminal dideoxynucleotides, which are then separated with capillary electrophoresis	High accuracy for SNPs; gold standard for confirmatory testing	Labour intensive, slow and expensive on a large scale; unsuitable for the detection of complex variants such as copy number variants, insertions and deletions
Fragment analysis	Repeat-primed PCR produces fragments of a repeat region, enabling the sizes of DNA fragments from the region, including pathogenic lengths, to be plotted	Can detect nucleotide repeat expansions even when extremely large and intractable to simple PCR-based approaches	Labour intensive; not suitable for the detection of smaller variants
Southern blot	Oligonucleotide probes that match a repeat expansion are hybridized to target DNA fragments, washed, separated by electrophoresis and visualized by incorporating radioactivity or with a luminescent dye	Can detect and approximate the size of nucleotide repeat expansions, even when very large	Labour intensive; not suitable for the detection of smaller variants
Multiple gene testing			
Targeted gene panels	PCR amplicons of interest are selected using primers and combined into a sample library, which is amplified further, sequenced and read on the sequencing platform; sequences are assembled by aligning to a reference genome	Targets genes relevant to a phenotype, including rarer causes; cheap and easy to analyse; high accuracy for SNP detection and small insertions and deletions; can cover several related conditions (for example, AD and FTD)	Mostly only suitable for conditions for which most cases are caused by a limited number of genes; not suitable for repeat disorders or copy number variants; newly discovered genes can only be incorporated after a delay
Whole-exome sequencing	Similar to targeted gene panels but selected amplicons cover all transcribed regions; samples are sequenced on a high-throughput platform and sequences assembled to a reference genome	High benefit–cost ratio; coverage approaches that of gene panels[146]; high accuracy for SNPs and small insertions and deletions; useful in heterogeneous disorders; reduced bias; enables exon-based re-analysis if new information becomes available	Risk of incidental findings in unrelated genes[21,22]
Whole-genome sequencing	Usually amplicon-based but genome can be sheared into fragments instead of PCR step; sequenced on the same platforms as whole-exome sequencing and sequences are assembled to a reference genome[147]	High accuracy for SNPs and small insertions and deletions; particularly useful for heterogeneous disorders; little bias; enables re-analysis if new information becomes available; PCR-free sequencing enables the detection of copy number variants	High cost, especially with higher coverage; risk of incidental findings in unrelated genes[148,149]
Pacific Biosciences' (PacBio) single-molecule real-time sequencing (long-read)	Zero-mode waveguide used to create a single-nucleotide observation space with a DNA template and a polymerase; each time a nucleotide is incorporated, the zero-mode waveguide detects the change in fluorescence related to the addition of a single nucleotide	Can achieve read lengths of several thousand base pairs so can detect complex variants and tandem repeats; the best method to date for sequencing through repeat expansions	Not as accurate as existing platforms for the detection of SNPs; expensive
Oxford Nanopore Technologies (ONT) sequencing (long-read)	Protein nanopores are set in an electrically resistant membrane, through which an ionic current is passed, creating a constant voltage; as the DNA strand passes through the pore, each nucleotide creates a distinct change in current	Can achieve read lengths of several thousand base pairs so can detect complex variants and tandem repeats; sequencing device is small, cheap, portable and can be scaled up	Not as accurate as existing platforms for the detection of SNPs

AD, Alzheimer disease; FTD, frontotemporal dementia.

Long-read sequencing platforms have been developed in an attempt to overcome the limitations of current NGS[38] (TABLE 1). The read lengths of typical NGS platforms peak at several hundred base pairs, whereas long-read sequencing platforms can reach several thousand base pairs and sequence, at least partially, through long nucleotide repeat expansions[38]. However, these platforms cannot yet match the accuracy and reliability of more established platforms for the detection of SNPs[39,40].

Towards mainstream genetic medicine

The availability of genetic testing in mainstream clinical practice is increasing but varies between countries. In the UK, links between the National Health Service (NHS) and research laboratories have enabled relatively easy access to genetic testing compared with other countries, where the need for insurance funding or the limited availability of genetics services can make testing inaccessible to many. Supporting equity of access in the UK is the NHS Genomic Test Directory[41], a publicly available

Box 1 | **Limits of short-read sequencing**

Current clinically used next-generation sequencing platforms depend on DNA reading by sequencing and automated detection of light as nucleotides are incorporated. Typically, sequenced fragments reach several hundred base pairs before the DNA polymerase detaches. The complete sequence is then assembled from these fragments by matching regions that overlap. Tandem repeats are, by nature, highly repetitive and repeat expansions consequently render the fragment assembly virtually impossible because the position of each fragment cannot be determined. This limitation prevents the detection of repeat expansions, especially if they are novel; it also limits the identification of breakpoints for structural variants if they fall into a repetitive region. Paired-read sequencing compensates for these limitations to some extent but cannot yet detect repeat expansions reliably enough for clinical use.

list of tests, their indications and of who can access them. The available tests were previously restricted to single-gene tests or gene panels because WES and WGS were unjustifiably expensive; however, these tests are now also being implemented. Indeed, in neonatal and paediatric intensive care, rapid WGS has already been implemented in the UK. The turnaround time is ~1 week and the rate of molecular diagnosis is 42%[42] — this approach is transforming clinical care and illustrates what future care could look like in other specialties.

If parent–child trios are not available — as is usually the case with dementia, where the age of onset is late — the diagnostic rate of WES in adult simplex cases (across specialities) is typically 20–25%[43]. A similar diagnostic rate (22.1%) has been achieved with the use of a targeted dementia panel that covered 17 genes and was supplemented with PCR-based tests of the *C9orf72* expansion and *PRNP* octapeptide repeat alteration in a mixed referral-based cohort with dementia (AD, FTD and prion disease)[23]. However, the potential for later re-analysis with WES and WGS as new information about genes and variants of uncertain significance becomes available is not to be underestimated. For these reasons, many laboratories worldwide have moved to the use of targeted WES-based panels, for which all genes are sequenced but only those associated with the conditions of interest are analysed. A similar approach with WGS could now be used for early-onset and familial dementia and other neurological disorders.

Analysis of genome sequencing data is demanding — variants in known causative genes (for example, a dementia gene panel) need to be identified and interpreted and copy number variations and repeat expansions need to be assessed. When a patient's phenotype is ambiguous and genetic findings are unusual, multidisciplinary clinical and diagnostic teams can be beneficial because additional clinical phenotypic details can confirm the diagnosis or indicate additional genes to examine; for example, leukodystrophy on MRI indicates the analysis of a leukodystrophy panel or a history of recessive inheritance in the family could substantiate an ambiguous homozygous mutation. Similarly, recruitment of additional unaffected and affected family members could increase the genetic yield by allowing segregation analysis of variants.

As dementia genetics advances, new technologies, such as long-read sequencing, will need to be incorporated into the diagnostic testing protocol to more effectively identify and determine the size of copy number variants and repeat expansions. Another important need is an international database of variants and mutations in patients with dementia and controls of different ethnicities. This information is particularly important because parent–child trios are rarely available for testing. As a result, online population databases, such as gnomAD, have been critical in judging the pathogenicity of variants[44,45]. As the size and content of such databases increase, so will their utility and statistical power. Given that most probands whose genetic data constitutes these databases are tested in early and middle-aged adulthood, pathogenic variants in Mendelian dementia will, unlike those in rare paediatric diseases, inevitably end up in population databases because of the typically late age of onset and the possibility that penetrance of these variants is low. The disease prevalence and frequency of a given variant in patients and in the population therefore need to be considered when judging its likely pathogenicity[45]; consequently, greater statistical power of patient and population databases contributes enormously to variant classification.

Who to test and which test to use

In the past 20 years, the number of genes known to cause dementia has increased considerably (revealing the genetic heterogeneity) as has our understanding that a spectrum of phenotypes can result from the same or different mutations in the same gene (pleiotropy) and of the clinical overlap between different dementia syndromes. For these reasons, different types of genetic testing are needed depending on the clinical phenotype, whether a genetic, clinical or pathological diagnosis has been made in a relative, whether biomarkers of molecular pathology are available, and on the number of implicated genes and the type of mutation expected (TABLE 2).

Patients with dementia (or potentially with antecedent syndromes or focal cognitive disorders) should be offered a full diagnostic assessment to determine their likely clinical diagnosis. This assessment should include a detailed neurological examination and a multi-generation family history that can indicate the likelihood of an autosomal dominant trait with the use of, for example, the modified Goldman score[23,46,47] (BOX 2) — in our experience, this score strongly predicts the likelihood of finding a genetic explanation for the disease[23]. An important pitfall to avoid is mistaking an incomplete family history or a history that includes unrelated early deaths for a negative history, although even a negative family history does not preclude a genetic diagnosis. In a clinical diagnosis referral series of patients with a censored or negative family history but in whom the prior expectation of a pathogenic variant was high, the discovery rate was 3.5% in AD, 8.6% in FTD and 10.7% in prion disease[23]. The lack of a family history in these patients could be due to factors such as the difficulty of accurate diagnosis, misdiagnosis, or early deaths from

Segregation analysis
Genetic analysis of affected and unaffected members of a family for their carrier status with regards to a particular genetic variant.

Anticipation
A phenomenon in which age at onset decreases and the severity of the phenotype increases from one generation to the next in some genetic diseases; typical of some trinucleotide repeat disorders in which the number of repeats is linked to the age at onset and the severity of disease.

other causes in previous generations and/or anticipation in some diseases. On this basis, a genetic test might be warranted even with a negative family history[48]; for example, this could be the case for patients with an early age at onset, a particular clinical syndrome that has a high rate of genetic causes, or a family history with likely diagnostic uncertainty owing to historical or geographical factors. Symptoms of other family members can also add to the diagnostic picture and enable testing and diagnosis earlier in the course of the disease[49].

Historically, predictive testing of unaffected relatives has not been recommended in the absence of a known familial mutation, particularly for conditions that have genetic and non-genetic or polygenic aetiologies. However, in conditions for which preventive action can be taken, such as breast cancer, testing of unaffected individuals is sometimes offered if the family history strongly suggests a monogenic aetiology. Such testing cannot rule out a genetic cause yet a negative test reduces the likelihood, although the absolute risk reduction for an individual is hard to quantify. Similar strategies are likely to become more appropriate in dementia in the future, particularly if progress is made in the development of preventive therapeutics.

Testing for specific point mutations and small insertions or deletions that cause frameshifts or in-frame protein changes is highly reliable. However, testing one gene in a diagnostic setting is only really suitable for disorders with highly distinctive clinical presentations, such as HD and prion disease, because the odds of detecting a causal variant are otherwise low. Furthermore, clinical overlap and pleiotropy mean that a clinical diagnosis does not reliably correspond to the expected genetic cause and vice versa (FIG. 1). In addition, even if single-gene testing identifies a causal mutation, it cannot detect concurrent mutations, which are found notably more often in FTD than expected by chance[23,50–52]. Moreover, synergistic effects between novel variants and those that have not been unequivocally proven as deleterious variants can also lead to disease[53]. A computer algorithm has been developed to partially automate the assessment of such double variants[54], but tools like these have not yet been evaluated for their clinical utility. Other than for confirmatory testing, single-gene testing is therefore not recommended in AD or FTD.

We suggest the introduction of dementia gene panel testing into routine neurological, psychiatric and geriatric care whenever a genetic cause could be plausible. Routine testing will increase the number of patients with a definite genetic diagnosis and will identify family members who are at risk, who would then be eligible for targeted treatment as and when it becomes available. A definitive genetic diagnosis can also reduce the number of other diagnostic investigations required and enable the optimization of care and treatment. Changes in practice require new skills, can raise anxieties in patients and affected families, and increase direct costs and the need for counselling. A prospective evaluation of different strategies — perhaps a randomized trial of gene panel testing versus standard care — might be useful to establish the benefits or harms of a change in strategy.

Alzheimer disease

AD, both early onset (before age 65 years)[55] and late onset, is the most common cause of dementia. AD is often used as a default diagnosis for patients with dementia; therefore, a family history of AD should be treated cautiously if not yet confirmed with a biomarker or by pathology. Genetic testing is useful for the diagnosis of autosomal dominant AD but is not useful for sporadic AD, which has a mixed aetiology involving multiple risk variants. The prevalence of autosomal dominant AD is not firmly established but it probably accounts for <1% of all cases[56]. Determining when and who to test for this condition requires an understanding of its clinical and genetic heterogeneity.

Autosomal dominant AD. Autosomal dominant AD is typically an early-onset disease with onset in the fourth to sixth decades of life. The most common causes are mutations in *PSEN1*, *PSEN2*, and *APP* and duplication of *APP*; *PSEN1* mutations are the most common. The mean

Table 2 | **Mutation types found in different forms of dementia**

Mutation type	Examples	Possible mechanism of effect
SNP	Missense mutations in *APP*, *PSEN1* and *PSEN2* cause AD	Increased production or amyloidogenicity of amyloid-β peptides[150]
Small insertions and deletions	Insertions and deletions in *PSEN1* cause AD	Increased production or amyloidogenicity of amyloid-β peptides[150]
Large exon deletions, insertions, duplications and copy number variants	*APP* duplication (including trisomy 21) causes AD	Increased expression of amyloid-β peptides[151]
Splice-site mutations	Splice-site mutations in *GRN* and *MAPT* cause FTD	Loss of *GRN* function[130]; differential splicing of *MAPT* causes an imbalance between 3-repeat and 4-repeat tau[25]
Repeat expansions	CAG expansion in *HTT* causes HD and GGGGCC repeat expansion in *C9orf72* causes FTD, ALS and HD-like syndromes	Gain-of-function of *HTT*[114,152]; gain-of-function or possibly loss-of-function of *C9orf72* (REF.[153])
Chromosomal region inversions	Genomic inversion of *MAPT* is a risk factor (with low penetrance) for tangle-dominant dementia[154]	Causes formation of extracellular 3-repeat and 4-repeat tau tangles[155]

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; HD, Huntington disease.

Box 2 | **The modified Goldman score**

The modified Goldman score enables the stratification of a family history based on the number of a patient's relatives who are or were affected. The score strongly correlates with the likelihood of identifying a causal mutation[93]. A modified Goldman score of 1 corresponds to a family history consistent with the proband's clinical syndrome with an autosomal dominant inheritance pattern, with at least three people who are affected in two generations and who are linked by a first-degree relative. A modified Goldman score of 2 indicates familial aggregation of three or more affected relatives but without meeting the criteria for a score of 1. A modified Goldman score of 3 denotes one other affected relative (the score is 3 if the age of onset is <65 years or 3.5 if the age at onset is >65 years). A modified Goldman score of 4 signifies no known family history of neurodegenerative disease[93].

age of onset is younger among people with *PSEN1* mutations than among those with *APP* mutations; *PSEN2* mutations are relatively rare and are associated with a somewhat later age of onset[57]. Nevertheless, mutations in each of the causative genes can cause disease with an age of onset >60 years. The age of onset is relatively consistent within families and correlates with parental age of onset and the mean age of onset associated with the specific mutation[57]; nevertheless, the age of onset can vary between families with the same mutation[58]. A reduced penetrance of mutations that cause autosomal dominant AD has been reported[59–61], which indicates the existence of other, currently unknown, modifiers.

As with sporadic AD, most patients with autosomal dominant AD present with progressive memory impairment. However, this typical amnestic syndrome can also be caused by non-AD genetic dementias such as FTD due to *MAPT* mutations (with matching medial temporal lobe atrophy on MRI, mimicking AD[62]) or inherited prion disease caused by, for example, octapeptide repeat insertions in *PRNP*[63]. Indeed, in a study in 2018 among patients with a clinical diagnosis of AD who had or were likely to have a deleterious variant, genetic causes that are not associated with AD were found in >30% of patients; affected genes included *MAPT*, *GRN*, *VCP*, *CSF1R*, *PRNP*, *SQSTM1*, *TARDBP* and *C9orf72* (REF.[23]). Conversely, atypical presentations of autosomal dominant AD can occur, so that patients with mutations that cause AD receive clinical diagnoses other than AD; for example, *PSEN1* mutations have been identified in patients who have been diagnosed with FTD, prion disease and dementia–motor syndromes[23,64,65]. Interestingly, the posterior cortical atrophy variant of AD, which involves progressive impairment of higher visual processing, has a young age of onset but is almost invariably a sporadic condition[66–68] and has only rarely been reported as possible autosomal dominant AD (a novel *PSEN1* variant)[69].

Considerable clinical phenotype heterogeneity also exists in autosomal dominant AD, influenced by the affected gene, the specific variant and the affected functional domains. People with *PSEN1* mutations can develop atypical cognitive deficits, including initial behavioural changes, language impairment, dyscalculia or a dysexecutive phenotype[66], and *PSEN2* mutations can lead to early delusions and hallucinations[70]. Motor symptoms, including spastic paraparesis and extrapyramidal and cerebellar signs, have been associated with mutations in *PSEN1* but not in *APP*[71]. These atypical presentations as well as later age at onset, more white matter hyperintensities on MRI and more severe cerebral amyloid angiopathy, are associated with *PSEN1* mutations beyond codon 200 (REFS[66,72–75]). *APP* duplications and mutations within the amyloid-β coding domain can also lead to particularly severe cerebral amyloid angiopathy, recurrent cerebral haemorrhages, focal neurological symptoms and seizures[76,77]. Seizures can be an early feature of all autosomal dominant AD — approximately one-third of patients have a first seizure in the first 5 years of their illness, often preceded by myoclonus — but seizures tend to occur earliest in patients with *APP* duplications and later in those with *PSEN1*, *PSEN2* and *APP* mutations[66,78].

Testing for autosomal dominant AD. Given the wide phenotypic heterogeneity of autosomal dominant AD and the diversity of genes that can underlie the condition[23], targeted gene panels, WES or WGS are the most appropriate choice for genetic testing in this context. Greater use of gene panels to investigate dementia in an unbiased manner is likely to make the breadth of the clinical phenotype of autosomal dominant AD more apparent.

We recommend offering genetic testing to patients with AD who have a strong family history of dementia (modified Goldman score 1–2), regardless of the age of onset, and to patients with an age of onset <60 years. We consider genetic testing for patients of all ages who have a modified Goldman score of 3 and for those with an age of onset of between 60 and 65 years, depending on individual patient factors, such as relatives with other neurodegenerative diseases or family histories that are limited owing to small family sizes, unrelated early deaths and geographical limits of communication.

This approach of positively weighting a relevant family history and early age at onset is based on data from 2018, in which 17% of deleterious variants identified in patients with AD were in patients with an age of onset of ≥65 years. Of these patients, 42% had a relevant family history and the rest had an incomplete family history. By comparison, 50% of patients with an age of onset of between 60 and 65 years had a relevant family history[23].

***Risk loci and* APOE.** In addition to the autosomal dominant mutations that make the development of AD almost inevitable, more than 30 genetic loci are known to modestly increase the risk of AD[79–82]. Each of these risk loci alone increases the risk only slightly but, when combined with demographic factors, they can predict a diagnosis of AD with accuracies of over two-thirds[83]. The most well-known risk locus for sporadic AD, which also contributes most of the risk, is *APOE*, which encodes apolipoprotein E (ApoE). Three isoforms of ApoE exist: ε2, ε3 and ε4 (REFS[84,85]). Possession of an ε2 allele protects against AD and ε4 confers risk. The estimated risk conferred by an ε4 allele varies between studies and ethnic

groups but reported odds ratios are 1.8–9.9 (REFS[86–89]), and, according to one study, people who are homozygous for the ε4 allele have an odds ratio of 17–59 compared with those who are homozygous for the ε3 allele[90].

Despite the associated increase in risk, the ε4 allele is neither necessary nor sufficient to cause AD, and therefore clinical genetic testing for *APOE* or other risk loci genotypes is not recommended. Nevertheless, some direct-to-consumer genetic testing companies offer *APOE* genotyping, usually with limited or no pre-test explanation of the implications of the different results and no support or follow-up. This practice has caused considerable concern within the medical community, not least because individuals who have identified themselves as being at risk of AD are increasingly being referred to clinics where such testing is not performed. Aside from recommending standard lifestyle modifications to reduce the overall risk of dementia and providing information about recruitment to research studies, no specific recommendations can be made to individuals who are positive for *APOE* ε4. Guidelines for counselling and disclosure of *APOE* testing results in the context of clinical trials are currently being considered[91].

Frontotemporal dementia

FTD is a heterogeneous disorder that encompasses multiple clinical and pathological conditions[92]. Approximately 30% of FTD is familial and most genetic causes are autosomal dominant[93,94]. Since Mendelian mutations in the *MAPT* gene were discovered to cause FTD in 1998 (REFS[95–97]) (common variants in *MAPT* are associated with AD), mutations in multiple genes have been associated with FTD. Only two others are common causes of genetic FTD: mutations in *GRN* and hexanucleotide expansions in *C9orf72* (REF.[97]). Mutations in other genes, including *TBK1*, *VCP*, *CHMP2B*, *FUS*, *SQSTM1*, *TARDBP*, *CHCHD10*, *TIA1* and *CCNF*, are rare causes of FTD[97].

Each causal gene is associated with different clinical phenotypes, including each of the canonical FTD syndromes (behavioural variant FTD (bvFTD) and the primary progressive aphasias (PPAs)), the FTD spectrum disorders (amyotrophic lateral sclerosis (ALS), corticobasal syndrome[98] and progressive supranuclear palsy) and non-FTD disorders, including AD-like, Parkinson disease-like and HD-like phenotypes[99]. For example, ALS and FTD–ALS are associated with

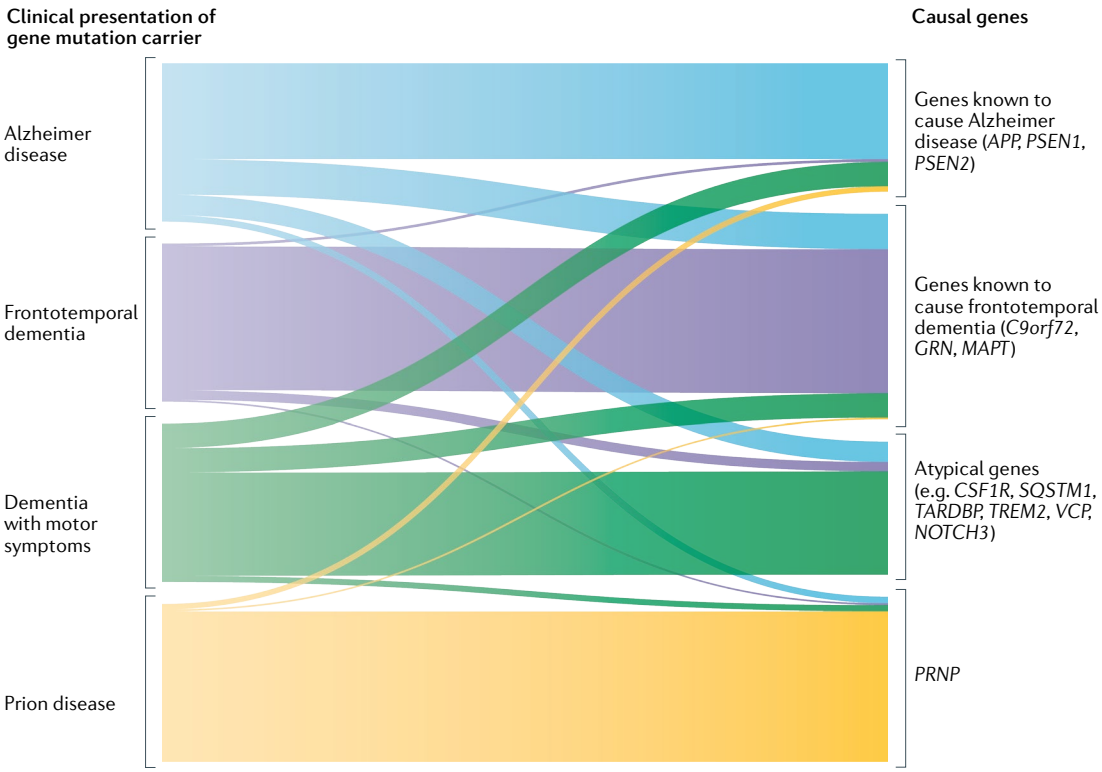

Fig. 1 | **Diagnostic uncertainty and pleiotropy in dementia.** Among patients with each clinical presentation of dementia (left column), a proportion have deleterious variants in genes normally associated with other diseases (right column); the lines shown indicate the crossover and their thicknesses are correlated to the proportion of patients in each group that carry deleterious variants in each gene category. Alzheimer disease can often be used as a default or provisional diagnosis for patients with dementia, so a proportion of patients with a clinical diagnosis of AD and genetic aetiology have gene mutations that are typically associated with other disorders. Frontotemporal dementia encompasses diverse clinical presentations and can consequently be mistaken for other dementia disorders. Dementia with motor symptoms, which encompasses atypical dementia syndromes with additional hypokinetic or hyperkinetic motor symptoms that are not caused by Huntington disease, can be difficult to diagnose and classify and have diverse genetic causes. For prion diseases, diagnostic rates for single-gene tests are consistently high. Atypical genes are genes that have been linked to dementias but are uncommon causes or cause additional features. Adapted from REF.[23], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

C9orf72 expansions rather than with *GRN* or *MAPT* mutations, whereas PPA is more commonly associated with *GRN* mutations; other associations are more subtle. Cognitive profiles differ according to whether *GRN*, *MAPT* or *C9orf72* are affected. *GRN* mutations are associated with poor and rapidly worsening attention, *MAPT* mutations are associated with impaired memory function, and *C9orf72* expansions are associated with global but relatively stable cognitive impairment[98]. Age at onset can be any time from adolescence and varies in all genetic forms; in FTD with *GRN* mutations or *C9orf72* expansions, onset in family members can differ by >20 years[99]. The heritability of FTD varies according to phenotype[93]. The most heritable form is bvFTD, followed by FTD–ALS, PPA (the non-fluent variant is more heritable than the semantic variant) and the atypical parkinsonian syndromes[93,100–102].

We advocate offering testing to all people with bvFTD or FTD–ALS. Among people with PPA and the atypical parkinsonian syndromes, we recommend offering testing only to those with a strong family history (a modified Goldman score <3) because the likelihood of finding a genetic cause in these conditions without a family history is typically low[103,104]. We suggest that targeted panels and WES or WGS are combined with testing for the *C9orf72* expansion[23] because some families have pathogenic mutations in *C9orf72* and in one of the other FTD-related genes[23,50]. Large-scale cohort studies of people with or at-risk of genetic FTD[105,106] have paved the way for the clinical trials of *GRN* replacement therapy in genetic FTD that are now starting[9,107–109] and are likely to increase the uptake of genetic testing as many trials will require knowledge of genetic status.

Prion disease and HD

Unlike in other forms of dementia, testing for mutations in a single gene is warranted in prion disease and HD, as the typical symptoms and presentations and, in many cases, the family history suggest the diagnosis even if a genetic diagnosis has not previously been made within the family.

Prion diseases — Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker disease, fatal familial insomnia, octapeptide repeat insertion-related disease, and prion protein systemic amyloidosis — are defined by the accumulation of abnormal prion protein[110]. Approximately 10–15% of cases of prion disease are caused by a mutation in *PRNP*[63] and can be detected by Sanger sequencing. Creutzfeldt–Jakob disease is the most common form and is defined by rapidly progressive dementia, myoclonus and ataxia. Gerstmann–Sträussler–Scheinker disease involves a frontal syndrome and cerebellar ataxia with peripheral loss of sensation, whereas fatal familial insomnia causes fragmented sleep, gait abnormalities and autonomic symptoms. Octapeptide repeat insertion-related disease is also known as HD-like 1 because patients can present with chorea or other movement disorders in addition to rapidly progressive dementia and psychiatric symptoms[111]. Prion protein systemic amyloidosis causes a late-onset hereditary sensory and autonomic neuropathy without dementia, comparable to familial amyloid polyneuropathy[112]. Features such as myoclonus or insomnia as well as the rapid cognitive and physical deterioration typically lead to clinical suspicion of prion disease, complemented by specific investigations that can then prompt a focused genetic test.

HD is one of the most common autosomal dominant neurodegenerative disorders[113,114]. The disease is typically defined by a triad of progressive movement, cognitive and psychiatric symptoms[115]. For many clinicians, chorea is the defining feature of HD and unequivocal motor extrapyramidal symptoms are important for diagnosis, but symptoms can range from hyperkinetic to hypokinetic and patients often experience a prodromal phase that involves cognitive impairment, anxiety and depression[116]. HD was the first neurodegenerative disease for which a likely genetic location was identified via genetic linkage (and later confirmed)[117] and has since become a model disease for the development of ethical guidelines for predictive testing[118]. HD is caused by a CAG triplet repeat expansion in the *HTT* gene on chromosome 4; the expansion can be detected with fragment analysis or Southern blot[119] (TABLE 1). Penetrance is incomplete if the CAG repeat number is 36–39 but complete if it is >40 (REF.[120]). The number of repeats inversely correlates with age at onset and often increases from one generation to the next (known as anticipation), especially when paternally inherited, although other genetic modifiers, including DNA repair genes[121] and gene promoters[122], also influence age at onset. As a result of the distinctive combination of symptoms, the diagnostic rate for the HD test is high — when the test first became available, only ~1% of patients with HD symptoms tested negative for the *HTT* expansion[123]. However, the negative test rate has increased because the low cost and ready availability of the test means that clinicians often request it to exclude the disorder even if the clinical syndrome is atypical. If the HD test is negative, the differential diagnosis is wide[115] and gene panel testing is often unsuccessful[124].

If a genetic cause continues to be suspected after a negative test for either prion disease or HD, patients can be offered WES or WGS to improve diagnostic rates. These techniques should be supplemented by testing for the *C9orf72* expansion, which is the most common cause of HD phenocopy syndromes[125] (FIG. 2).

Challenges and ethics

Variant classification

NGS technology leads to the identification of a large number of variants, which can be classified with the American College of Medical Genetics and Genomics and the Association of Molecular Pathology (ACMG–AMP)[126] guidelines. In these guidelines, all available evidence — including population, variant and disease-specific databases — is used to classify variants into one of five categories: benign, likely benign, variant of uncertain significance, likely pathogenic or pathogenic (BOX 3). For variants that are classified as likely pathogenic or pathogenic, diagnostic, predictive or prenatal testing can be offered to other family members. However, many variants are classified as variants of unknown significance because the evidence is either

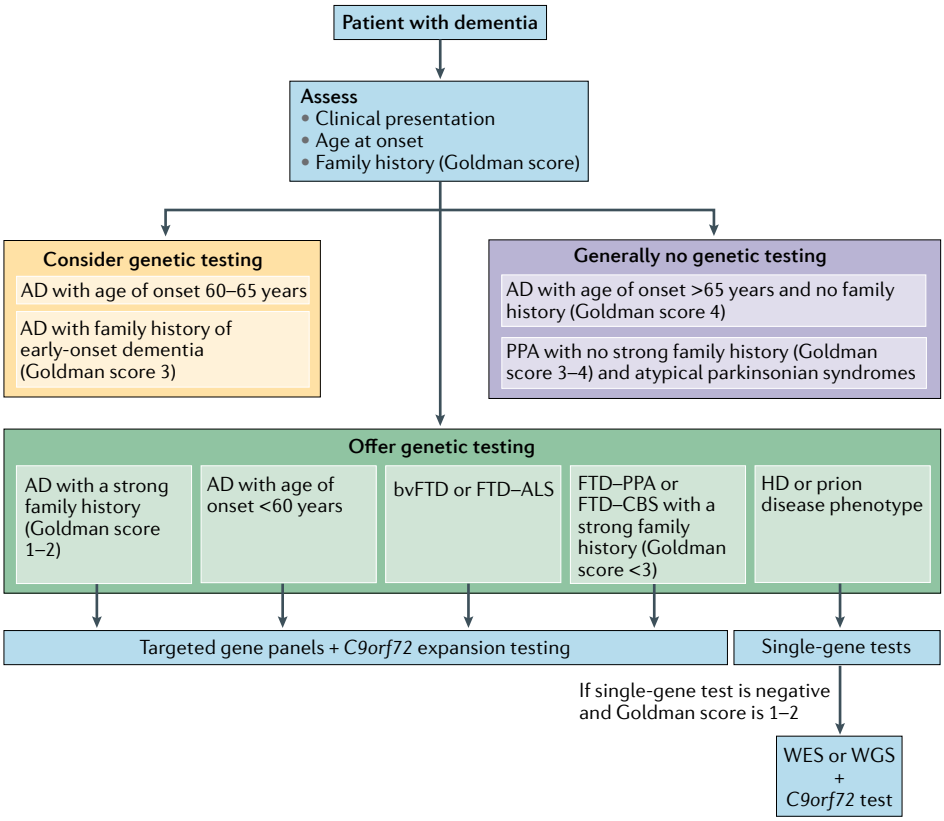

Fig. 2 | **Algorithm for genetic testing of patients with dementia.** The likelihood that patients with dementia have a genetic cause for their disease can be stratified on the basis of their clinical phenotype, their age at onset and their family history expressed as the modified Goldman score (BOX 2). We recommend testing all patients with Alzheimer disease (AD) and a strong family history or early-onset disease (<60 years; with the exception of posterior cortical atrophy, which is not usually associated with one of the typical AD genes), all patients with behavioural variant frontotemporal dementia (bvFTD) or frontotemporal dementia–amyotrophic lateral sclerosis (FTD–ALS), and patients with primary progressive aphasia (PPA) or a corticobasal syndrome (CBS) and a positive family history. Patients with Huntington disease (HD) or prion disease phenotypes should undergo a single-gene test for the relevant condition first and, if this test is negative and their modified Goldman score is <3, whole-exome sequencing (WES) or whole-genome sequencing (WGS) should be performed. Patients who do not meet any of the above criteria but have early-onset dementia or a relative with early-onset dementia should be considered for genetic testing, subject to other factors such as limited information about the family history or suggestive disorders in the family. Patients with AD, age of onset >65 years and no family history should generally not be offered genetic testing. Adapted from REF.[23], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

insufficient or conflicting. The classification criteria are conservative and designed to ensure that a variant remains a variant of uncertain significance unless compelling evidence shows that it is pathogenic or benign because the risks of misclassifying a variant are considerable. Nevertheless, a variant that is initially classified as a variant of uncertain significance could be re-classified as the evidence base expands. No consensus exists about when, how often or by whom variants should be reconsidered and re-classified, but as population databases expand and the use of WES and WGS increases, the classification of variants will improve.

Evidence suggests that people in whom a variant of uncertain significance is identified find this information difficult to process psychologically and no consensus exists about when patients should be informed about a variant of uncertain significance[127,128]. Local protocols for pre-testing and post-testing counselling on this issue are particularly important when patients are offered genetic testing for a condition.

One possible strategy for dealing with variants of uncertain significance would be to inform patients about those with insufficient evidence for pathogenicity, primarily to enable testing for segregation in relatives or further functional studies, and to enable the treating physician to pursue updates about classification at follow-up assessments. This strategy could be particularly useful in the dementias, as their typical late onset usually precludes testing of patient–parent trios that are typical in paediatric genetic testing.

In this context, databases of variants of uncertain significance could be helpful. GeneMatcher, an existing database of variants of uncertain significance, is designed to connect researchers and patients who are interested in variants in the same gene. However, it does not highlight variants with additional indicators of pathogenicity, such as rarity in the general population or in silico predictions of pathogenicity, and is not searchable for others' submissions unless they match to one's own[129], which limits its accessibility and the identification of new

Box 3 | **Application of the ACMG–AMP guidelines**

The American College of Medical Genetics and Genomics and the Association of Molecular Pathology (ACMG–AMP) guidelines for the classification of variants are designed to combine several pieces of evidence for accurate classification. Each piece of evidence is itself classified according to its level of reliability and whether it indicates pathogenicity. The classification of each variant then depends on the sum of all available evidence. For example, a variant can only be classified as pathogenic if at least two strong pieces of evidence indicate its pathogenicity. If these criteria are not met or if evidence is contradictory, the variant remains a variant of uncertain significance. The complexity means that multidisciplinary teams, including clinicians and geneticists, are often required to classify variants. Examples of evidence that is used to classify variants are given below:

Evidence that a variant is pathogenic

- The variant is a coding amino acid change that has previously been identified as deleterious
- The variant is absent or very infrequent in population databases
- The variant is in a mutational hotspot
- Two or more independent in silico prediction models suggest that the variant is damaging

Evidence that a variant is benign

- The variant is common in population databases
- Previous studies have indicated that the variant is benign
- The allele frequency is greater than expected in the general population to be a fully penetrant cause of a rare disorder

mutational hotspots. A repository of such suspicious variants of uncertain significance that includes some general clinical information, such as the associated clinical condition and age at onset, would be a rich resource for scientists as it could help to identify more associated genes and increase knowledge about gain-of-function and loss-of-function mechanisms, thereby directing drug discovery. The online resources that are currently available (the Human Genetic Variation Database and Alzgene) cannot be searched specifically for this type of variant of uncertain significance for which some information indicates pathogenicity. Such a category of 'potentially pathogenic variants' might stimulate attempts to develop biochemical, cell biology or computational methods to resolve the roles of variants of uncertain significance for specific genes, which would be a major advancement[130].

Another problem with the current method of variant classification is that some variants were erroneously classified as pathogenic before the development of large population databases. Therefore, when curating clinical databases, caution must be exercised when looking at variants that were classified before the establishment of population databases in 2016 (REF.[44]). For example, some *PRNP* variants that were classified as pathogenic are too frequent in the population to be considered fully penetrant in such a rare disease[45]. Similar calculations have been performed for early-onset AD and FTD and some variants that were thought to be deleterious seem not to be fully penetrant[23]. For these reasons, public databases of variants are inadequate as the sole source of variant annotation; additional review of clinical data and manual collation of information is still necessary[131].

In the context of variant classification, direct-to-consumer genetic tests can be a problem because the interpretation of a mutation's pathogenicity requires consideration of personal and family history. As more people use direct-to-consumer genetic tests without being offered appropriate pre-test or post-test counselling or adequate information about variants that are identified, the counselling burden on clinical services is likely to increase further.

Secondary findings

As the use of comprehensive genetic testing approaches, such as WES and WGS, increases, so too does the possibility of clinically relevant secondary or incidental findings. Secondary findings are mutations that are unrelated to the condition being tested for but could have implications for future health. Examples include but are not limited to mutations that predispose to cancer, aortopathy or arrhythmia, and mutations that cause autosomal recessive conditions. Study findings indicate that such mutations are identified in 4.6–12% of tested individuals[21,132].

The ACMG-AMP currently recommends that, if WES or WGS are used clinically, secondary findings in 59 specific genes should be looked for and reported[22]. The genes included are associated with diseases in which screening and/or early treatment can improve patient outcomes and therefore genes associated with dementia are not currently included. However, such genes could be included in future if treatments are developed, particularly if the initiation of these treatments in the early stages of the disease provides the most benefit. Studies have shown that following the current ACMG-AMP recommendations would mean that secondary findings would need to be reported to ~3% of people tested; the time and cost implications of returning secondary findings are therefore substantial[133–135].

If patients are offered WES or WGS, specific consent needs to be obtained for the reporting of secondary findings and they must be given an opportunity to opt out. Studies have shown that patients are broadly in favour of the disclosure of secondary findings[136–138]. However, it is difficult to be sure that consent is fully informed when such a large number of genes are involved because the implications for each are different. In addition, the list of secondary findings that should be reported for children differs from that for adults and therefore consideration needs to be given to whether further secondary findings should be reported when these children reach adulthood and how this would be done.

Consent and counselling

When genetic testing is considered, informed consent requires careful counselling of the patient, even if the test is diagnostic rather than predictive. The term counselling does not imply that this process only involves genetic counsellors — practicing neurologists and geriatricians often perform this duty for their own diagnostic testing. Obtaining consent can be particularly challenging when the patient has impaired cognition. The decision to test an individual who lacks the capacity to provide informed consent should be based on their best interests and should ideally involve discussion with family members to ascertain what the wishes of the patient

in relation to genetic testing were before their disease progressed. Other factors to consider include whether the patient has the cognitive ability to understand the results and whether the results could exacerbate their condition; for example, if anxiety or psychiatric features are part of their presentation.

Diagnostic genetic testing of symptomatic patients is usually requested by treating physicians but predictive testing for asymptomatic individuals with a family history has traditionally been the remit of clinical geneticists and genetic counsellors. The protocol for predictive testing in HD and genetic dementias provides a framework for such predictive testing — this protocol ensures that the individual is informed of the risks and benefits of testing, the implications for employment and insurance, the availability of screening and/or risk-modifying treatment, and the implications for offspring and other relatives[47,118]. A key feature of this protocol is multiple appointments, which provide individuals with time to consider the consequences of testing and the opportunity to change their decision about whether to undergo testing. A shortage of clinical geneticists and counsellors worldwide makes it difficult to provide these opportunities to everyone but predictive testing is not without risk and should not be undertaken lightly[139]. If access to genetic counselling is impossible, at-risk individuals should be counselled by the testing clinician about the risks and benefits and should be given the opportunity to consider these aspects before proceeding. Consideration should also be given to the manner in which results are communicated and the arrangements for follow-up with patients whose test is positive. Additional counselling, which might involve relatives or additional support, might be needed in complex family situations such as the testing of monozygotic twins or when testing an individual will provide a de facto result for a parent who has refused testing, or if patients are at risk of a poor psychological outcome after testing.

A genetic diagnosis can offer many benefits but also carries risks (BOX 4). Consequently, the decision for or against a predictive test can be distressing and uptake is generally low; for example, the uptake of predictive testing for HD is 5–20% among at-risk relatives of patients and uptake among those at risk of prion disease is ~25%[140]. However, with the advent of treatment trials in genetic neurological diseases, such as HD, spinal muscular atrophy and transthyretin amyloidosis, and in dementia (for example, trials of *GRN* gene replacement), we (the UCLH Neurogenetics Laboratory) have seen an upturn of ~50% in the uptake of predictive testing. Even in conditions with available treatments, the counselling and testing process should still ideally follow the protocol for HD[46,118] in a specialist neurogenetics clinic with close laboratory support — counselling should take place over three appointments and the turnaround of the genetic test once blood has been taken should be rapid (ideally within 2 weeks). However, with an increase in uptake, a shortage of clinical geneticists and genetic counsellors worldwide could limit the availability of pre-test and post-test counselling. Another factor that has increased the uptake of predictive testing is the availability of pre-implantation genetic diagnosis (PGD) for a growing number of genetic conditions. This procedure involves genetic testing of blastomeres before reimplantation during in vitro fertilization and PGD can be carried out without genetic testing of the at-risk parent, a process known as exclusion PGD.

Box 4 | **Benefits and detrimental effects of a genetic diagnosis**

Beneficial effects

- Provides diagnostic near-certainty and enables adequate disease monitoring
- Further diagnostic tests are unnecessary
- Enables the initiation of symptomatic treatment and discontinuation of ineffective treatments
- Facilitates reproductive strategies, such as in vitro fertilization with pre-implantation genetic diagnosis or invasive genetic testing in pregnancy
- Provides access to support groups, clinical trials and targeted treatments when they become available

Detrimental effects

- Can cause psychosocial difficulties
- Can lead to the breakdown of social relationships
- Identification of pathogenic mutations can affect job and insurance prospects
- Identification of a variant of uncertain significance neither excludes genetic disease nor permits predictive testing for relatives[47,156]

Implications for relatives

Genetic testing is distinct from other medical investigations because it frequently has implications for the relatives of the person being tested. The principle of confidentiality in medicine holds in genetic testing but given that most people want to have genetic testing, at least in part, to assist other family members, confidentiality is rarely an issue. Occasionally, however, a patient declines to tell their relatives of a genetic diagnosis, which poses an enormous ethical problem. This scenario occurred in the legal case of ABC versus St George's Hospital NHS Trust in the UK, in which a patient with cognitive capacity refused to tell his children the result of his positive diagnostic test for HD. The judgement made clear that clinicians have a duty to balance the right of the patient to confidentiality with the right of an interested third party to be informed of results that affect them[141,142]; therefore, under certain circumstances and potentially after taking advice from an ethics committee, a clinician might be allowed to disclose such results without the patient's consent.

Estimates suggest that up to 20% of relatives are not informed of genetic test results that are relevant to them, with reasons ranging from wishing to protect relatives to being unaware that the information was relevant[59,143]. This ethical area is clearly complex and, if a patient is being asked to pass on potentially life-changing information to a relative, the ability of the patient to make decisions must be considered. In the UK, the Joint Committee in Genomic Medicine has provided guidance on how to proceed when issues about data sharing arise[144].

If the results of a genetic test are unlikely to change the management of a patient, for example, if treatment is unavailable and investigation and monitoring will not be changed, then the timing of genetic testing should also be carefully considered. For instance, a genetic test is needed to clarify the risks to a patient's relatives but,

in some cases, such as if issues exist in relation to an individual's capacity to consent or if the results could be distressing to the patient, storage of DNA for later testing or collection of samples during autopsy might be more appropriate. However, such a delay can cause problems; for example, relatives might want to understand their risk before having children or, if the next-of-kin does not allow testing of samples after the patient's death, other relatives could be denied the chance to clarify their risk. Testing of unaffected individuals in the absence of a known familial mutation is rarely offered owing to the heterogeneous nature of many genetic conditions, uncertainty with respect to penetrance and limitations in the interpretation of variants.

Finally, the results of predictive genetic tests can have implications for insurance. In the UK, members of the Association of British Insurers must abide by a code that prevents them from asking people to have predictive genetic tests or to disclose the results of predictive genetic tests. One exception is HD, for which disclosure of known genetic test results is mandatory for critical illness insurance amounts above specific thresholds[145]. In addition, insurers will not (in line with the code of conduct they abide by) ask for or consider the results of predictive tests obtained in the course of scientific research. This code came into effect in October 2018 and will be reviewed every 3 years. Implications for insurance differ between countries and relevant aspects should be discussed with patients as part of pre-test counselling for any predictive test.

Conclusions

Widespread genetic testing is transforming clinical practice. Though only select patient cohorts are currently eligible for the first trials of disease-modifying drugs in neurodegenerative diseases, the number of patients who are eligible will only grow with the advent of preventive and therapeutic approaches. For most dementias, the most appropriate genetic test is a dementia gene panel, which can be performed by analysis of WES or WGS to enable subsequent analysis of further genetic information if appropriate, supplemented by testing for the *C9orf72* expansion. For specific disorders with known single-gene causes, such as HD and prion diseases, single-gene tests remain a suitable choice. In future, long-read sequencing will enable simultaneous testing for SNPs and expansion disorders, though this technique is not yet sufficiently accurate or affordable for clinical practice. However, as greater numbers of patients are tested for deleterious variants in an increasing number of genes, secondary findings and variants of uncertain significance are bound to be identified more frequently, creating new challenges such as an increased need for pre-test and post-test counselling and the need for re-analysis as new information becomes available. Ethical aspects, such as the ability of patients with dementia to provide consent and the rights of relatives, will need to evolve as personalized medicine based on genetic testing becomes the reality.

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