DELPHI CONSENSUS STUDY FOR GENETIC TESTING IN FRONTOTEMPORAL DEMENTIA

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Chapter 1. Developing a tailored diagnostic testing protocol for use in frontotemporal dementia

1.1. Chapter overview

This chapter uses a Delphi consensus methodology to provide expert recommendations regarding to whom diagnostic testing should be offered, and amendments to the current HD protocol regarding how this should be carried out. Diagnostic testing in FTD is a key element of the at-risk experience as this is often the point at which many people learn of their risk. Diagnostic testing to provide confirmation of a genetic mutation within the family is also critical to allow for future predictive testing for those at-risk. However, due to the lack of guidance regarding this process in FTD, unnecessary barriers may be formed which pose challenges for future generations, as well as for the individual themselves. This will also become increasingly important as clinical trials progress to ensure timely diagnosis and early access to available treatments.

1.2. Introduction

Despite two decades of research into both familial and sporadic FTD, the discovery of the causative link between the three most common FTD genes was relatively recent in comparison to other genetic disorders (*MAPT*, Hutton et al., 1998, *GRN*, Baker et al., 2006; Cruts et al., 2006, *C9orf72*, DeJesus-Hernandez et al., 2011; Renton et al., 2011). The progress of research within the realm of FTD has not been reflected in the development of an FTD-specific protocol for genetic testing, therefore, much is still extrapolated from diseases such as Huntington's disease. The 'gold standard' for both predictive and diagnostic genetic testing for neurodegenerative conditions such as FTD was originally developed for use in HD. This protocol is largely applicable to FTD however there are a number of issues specific to genetic testing in FTD that are not addressed.

1.2.1. Diagnostic testing issues in FTD:

1. The challenge of testing for FTD-related genes

The introduction of next generation sequencing (NGS) was transformative for diagnostic testing as NGS sequencing panels provide a much more efficient way to test for FTD-related mutations compared to the previous method of single gene testing. Many laboratories now offer 'dementia' or 'FTD/ALS' NGS panels which often include the *MAPT* and *GRN* genes amongst many others. However, few of these panels contain a standardised list of genes. This poses a challenge as local panels require regular review to ensure all genes with strong evidence for pathogenicity are included within their panel. Whole genome sequencing is likely to soon supersede NGS panels and would identify mutations which have only recently been associated with FTD.

Similarly, *C9orf72* expansions are not easily identified using NGS. Repeat primed PCR (RP-PCR) is used by many laboratories to detect hexanucleotide repeat expansions. RP-PCR may then be followed by Southern blotting which is considered the 'gold standard' for confirming repeat expansions such as that in *C9orf72.* A large multicentre study by Akimoto et al. (2014) found that only five of 14 laboratories were able to achieve concordant results with Southern blotting using PCR alone. Therefore, they suggest that due to the high risk of misgenotyping using only PCR and the clinical

consequences of this misgenotyping, Southern blotting should always be used to confirm RP-PCR results in a clinical setting. However this method is costly, time consuming and requires large, high quality DNA samples (Akimoto et al., 2014; Cleary, 2016) and as such, many laboratories use only RP-PCR, without the confirmatory Southern blotting procedure.

2. Special circumstances; challenges in interpreting pathogenicity of FTD-causing genetic mutations:

The American College of Medical Genetics and Genomic (ACMG) guidelines (Richards et al., 2015) are commonly used to interpret pathogenicity of a variant, however there are a number of points specific to FTD that are also important to consider when determining pathogenicity.

Firstly, the repeat length at which a *C9orf72* expansion is pathogenic remains unclear. In the initial studies of *C9orf72*, an expansion length of >30 repeats was considered pathogenic, although it was noted that most symptomatic patients had repeat lengths ranging from hundreds to hundreds of thousands of repeats (DeJesus-Hernandez et al., 2011; Renton et al., 2011). In contrast, in healthy controls the vast majority of people have repeat lengths of <20, most commonly 2-8 repeats (Ng & Tan, 2017). An 'intermediate' length expansion was initially considered to be between 20 and 30 repeats with possible pathogenicity e.g. expansions of 20-22 repeats were found in five people with FTD, three of which had a modified Goldman score of two suggesting a strong family history (Gomez-Tortosa et al., 2013). Another study showed a higher frequency of psychiatric presentations in intermediate expansion carriers (Ng & Tan, 2017), and several studies have demonstrated an association with atypical parkinsonian syndromes (Cali et al., 2019; Cannas et al., 2015; Schottlaender et al., 2015). In a cohort of 354 pathologically confirmed CBD cases, there were significantly more *C9orf72* repeat expansions found compared to controls (3.7% vs 0.52%) using a minimum cut off of 17 repeats, however, no expansions larger than 29 repeats were detected (Cali et al., 2019). A post-hoc analysis found that *C9orf72* repeat length as low as 10 was associated with CBD, indicating that intermediate repeat expansion length may be a risk factor for CBD, with increasing risk with higher repeat sizes (Cali et al., 2019). However, uncertainty remains over their significance, and the lower limit of pathogenicity, which poses a challenge when 'intermediate' expansions are

identified in clinic. Crook et al., (2019) report a case in which highly discordant repeat length results were obtained via differing laboratories using RP-PCR and Southern blotting procedures. Expansion lengths of between >15 to 28 were recorded and interpretations provided by laboratory thresholds included inconclusive, intermediate, negative (<30 repeats) and pathogenic. However, the expansion was not detected by Southern blotting. These findings emphasise the lack of clarity regarding the discovery in patients of *C9orf72* expansion lengths that are not clearly pathogenic (i.e., those that are not in the thousands to hundreds of thousands) and the authors highlight the impact that this may have on the individual, their children or potential children as a result of increased uncertainty, confusion and potential psychological risk.

Secondly, in addition to the pathogenicity problem in *C9orf72* repeat expansions, there are also a number of issues in interpreting pathogenicity of some progranulin mutations. Studies have demonstrated the association between pathogenic *GRN* mutations and low levels of progranulin in CSF (Ghidoni et al., 2008), plasma (Finch et al., 2009; Galimberti et al., 2018; Ghidoni et al., 2008) and serum (Sleegers et al., 2009). However, there is currently no definitive cut-off level to determine pathogenicity. With the commonly used Adipogen ELISA, levels of 61.5 (Ghidoni et al., 2012) or 71 (Sellami et al., 2020) have been used in plasma or serum. However, there is some overlap around 55-85 between controls and *GRN* mutation carriers. No cut-off level for CSF has been identified but some cases have been shown to have low CSF but normal serum progranulin levels (Wilke et al., 2016). Similarly, multiple missense mutations have been reported in *GRN*, many of which have unclear pathogenicity and can have variable progranulin levels in blood or CSF. Functional biological studies have been carried out to investigate pathogenicity in only a small number of such mutations e.g. *A9D* and C105Y (Karch et al., 2016; Mukherjee et al., 2008). 'Normal' progranulin levels are observed with a number of missense *GRN* mutations (suggesting they are not pathogenic) while others give rise to 'intermediate' progranulin levels lying somewhere in between 'normal' and the much greater reduction seen in loss of function *GRN* mutations. More recent research suggests many missense variants may be risk factors for dementia without being directly pathogenic (Redaelli et al., 2018).

Thirdly, although uncommon, a number of families with more than one pathogenic mutation have been reported. This has been most commonly reported in families

carrying a *C9orf72* expansion alongside another mutation in *GRN* or *MAPT* (Lashley et al., 2014; van Blitterswijk et al., 2013). However, in reality, dual mutations are likely to be more prevalent than currently reported as many centres do not test for additional mutations once a *C9orf72* expansion is detected. There are also reports in the literature of dual mutations in rarer genes, for example dual *C9orf72* and *TARDBP* mutations (Origone et al., 2015). This phenomenon, although rare, poses difficulties for genetic counselling of family members, and in the practice of sequential genetic testing with *C9orf72* expansion testing followed by NGS sequencing only if the initial test is negative.

Lastly, diminished capacity to consent for diagnostic testing and communication problems may pose an increased problem in FTD compared to other neurogenetic disorders (Crook et al., 2021). Therefore, there may be increased burden on family members regarding diagnostic testing decision-making, not limited to the diagnostic test itself but also regarding storage of samples for future testing. Issues may arise in particular when family are not in agreement regarding these factors and, as such, care must be taken to counsel families throughout the decision-making process.

Therefore, this study aimed to provide clarity on the above issues by developing expert consensus recommendations for diagnostic testing in FTD using a Delphi methodology.

1.3. Methods

1.3.1. Delphi consensus methods

1.3.1.1. Participants

Participants were members of either the GENFI Investigators Group or the UK Predictive Testing Consortium. All participants were either neurologists, clinical geneticists or psychiatrists with a specialist interest in either FTD or neurogenetics. Twenty-three GENFI principal investigators (all of whom were consultant neurologists, clinical geneticists or psychiatrists), were initially invited to participate. International participants also recommended suitable collaborators to participate who were either neurologists or local geneticists associated with the study at their site. Eleven clinical geneticists were also invited to participate via the UK-based geneticists from the UK Predictive Testing Consortium. The introductory invitation to participate was followed by two subsequent reminders. Those who did not respond following the final reminder email were excluded, resulting in a final panel of 18 neurologists, three psychiatrists and seven clinical geneticists. Three panellists dropped out throughout the duration of the study: one neurologist and two clinical geneticists. For distribution of professionals across each round see Table 1. Experts also indicated their professional area of interest; FTD (n=20), neurogenetics (n=16) or both FTD and neurogenetics (n=8).

Table 1 - Panellist distribution across professional specialism

	Neurologists	Psychiatrists	Geneticists	Total
Round 1	18	3	7	28
Round 2	17	3	6	26
Round 3	17	3	5	25

1.3.1.2. Procedures, design and survey development

The Delphi technique was employed to determine consensus amongst a group of experts. The Delphi process comprised of three rounds **(**Figure 1). The topic was first

discussed during an investigator meeting of the GENFI consortium in 2019 and a number of key questions were identified which were used to develop the first questionnaire. In Round 1 of the questionnaire, participants were asked to answer a total of 20 questions from a selection of multiple-choice options. A free-text answer 'other' option was also available. The questionnaires used and adapted throughout the study can be found in appendices 15 to 17. Family history was quantified using the modified Goldman score, outlined in Table 2 (Beck et al., 2008; Rohrer et al., 2009).

Table 2 - The modified Goldman score

Modified Goldman score	Family history description
1	Autosomal dominant family history
2	Three or more family members with FTD but not meeting criteria for autosomal dominance
3	One first degree relative with young onset dementia
3.5	One first degree relative with dementia onsetting over the age of 65
4	No family history

In Round 2, all multiple-choice options with less than 10% uptake were removed and one additional option was added as suggested by participants (see appendices 10 to 14). The percentage of respondents who selected each option in the previous round was highlighted and participants received individualised questionnaires indicating their previous response. They were then asked to reconsider their answer based on this information.

Although consensus was achieved on a number of items, a third questionnaire round was carried out as this is reported to be an optimal number of rounds to achieve a consensus (Iqbal & Pipon-Young, 2009; Vogel et al., 2019). Here, all items that had achieved consensus were removed and again, items with less than 10% uptake were removed. The percentage of respondents who selected each option in the prior round was highlighted and each participant saw their previous response indicated and were asked to reconsider based on the information provided. Throughout the study, for each round, participants were given three opportunities to respond. As demonstrated in

Figure 23 below, three participants failed to respond between round one and round three. Missing data was clarified for incomplete responses. A number of geneticists objected from responding to questions outside their area of specialism. For these questions the analysis was adjusted accordingly to maximise the utility of the data gathered.

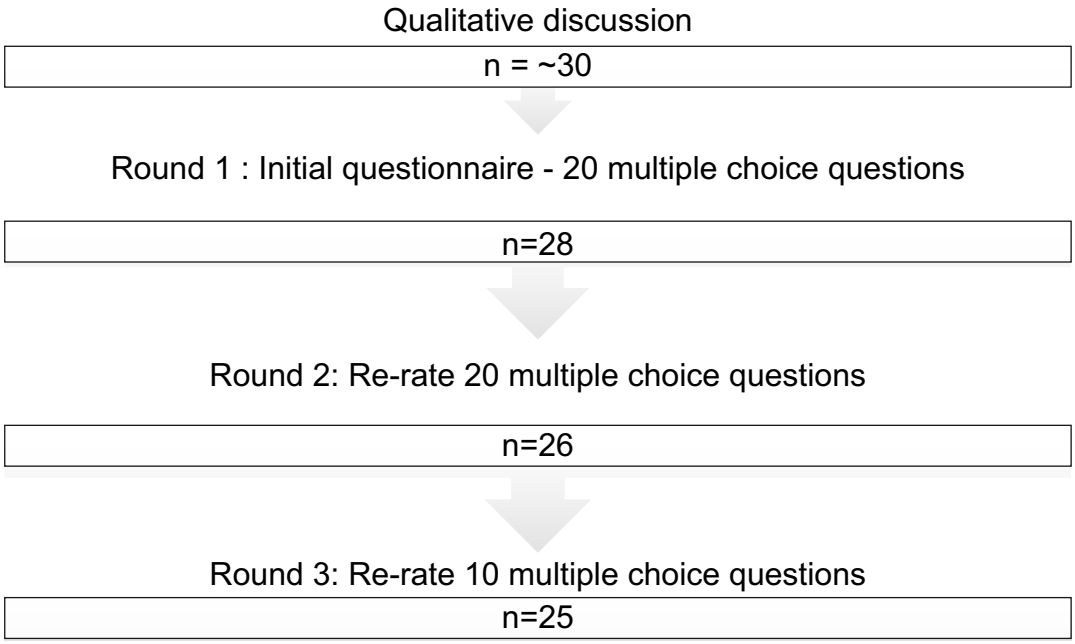

Figure 1 - Flow chart demonstrating the Delphi procedure and number of participants and questions at each stage

1.3.1.3. Analyses

Questionnaire responses were summarised after each round using descriptive statistics, computed using Microsoft Excel (*Microsoft Excel*, 2018). The percentages of experts who chose each multiple-choice response were calculated for each item (see appendices 10 to 14 for responses across all Delphi rounds). Criteria for strong consensus was determined to be the answer selected by >80% respondents and moderate consensus was >70%. The literature suggests that consensus of >70% is an adequate level of agreement (Vogel et al., 2019). Free-text data informed the development of the subsequent questionnaire iterations.

1.4. Results

Consensus results are reported following three rounds of questionnaires. According to the Delphi methodology consensus was not achieved during the first round. In Round 2, strong consensus (>80%) was achieved for eight items and moderate consensus (>70%) for two additional items. At round three all items reached strong or moderate consensus, except for three diagnoses; lvPPA, CBS/PPA overlap and PSP and one further item regarding minimum symptoms for diagnostic testing. Age was not a factor in the final consensus results. See appendices 10 to 14 for full results after each questionnaire round.

Regarding to whom diagnostic testing should be offered based on phenotype, age and family history, it was recommended that diagnostic testing is offered to all individuals presenting with the following phenotypes: bvFTD, FTD-ALS, bvFTD/PPA overlap syndrome, nfvPPA, lvPPA with negative AD biomarkers and PPA-NOS. For diagnoses of svPPA and CBS, it was recommended to offer diagnostic testing to individuals with a modified Goldman score of 1 to 3.5, indicating a first degree relative with a dementia diagnosis over the age of 65. Experts also recommended that those with late onset psychosis and schizophrenia with a modified Goldman score of 1-2 should be offered diagnostic testing.

Consensus above 70% was not met for lvPPA with unknown biomarkers, lvPPA with positive AD biomarkers, PSP and CBS/PPA overlap. However, as these items still achieved over 60% consensus, they may be used as suggestions rather than guidelines.

Table 3 - Percentage consensus for whom diagnostic testing should be offered, based on phenotype and family history

Phenotype	All	Goldman score of 1-3.5 (at any age)	Goldman score of 1-3 (at any age)	Goldman score of 1-2 (at any age)
BvFTD	83%			
FTD-ALS	92%			
bvFTD/PPA overlap	70%			
nfvPPA	76%			
svPPA		72%		
lvPPA (AD biomarkers unknown)			60%	
lvPPA (AD biomarkers positive)				64%
lvPPA (AD biomarkers negative)	80%			
PPA-NOS	80%			
CBS		76%		
PSP				64%
CBS/PPA overlap				60%
Late onset psychosis/ schizophrenia				73%

In addition, participants were asked whether blood or CSF progranulin levels should be used to supplement guidelines for determining pathogenicity in *GRN*. Eighty-two percent recommended that low blood or CSF *GRN* levels should be considered supportive of pathogenicity but not definitive.

When asked whether we should consider minimum criteria for diagnostic testing in prodromal FTD, experts did not meet the consensus threshold, however 64% were in agreement that patients should display minimal cognitive and/or behavioural impairment, displaying at least one symptom described in the Rascovsky criteria.

1.4.1.1. Proposed FTD diagnostic testing recommendations

The recommendations outlined below may be considered supplementary to those described by Craufurd et al., (2015), for diagnostic testing in FTD. Additional adaptations to Craufurd et al's (2015) guidelines are also described.

When should we consider diagnostic genetic testing?

Recommendations refer to those supported by the consensus threshold, guidelines refer to those items that did not meet 70% consensus but clinicians may consider using their discretion on a case by case basis.

Proposed FTD recommendations
Recommendations (RECs) 1-3: 1. Experts recommend that diagnostic testing is offered to all those given the following clinical diagnoses regardless of family history: - Behavioural variant FTD - FTD-ALS/MND - Behavioural variant FTD/Primary progressive aphasia overlap syndrome - Non-fluent variant primary progressive aphasia - Logopenic aphasia (once AD biomarkers are confirmed to be negative) - PPA-not otherwise specified 2. Experts recommend that diagnostic testing is offered to those with the following diagnoses, with a family history of a dementia diagnosis over the age of 65 (mGS 1-3.5) - Semantic variant primary progressive aphasia - Corticobasal syndrome 3. Experts recommend that diagnostic testing is offered to those with the following diagnoses, with a family history involving 3 or more family members with FTD but not meeting criteria for autosomal dominance (mGS 1-2). - Late onset psychosis or schizophrenia
GUIDELINE 1: Clinicians may want to consider offering diagnostic testing to those with a diagnosis of progressive supranuclear palsy or corticobasal syndrome/primary progressive aphasia overlap with a family history involving a 1 first degree relative with young onset dementia (mGS 1-3). However please note that this did not meet consensus threshold and therefore should be considered on an individual basis and at the

discretion of the clinician.
GUIDELINE 2: Clinicians may want to consider a minimum symptom threshold for diagnostic testing, with individuals requiring minimal cognitive and/or behavioural impairment, displaying at least one symptom outlined by the Rascovsky criteria to qualify for diagnostic testing. However, this should be considered on an individual basis and predictive testing protocols may often be most appropriate, particularly due to the additional counselling element and should be employed in situations where there is doubt regarding the appropriateness of diagnostic testing.

How should diagnostic testing be carried out?

From Craufurd et al., (2015), amendments highlighted in **bold**: Where **FTD** seems possible, the neurologist may suggest proceeding with genetic testing. It is best to inform both the patient and immediate relatives about the hereditary nature of the disease before carrying out the test. If the diagnosis is confirmed, the clinician must recognise the needs of the entire family as well as the index patient and ensure that family members can access appropriate genetic counselling services.
Clinicians should always offer follow-up to the patient and **their** family. The opportunity to participate in research such as the **GENFI or ALLFTD studies** provide the patient with a sense of purpose and may also offer future opportunities to participate in clinical trials. Family members may want to access genetic counselling, and the neurologist should be aware of the nearest genetic counselling unit and be able to provide details of the lay organisation for support (**e.g. RDS, AFTD** or other local organisations).

Additional recommendations/considerations:

REC 4: Low blood or CSF *GRN* levels should be considered supportive of pathogenicity but not definitive and may be used in conjunction with ACMG guidelines to determine pathogenicity of variants of unknown significance.
Lack of insight – adapted from Craufurd et al., (2015): Commonly in **FTD**, the person living with **FTD** may have little insight into their own symptoms, thus their partner or family members often suspect the diagnosis before the individual acknowledges their symptoms themselves. In some cases, family may have prompted the referral. Therefore, such individuals may be unprepared for the diagnosis, affecting their ability to provide informed consent. The diagnostic and genetic testing process requires care and sensitivity and exploration of the individual's understanding of the situation may be necessary prior to proceeding with genetic testing. An additional appointment and/or offering additional support before diagnostic testing may help.

Adapted from Craufurd et al., (2015):

Checklist before diagnostic genetic testing

‣ Has the test been requested by a neurologist or psychiatrist with relevant experience?

‣ Has the patient been appropriately counselled about the implications of genetic testing and possible test outcomes?

‣ Has the neurological examination shown evidence of motor symptoms?

‣ Have the patient's family or caregiver been included in discussions about the diagnostic genetic test and hereditary implications of **FTD**?

‣ Has the family been informed about the option of referral for genetic counselling?

‣ Has appropriate informed consent for diagnostic genetic testing been obtained by the patient/legal representative/person with parental responsibility?

‣ Is the laboratory to which the sample is being sent accredited and do they have experience of performing **FTD** genetic testing?

‣ Have full clinical details, contact details of the requesting clinician and evidence that

consent has been obtained noted on the laboratory request card?

- Has the timescale for expecting a result been made clear to the patient family and the laboratory?
- Has a face-to-face appointment with the person requesting the genetic test been arranged to give the result?

Checklist following a genetic diagnosis of FTD

- Has a plan for follow-up been discussed with the patient and his/her family?
- Have details of the lay organisation been provided?
- Have options to participate in research been discussed?
- Do the patient's relatives wish to be referred for genetic counselling?

1.5. Discussion

This study uses expert opinion to develop guidelines for diagnostic genetic testing in fFTD. Recommendations build upon those used as a 'gold standard' for testing in HD, allowing for the added uncertainty and unpredictability seen in fFTD, due to variable age at onset, phenotypic heterogeneity and other 'special circumstances' discussed above.

1.5.1. Summary of main findings

This study achieved consensus on all but a small number of items, including diagnoses of lvPPA, CBS/PPA overlap and PSP and a question regarding minimum symptoms for diagnostic testing. Most of those which met consensus, did so at a level of over 80% indicating strong consensus within the group of experts.

The results of this study highlight that it is important to offer testing to those phenotypes commonly observed in fFTD. Experts were in agreement that diagnostic testing should be offered to all of those presenting clinically with a bvFTD or FTD-ALS diagnosis. Despite these phenotypes both occurring sporadically, they are the most common phenotypes observed within familial FTD. As diagnostic testing occurs in those who have already developed symptoms, therefore it may be reasoned that in these cases, if the individual and their family would like to proceed with it, diagnostic testing would cause minimal harm, but should a mutation be identified, this may be important information for other family members. Similarly, although there is currently no treatment for FTD, identifying individuals in the early stages of the disease with a genetic cause may allow them, in future, to participate in clinical trials or receive potentially disease modifying treatments.

Similarly, the panel of experts recommended that testing should be offered to those with a late onset psychosis or schizophrenia diagnosis who displayed a strong family history of FTD-related disorders, which may include FTD, MND, Parkinsonism and late onset psychiatric diagnoses. A strong family history was classified either as an autosomal dominant history (modified Goldman score of one) or familial aggregation of three or more family members with dementia including FTD/PSP/CBS/ALS (modified Goldman score of two). Although adult-onset psychiatric diagnoses alone

are not necessarily indicative of FTD, many individuals with FTD are misdiagnosed with a primary psychiatric illness, therefore diagnostic testing may be a helpful tool to ensure the correct diagnosis and care for those with a strong family history of FTD related disorders.

The expert panel also recommended that low blood or CSF progranulin levels may be considered supportive of pathogenicity, used in conjunction with ACMG guidelines for determining pathogenicity, however low progranulin levels should not be considered definitive of pathogenicity. As discussed above, there is no set cut-off to determine pathogenic progranulin levels, and missense mutations often demonstrate variable progranulin levels, some lying between 'normal' and clearly pathogenic levels. Levels can also vary depending on whether they are measured in blood or CSF (Wilke et al., 2016). However functional biological studies have been carried out for only a small number of mutations . Therefore, although progranulin levels can provide useful information in support of pathogenicity, they should not be considered definitive.

The recommendations for diagnostic testing provided within this study take into account work in HD (Craufurd et al., 2015), as well as more recent work in ALS and FTD (Crook et al., 2022). Crook and colleagues also used a modified Delphi methodology to identify diagnostic testing recommendations which are complementary to those outlined in this study. They identified a number of recommendations relating to the diagnostic test counselling procedure, for example, the presence of a consistent healthcare provider, information provided in various formats and a flexible and family centred approach to diagnostic testing. They detail much of the content that a healthcare provider should cover while counselling a family ahead of diagnostic testing. This fits well with the recommendations provided within this study, which largely focus on ensuring clarity regarding eligibility for diagnostic testing. Therefore, it may be useful in future to combine both resources to form a combined FTD and ALS diagnostic testing protocol.

Age was not considered a factor in any of the final consensus results. This may be due to a number of factors; firstly there is a variable age at onset observed across fFTD, most commonly ranging between the ages of 49 to 65 years (Moore et al., 2020). This large variability in onset may pose a challenge in applying age-related boundaries in genetic testing guidelines and may increase the risk of individuals outside these

arbitrary age brackets not being offered appropriate genetic testing. Similarly, studies (Moore et al., 2020) suggest that there is age related penetrance observed in *GRN* and *C9orf72*, therefore age cut-offs favouring young-onset dementia (i.e. under the age of 65) may disadvantage those where age-related penetrance is an issue. Finally, as age at onset within families is not predictable, aside from in *MAPT* mutations, age boundaries for genetic testing may be seen as arbitrary and as such creating barriers to accessing appropriate and important clinical care and support. The additional qualitative data explored within this study highlights the importance and emotive nature of genetic testing for families affected by fFTD, therefore it is important that the relevant services are as accessible as possible, hence the importance of defining guidelines for testing.

1.5.2. Evaluation of the Delphi methodology

The Delphi methodology utilised in this study provides many advantages that made it a suitable method for creating expert recommendations. Firstly, it provides anonymity and encourages reflection, allowing for collaboration of a diverse group of expert panellists. As FTD is a niche field of research, this method allowed for collaboration of experts from across the globe, both allowing for cross-cultural perspectives but also facilitating investment of clinical professionals within the field, in the subsequent guidelines generated. Due to the consensus nature of the methodology, a 'best-fit' scenario is generated, reducing the noise in the data and reducing the impact of dominant individual's viewpoints. This is particularly advantageous over other consensus methods such as in-person discussion, as within academia there may be a social desirability bias towards senior clinicians and academics, leading panellists to conform rather than indicate their true opinion. Furthermore, the reflexivity of the method, reflecting using feedback over multiple rounds of questionnaires, increases the validity of the findings (Donohoe & Needham, 2009; Fink-Hafner et al., 2019; Hsu & Sandford, 2007).

Although supporters of the Delphi methodology argue that group decisions, specifically those made by informed expert opinion, are more reliable than decisions made by a single person, particularly where there is minimal literature or historical context regarding the problem in question (Franklin & Hart, 2006) this methodology is not without its limitations. The lack of active discussion involved in the process may limit

the responses given, particularly as there is limited opportunity to share reasoning behind decision-making with other panellists. Similarly, the development of the initial questionnaire can be subjective and may limit or bias responses due to the choices offered. This study attempted to overcome this limitation by developing the initial questionnaire from a group discussion on the topic and allowed qualitative feedback in the first iteration of the questionnaire so that panellists could make their own suggestions or provide reasoning which could be accounted for in the following iteration.

1.5.3. Limitations

Despite best efforts to limit any limitations within this study, there are a number to be addressed. Firstly, although the panel encompassed experts from across the UK, Europe and Canada, the judgements made by the panel may not be representative of other countries and cultures and therefore not generalisable, particularly as it takes a particularly 'Western' stance towards medicine and healthcare. Additionally, due to a focus on NHS systems, the implementation of these recommendations may not be possible within the constraints of other healthcare systems. Furthermore, the overrepresentation of neurologists in the expert panel may have led to recommendations that are unrealistic for application within a genetic counselling or testing real-life scenario. There may also be limitations in terms of clinical and laboratory capacity for carrying out such tests, making the implementation of the above recommendations challenging. Furthermore, working with family systems raises the problem of discordant views regarding testing, which can complicate the diagnostic and predictive testing experience, particularly when the symptomatic individual lacks capacity to make this decision themselves. There are also complex ethical issues regarding the right to know the genetic information of family members when this impacts an individual's risk, as has been discussed in the high court of late. Additionally, there are further constraints relating to the rights and counselling of estranged family members, or those who cannot attend appointment due to geographical distance. Therefore, this process can be 'messy', and while the above recommendations are intended to assist this process, it also requires careful consideration on a case-by-case basis, with the option of DNA storage for future analysis potentially existing as a suitable compromise in these difficult situations. A

strength of this study was the panel size, as this exceeded the lower limit of 12 described in the literature (Vogel et al., 2019), drop out between questionnaire rounds was also very low. The use of the Delphi methodology in this study also allowed for a collaborative and cross-cultural approach to developing recommendations, allowing experts to make suggestions for changes and providing a method by which to find a best-fit solution to these complex problems.

1.5.4. Future work

Future work would be beneficial in the development of this field. Future research evaluating the implementation of the above recommendations will determine whether benefits are observed in patient experience and begin the process of generating an evidence-base for clinical practice. In addition, future work including non-western cultures and non-UK healthcare systems will improve application outside the UK and Europe, allowing for more uniform patient experience across the fFTD community.

1.5.5. Conclusions

Overall, this study uses a Delphi consensus methodology to explore the genetic testing experience in fFTD and provide expert recommendations for diagnostic testing. Healthcare professionals should be educated on the complexities of counselling individuals affected by fFTD and remain mindful of the psychological impact this may have. The recommendations outlined in this chapter provide a framework within which healthcare professionals can evaluate complex situations and ensure that best-practice is followed. Following the implementation of these recommendations within clinical neurogenetics services, future work should investigate whether improvements in patient experience are observed. Further work will also be needed to address whether the application of such recommendations in different healthcare systems is feasible.

Chapter 2. Developing a tailored predictive testing protocol for use in frontotemporal dementia

2.1. Chapter overview

Following on from the diagnostic testing recommendations presented in Chapter 1, this chapter outlines expert consensus recommendations for predictive testing. In addition to this, qualitative data was employed to provide a patient perspective to predictive testing, and guidelines for predictive testing. The findings outlined in **Error! Reference source not found.** and **Error! Reference source not found.** of this thesis demonstrate the psychological challenges associated with living at-risk, and for some predictive testing is a key part of this experience. The current predictive testing protocol used as a 'gold standard' in hereditary neurodegenerative diseases was designed for HD, although there are likely many overlapping aspects covered within this protocol, therefore also may be issues regarding the application within FTD. For example, these guidelines may be implemented in a less rigorous manner due to the need for extrapolation, and healthcare professionals unfamiliar with fFTD may also lack resources and information to thoroughly counsel those at-risk. Anecdotally, some participants seen within GENFI report difficult experiences with predictive testing, suggesting there is variation across services. Therefore, due to the significance of predictive testing for many at-risk individuals, and the potential psychological implications of this experience at an already emotionally challenging time, it is important to ensure a supportive and comprehensive predictive testing experience. Therefore, the aim of this chapter was to consult experts within the field, using a Delphi consensus methodology, as well as thematic analysis of qualitative interview data regarding predictive testing experiences, to inform the development of FTD predictive testing recommendations, and adaptation of existing 'gold standard' guidelines. The overarching goal of this is to improve the predictive testing experience and provide more well-rounded and supportive services in order to further improve wellbeing of those living at-risk of fFTD.

2.2. Introduction

Genetic counselling is recommended prior to predictive testing (MacLeod et al., 2013) and a detailed cost-benefit discussion is had to assist the individual's decision making. There have been a small number of studies that have looked at people's reasoning around testing with the most common factors in people who choose to have testing being: to know if children were at risk, financial and family planning, reducing uncertainty and anxiety and concern about developing symptoms (McRae et al., 2001; Steinbart, 2001b). Reasons for not having predictive testing included maintaining hope and the inability to cope with the psychological consequences of knowing they will develop the disease in the future (McRae et al., 2001). While predictive testing may relieve uncertainty, allow planning for the future, and inform decision-making regarding reproduction for some, there are also many limitations to undergoing this procedure (McRae et al., 2001; Steinbart, 2001). As fFTD research moves closer to identifying potential disease modifying treatments, requests for predictive testing are increasing (Amador et al., 2021; Crook et al., 2022).

The main limitation of undergoing testing is that once the result is disclosed, there is no way to remove this information. Adverse psychological reactions are also a risk to consider as this is difficult to predict as discussed in Chapter **Error! Reference source not found.**. A further issue is the uncertainty and lack of information available regarding disease onset (i.e. what age they will develop symptoms) and the presentation that an individual can expect (i.e. what symptoms they may develop) (Fong et al., 2012).

2.2.1. Predicting age at onset

Age at onset remains difficult to predict in genetic FTD in comparison to many other neurodegenerative conditions, and can be between 20 years of age and 90. Moore et al. (2020) recently showed that although age at symptom onset in an individual significantly correlated with both their parental age at onset and mean family age at onset across all three main FTD causing genes, the correlation was weak for *C9orf72* and *GRN* mutation*s,* and only relatively strong for *MAPT* mutations (r=0.45 for parental age at onset and r=0.63 for mean familial age at onset).

Both *GRN* and *C9orf72* mutations show age-related penetrance, with onset being seen into the 90s (Gass et al., 2006b; Moore et al., 2020; Murphy et al., 2017b). The *C9orf72* expansion has also been found in 0.15% - 1.2% of healthy older individuals (Beck et al., 2013; Galimberti et al., 2014). *MAPT* mutations are generally fully penetrant although onset can be into the 80s on rare occasions with some incomplete (likely age-related) penetrance reported (Anfossi et al., 2011; Moore et al., 2020; Munoz et al., 2007; Rossi et al., 2008; Van Herpen et al., 2003).

2.2.2. Prediction of phenotype

As previously discussed in the introductory chapter, numerous clinical phenotypes can exist within the same family and it cannot be predicted in advance which phenotype an individual may develop. This can be of concern within families at-risk of *C9orf72* expansions, who are unable to predict if they will develop FTD, MND or FTD-MND which can cause a significant burden when planning for the future.

There are also more complex issues such as variants of unknown significance, an unknown mutation but autosomal dominant family history, and genetic anticipation, that it might be pertinent to discuss with a patient. However, currently these issues are difficult to address owing to lack of conclusive findings within the literature (Fong et al., 2012). Furthermore, considering the lack of currently available treatment for FTD, knowing one's genetic status would not have an impact on an individual's medical treatment or provide clinical benefit while living asymptomatically. Genetic privacy may also be an issue to some, particularly in countries without a national healthcare system. The Genetic Information Non-discrimination Act prohibits genetic information being used to discriminate in terms of health insurance and employment in the US and in addition to this federal legislation, many states also have their own legislation (Fong et al., 2012). Therefore, discussing this issue during genetic counselling may put patients at ease regarding the wider impact of their genetic status.

As discussed above, there is a large amount of uncertainty and unpredictability associated with predictive testing in FTD which differs from diseases like HD which are more well understood. It is important to ensure predictive testing processes are standardised in order to ensure the best, evidence-based practice for patients and their families. Receiving genetic information is a psychologically challenging experience

which, as stated above, may have adverse psychological effects, therefore it is imperative that clinicians remain cognisant of this risk and take measures to limit this wherever possible. Therefore, both patients receiving genetic testing and health-care professionals involved in genetic counselling and testing, may benefit from an FTD-specific protocol to address some of these issues. As such, this study aimed to develop a tailored genetic testing protocol for use in FTD by use of expert opinion through a Delphi consensus methodology and using semi-structured interview to incorporate the patient perspective.

2.3. Methods

2.3.1. Delphi consensus methodology

For Delphi methodology, see Chapter 1.3.1.

2.3.2. The patient perspective of predictive testing - qualitative methods

A more detailed explanation of the methods employed in the qualitative arm of this project can be found in Chapter **Error! Reference source not found.**.

2.3.2.1. Participants and recruitment

Participants were a subset of the sample outlined in Chapter **Error! Reference source not found.** who had undergone predictive testing. Twelve individuals were recruited from the GENFI cohort at UCL. Seven individuals were identified as mutation carriers, with the remaining five, found not to possess the genetic mutation (non-carriers).

Participants were recruited by email as this study took place during the COVID-19 pandemic. Project details were outlined, following which, a number of individuals identified themselves as interested in participating. There was an underrepresentation of non-carriers within the initial sample and as such, a number of known non-carriers were approached and offered the opportunity to participate.

For participant demographics see Chapter **Error! Reference source not found.**.

2.3.2.2. Procedures

Semi-structured interviews explored the lived experience of being at-risk of fFTD. This study utilises a subset of this data, focusing on the predictive testing experience. Participants were specifically asked to outline their experience of predictive testing and the impact that this had, (for the full interview schedule see Appendix 2). Interviews took place in mid-late 2020 and lasted for between 30-90 minutes.

For a more detailed description of the procedures used within this study see Chapter **Error! Reference source not found.**.

2.3.2.3. Materials

As described in Chapter **Error! Reference source not found.**, interviews were conducted virtually due to COVID-19 lockdown. Both Zoom (Zoom Video Communications Inc., 2021) and Microsoft Teams (*Microsoft Corporation*, 2020) were used to host and record the interview sessions. Transcription was aided by the use of Trint software (*Trint*, 2021, https://trint.com).

2.3.2.4. Analyses

An inductive and reflexive approach to thematic analysis was used, following the methodology outlined by (Braun and Clarke, 2006). NVivo 12 Pro software (*NVivo*, 2018) aided the coding and thematic analysis procedure. A subset of codes were reviewed by an independent rater and themes derived were reviewed with JCS.

As above, a more detailed description of the analytic procedure can be found in Chapter **Error! Reference source not found.**.

2.4. Results

2.4.1. Delphi consensus

As in Chapter 6, findings are reported following three questionnaire rounds and a minimum of 70% is required to achieve consensus.

Participants were presented with a number of vignettes of an asymptomatic individual with a family history of FTD, presenting to clinic requesting predictive testing. They were asked what they would do in these four scenarios – how would they proceed with testing?

"An asymptomatic person with a family history of FTD but no known genetic mutation in the family at present…"

Scenario 1 –*… and a living, affected relative who is able and willing to consent to diagnostic testing.*

Eighty-five percent of experts recommended performing diagnostic testing on the affected relative, independent of their family history, to ascertain whether a mutation is present and then offering predictive testing to the asymptomatic individual.

Scenario 2 - … *and a living, affected relative who is unable to consent to diagnostic testing.*

Eighty-one percent of experts recommended performing diagnostic testing on the affected relative, independent of their family history, to ascertain whether a mutation is present *if they are able to assent to having a blood or saliva sample taken and the family are all in agreement* and then offering predictive testing to the asymptomatic individual.

Scenario 3 - … *and no living affected relative but a sample of DNA or tissue is stored from a non-living affected relative. The family are in agreement with testing.*

Eighty-four percent of experts recommended performing diagnostic testing on the affected relative's stored sample, independent of their family history, to ascertain whether a mutation is present and then offering predictive testing to the asymptomatic

individual.

Scenario 4 - … *and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member*

Eighty-eight percent of experts recommended not offering predictive testing in this circumstance i.e. no blind predictive testing of individuals.

Scenario 5: … *and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD. E.g., only fixed tissue available, no DNA has been able to be extracted.*

Eighty-eight percent of experts recommended performing targeted predictive testing in this circumstance, based on the underlying characteristic pathology e.g., 1) presence of dipeptide repeats in the brain would lead to testing for *C9orf72*; e.g., 2) presence of TDP-43 type D pathology would lead to testing for VCP.

2.4.2. Qualitative results – the patient perspective

There were five themes relating to the process of genetic testing and PGD. These themes describe the stages of predictive testing; deciding whether to get tested, preparation and expectations for genetic testing, the process of testing, receiving the genetic test result and preimplantation genetic diagnosis. The content of these themes are summarised below.

Theme 1: Deciding whether to get tested

All participants spoke about the decision regarding predictive testing. Some were advised against or discouraged from testing in some way, however around half felt strongly that they wanted to know their status.

> *The only thing that I was certain of when I found out she had it was I wanted to get tested.* (Participant 10)

Most participants mentioned factors they considered when making their decision to have predictive testing. These included family support, practical implications of knowing their status and whether they would feel better or worse for knowing. Some

individuals spent time deciding whether to go through the testing process, with one initiating counselling in order to help make their final decision, whereas others made the decision quickly.

Many individuals noted reasons in favour of predictive testing, including clarity, future planning, peace of mind, to understand the impact on family and children, to allow for having a child without the gene. A few individuals noted that they would be motivated to have predictive testing if clinical trials looked hopeful. Some individuals also noted reasons against having predictive testing, these included that they felt comfortable not knowing, the length of time one would potentially live with the knowledge of their positive status, the potential to overthink possible symptoms and question judgement and the lack of treatment available.

Theme 2: Preparation and expectations for genetic testing

Most participants spoke of their preparation and expectations for predictive testing. Around half of individuals expected psychological counselling as part of the predictive testing process. Some expected psychological support to automatically be in place throughout the testing process, while others expected more mental health support or simply more support in general. Many participants expressed that genetic counselling was not what they expected. Some individuals felt that the label of 'genetic counselling' was inappropriate as it implied more of a talking therapy style of support, rather than the psychoeducation that was provided. In addition, a few individuals felt that they did not receive adequate information during genetic counselling about what to expect from predictive testing.

Theme 3: Process of testing

Almost all individuals described problems with the predictive testing experience. Practical problems included disorganised appointments, accidental disclosure of results to GP and issues with follow up appointments. For some, this created additional stress and frustration, due to their already heightened emotional state at uncovering their risk. The length of predictive testing was an issue for ten individuals who felt that the process was too lengthy and waiting times were too long, both in terms of appointment waiting times and the 'cooling off period'. This was a source of frustration for some who were eager to find out their result and for those who needed to begin

PGD. Meanwhile a few participants felt that the length of predictive testing was suitable, with one stating that the ‘necessary slowness’ ensured the decision wasn’t rushed.

> *I mean, I felt, the one thing it was very useful for was I didn't feel like I was rushing into something that I would potentially regret. I did feel like the necessary slowness of it. I think it was once a month, I could be, it might have been once every fortnight but it, it seemed, it went on for a long time. And there was enough time in between sessions for these internal thoughts I was having and conversations I was having with friends, family and stuff or my sister. To. To influence what I was thinking about between each session, so I'd sort of, it wasn't like it was one once a day for a week. It was. There was enough time. So it was actually weighted quite well, I think. It was just it wasn't a sort of like session one; 'oh my God, I've never really thought about this I really need to think about it'. So in that sense, it was quite, that was probably the best thing about it.* (Participant 4)

Many participants noted negative experiences during the predictive testing process. Many of whom had issues during genetic counselling, feeling as though they did not gain information from this experience. In addition, a small number of participants stated that they had little or no counselling. Over half of individuals felt that they had a bad experiences in predictive testing, largely referring to the psychological difficulty of the process and the negative implications for their mental health and wellbeing. Disorganisation, miscommunication and disconnect between services were also issues in this experience.

Over half of individuals also mentioned positive experiences during predictive testing, this included feeling that it was thorough and helpful and ensuring that they considered a range of factors prior to testing.

Many participants also offered improvements for the predictive testing process. Suggested improvements included better management of expectations in terms of predictive testing, genetic counselling and time scales. It was also suggested that there was a need for greater clarity and depth of information given in counselling. Participants wanted more support throughout the predictive testing process and some

felt that they would benefit from the process being quicker.

Theme 4: Receiving the genetic test result

A number of participants had negative experiences receiving the results of their predictive test. Some individuals felt that they were not adequately prepared to receive their result and their expectations were not met in terms of the time frame in which they expected to receive their result. A few individuals reported poor delivery of results, including lack of compassion, poor timing and receiving results by letter. One individual noted that the counsellor's body language and behaviour was different in the appointment in which they received their results, leading them to assume they were going to receive an unfavourable result.

Most individuals spoke of their emotional reaction to their predictive test result. Some felt confused at their result and at the range of emotions they experienced. A small number of individuals also described having a difficult time adjusting to their genetic information, both positive and negative. Some individuals described negative reactions to their status, these were largely those who had received news that they were mutation carriers. While others also spoke of positive reactions to their status, largely those with negative status.

Theme 5: Preimplantation genetic diagnosis (PGD)

Around half of participants mentioned PGD, often linked with the predictive testing experience and experienced some of the same difficulties as with predictive testing, including waiting, frustration and administrative problems. One individual said that the information regarding PGD provided by their geneticist was helpful.

2.4.3. Proposed FTD predictive testing recommendations

MacLeod et al.,'s (2013) recommendations for predictive testing in HD provide comprehensive guidance for the predictive testing procedure. These recommendations are largely applicable in FTD with only some minor amendments, a table displaying MacLeod's HD recommendations amended for use in FTD can be found in Appendix 18.

The recommendations described below can be considered supplementary to

MacLeod’s original recommendations, based on the findings outlined above.

Additional recommendations:

Who should be offered predictive testing? Special circumstances

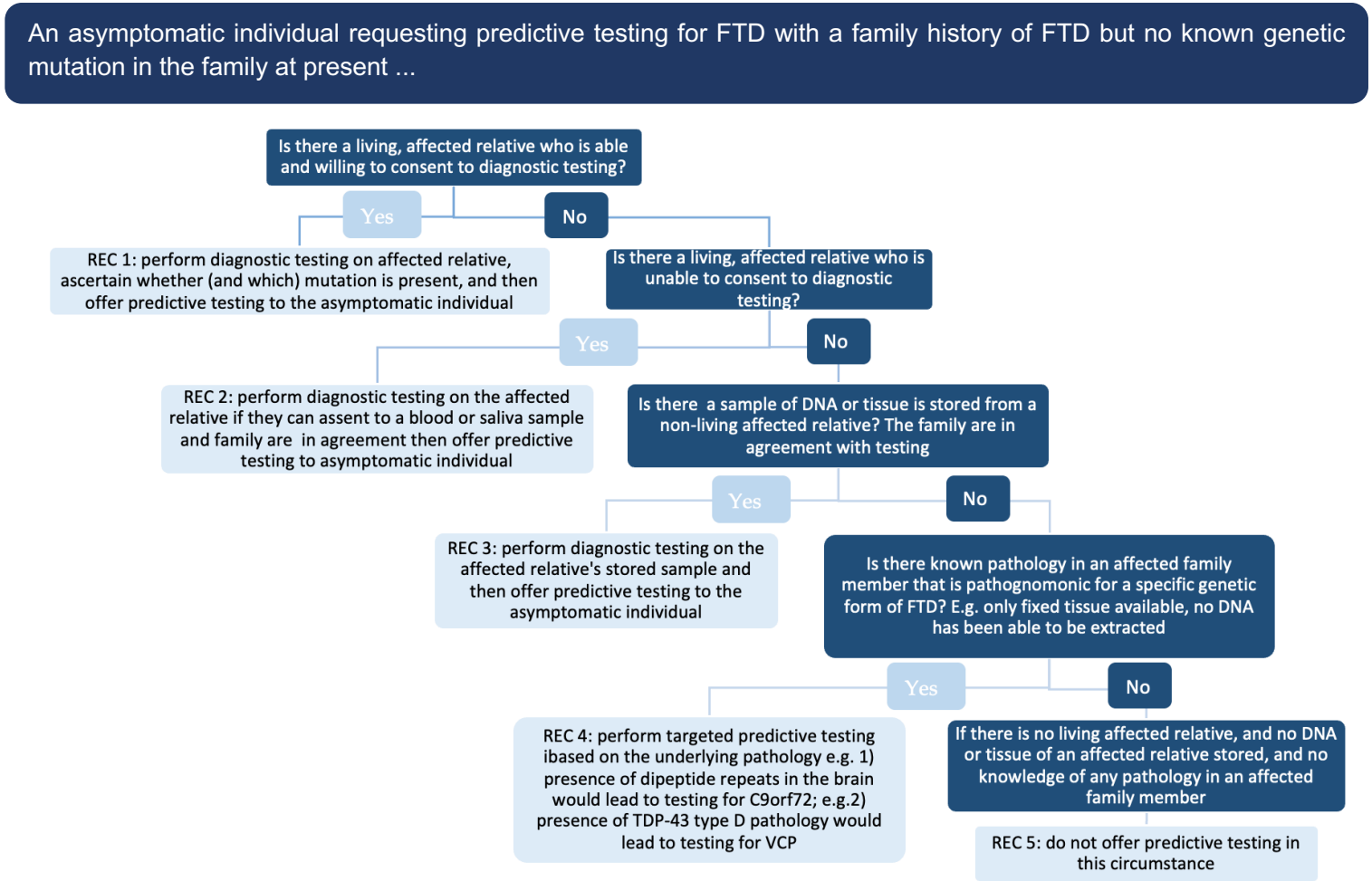

Figure 2- Decision-tree showing predictive testing recommendations for various special circumstances

How should predictive testing be carried out? The patient's perspective:

Pre-test
1. Minimisation of administrative issues
2. Management of expectations a. Expected timelines and waiting times should be clearly communicated to patients wherever possible to minimise frustration. b. Patients should be fully informed regarding the purpose and procedures involved in genetic counselling. There should be transparency regarding the support available throughout the genetic counselling process.
Counselling procedure
3. Access to counselling and/or specialist psychological support should be available in tandem with predictive testing for FTD. There should be clarity regarding how to access this support and participants should be informed of this at the beginning of the predictive testing process.
4. Predictive testing and genetic counselling should be tailored to the individual wherever possible: a. During the first genetic counselling session, a timeline for future appointments should be agreed with the patient, for some it may be appropriate to have fewer sessions or a shorter period between appointments due to other time-sensitive issues such as PGD. Therefore, it is important to assess on a case-by-case basis. b. As above, the length of the 'cooling off' period should be discussed and agreed with the patient, again to minimise frustration. For some a shorter cooling off period may be appropriate if they have communicated certainty on their decision throughout the counselling process, while those who remain undecided may request a longer period to make their final decision. **c.** The content of genetic counselling should be tailored to the individual's

knowledge base. The counsellor should assess the patient's baseline knowledge and what they would like to understand through the counselling process. For some, it may be pertinent to cover the basic elements FTD psychoeducation and heritability, such as possible phenotypes and potential age at onset. Others may already be well-read on such information and prefer a higher-level of understanding, with the guidance of a professional who may be able to help them understand more complex issues.

5. Genetic counselling should prepare patients for the wide-ranging and often turbulent emotions experienced following predictive testing and provide them with tools to manage this experience.

Test result

6. Delivery of results:
    a. A rapport should be built during the counselling process so that genetic counsellors can understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result they may receive.
    b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up and additional support if needed.
    c. If not already in progress, patients should be offered psychological support.

Follow-up

7. Follow-up should be considered a priority;
    a. At least one follow-up appointment should be scheduled during the final genetic counselling session or following the delivery of the genetic result.

b. Follow appointments should be in-person wherever possible, however video or phone appointments may also be suitable.
c. If a patient does not attend their follow up appointment, contact should be made via email or letter to provide contact details for follow up support.

8. Connect to support and research
    a. Regardless of test outcome, patients should be connected to available research studies e.g. GENFI (UK, Europe and Canada) and ALLFTD (US), genetic counsellors or geneticists may refer patients directly to the study, or provide contact details for the patient to self-refer.
    b. Regardless of test outcome, patients should be linked to appropriate support services e.g. Rare Dementia Support (UK) and AFTD (US).
    c. Regardless of test outcome, patients should be provided information on how to access further psychological support if necessary.

2.5. Discussion

This study uses expert opinion and patient perspectives to develop guidelines for predictive genetic testing in fFTD. Recommendations provide important additions to the 'gold standard' designed for use in HD, allowing for a more comprehensive counselling experience, and addressing current issues in predictive testing highlighted by experts by experience.

2.5.1. Summary of main findings

The vignettes presented to the panel covered scenarios that ranged from relatively common to more unusual scenarios that may present to clinic. Notably, there was strong consensus to recommend targeted predictive testing in cases where characteristic pathology has been identified post-mortem, for example, if dipeptide repeats were identified in the brain, targeted testing for *C9orf72* may be carried out and TDP-43 type D pathology would provide evidence for targeted testing for a *VCP* mutation. These vignettes range from typical situations presenting to a neurogenetics clinic, to some of the more complex and unusual clinical scenarios. Therefore, the expert recommendations may provide useful guidance for healthcare professionals who may have limited experience with FTD families, as well as providing guidance for practice and discussion when presented with more complex cases. Many clinical geneticists remain cautious regarding targeted predictive testing due to the potential of uncovering indeterminate findings. This is often due to the difficulties of counselling families regarding indeterminate results, as well as the impact that these results may have on the individual, such as increased uncertainty and anxiety. There is likely a fine line between being risk averse for the benefit of the patient and creating barriers to accessing predictive testing. The results from this study regarding this particular scenario were largely driven by expert neurologists rather than geneticists or genetic counsellors, highlighting differing opinions dependent on medical specialism. This suggests that implementation of such recommendation may be met with resistance by some geneticists who favour a more cautious approach to predictive testing, however the presentation of this data may open conversation between clinical geneticists and neurologists to assess this on a case-by-case basis.

Thematic analysis of qualitative data highlighted a number of issues regarding patient experience of predictive testing. The themes identified in this study can be further collated into four main areas for improvement in the predictive testing process, detailed below. It is important to note that 50% of individuals expressed positive views regarding parts of the predictive testing experience, indicating that it helped them to thoroughly consider their decision. Such recommendations for improvement should be viewed as an opportunity to improve clinical practice and patient experience, rather than as criticism of existing services.

2.5.1.1. Meeting expectations

Results from this thematic analysis indicated that expectations for genetic counselling were not met. This resulted from patient's lack of understanding regarding the process of genetic counselling and its distinction from psychological therapy or counselling. It is important that expectations are met in terms of what patients may expect from genetic counselling to ensure their engagement in the process. This may be done by early clarification of genetic counselling as a psychoeducation based reflective exercise to support the decision-making process. Some participants found the term 'genetic counselling' elicited confusion; therefore, it may be useful to exercise caution when using this term with patients, but rather outline the process in lay-terms instead.

Similarly, data revealed a need for better management of expectations in terms of timescale. This was reported across the predictive testing process and specifically when receiving results. Patients became frustrated at the lack of clarity regarding timescale of their counselling appointments and when they might expect to receive their result as this had a direct impact on other clinical care such as PGD. For those nearing the boundary of NHS age-related eligibility for PGD this was a source of stress and frustration. In addition, it is important to remember that the information revealed from predictive testing for fFTD is particularly emotive, therefore the time when waiting to receive results may be particularly anxiety inducing for some individuals. Therefore, where possible, as opposed to omission of this information, patients may benefit from increased transparency from clinical genetics services on when they might expect this information and may appreciate updates on delays if appropriate.

2.5.1.2. Need for psychological support

This qualitative data also highlighted the importance of psychological support in tandem with genetic counselling, as recommended by both MacLeod et al. and Crook et al. (Crook et al., 2022; Crook et al., 2022; MacLeod et al., 2013). Some patients found the process of predictive testing to be particularly psychologically challenging and had negative implications for their mental health and wellbeing. Negative emotions were also reported regarding the predictive testing experience as well as confusion at the emotions experienced on receipt of their genetic result. In addition, administrative problems and disorganisation of services added an extra element of distress to the already emotive experience. It is to be expected that predictive testing for fFTD is an emotionally charged experience, however, measures can be taken to mitigate this. Services may consider working with specialist mental health professionals, or local community mental health services in order to offer coordinated psychological support throughout predictive testing. Clear pathways to support should be signposted throughout appointments and information provided regarding specialist services such as Rare Dementia Support and GENFI who may be able to provide more specialist and ongoing support.

2.5.1.3. Administrative problems

Disorganisation, miscommunication and disconnect between services were reported as issues that created difficulties in the predictive testing experience. Unfortunately, NHS services in the UK are experiencing challenges regarding underfunding and understaffing, therefore many of these issues may result from systemic problems within the NHS as a whole. However, in order to improve the patient experience, an effort should be made to streamline services, ensuring effective communication between GPs, cognitive neurology clinics, clinical genetics services and other relevant services such as specialist fertility clinics. Patients reported that they found administrative issues difficult to manage due to the added demands of caring for symptomatic family members and managing their own risk. Therefore, attention should be paid to the impact of administrative errors on the patient and assistance may be provided from administrative staff to help resolve such issues.

2.5.1.4. Individualisation

Finally, some patients may benefit from greater individualisation during predictive testing. For example, some patients reported the length of predictive testing to be suitable, while some found it to be too lengthy. For those who found the process to be too lengthy it became less useful and more a source of frustration and 'jumping through hoops'. As mentioned above, for those who required their predictive testing result for further care (e.g., PGD) this was also a source of frustration, particularly due to lengthy waiting times for initial appointments. Therefore, it may be helpful to address these issues with the patient directly and create a dialogue to reflect throughout the process, ensuring both the patient and the genetic counselling requirements are satisfied.

Similarly, some patients expressed that they felt they did not gain information from genetic counselling and that they would have appreciated greater clarity and depth of information. Firstly, this highlights the importance of assessing the patient's baseline knowledge, in order to clarify any errors and assess where further information is needed. As this data was gathered from participants involved in a large cohort study, the sample may be biased towards particularly engaged individuals, therefore they may represent a subset of individuals more inclined to engage in their own research and information gathering regarding fFTD. In addition, a limitation of cohort studies in general is that the sample tends to be of more educated individuals, as such, the individuals in this study may have had a higher educational level and therefore increased opportunity to gather information on fFTD. For more educated or well-researched patients, a higher level of knowledge may be desired, however this may also present difficulty as much remains unknown about fFTD. In such cases the guidelines presented above may provide literature and insight into more specialist issues within fFTD to support healthcare professionals who are unfamiliar with fFTD in having these discussions.

Furthermore, this study also highlights the importance of compassionate delivery of predictive testing results. There should be an emphasis on sensitivity when disclosing such information, particularly as some individuals noted that the clinician seemed distressed at providing this information. Others also analysed body-language and the

clinician's behaviour to try to predict whether they would be receiving positive or negative information. It is important for clinicians to take care and consideration regarding the manner in which they feel it most appropriate to approach this. It may be helpful to be led by the patient themselves, observing their behaviour in prior sessions and building a suitable rapport in order to understand the most appropriate delivery.

The qualitative findings reported in this study, regarding the predictive testing experiences in fFTD are supported by findings reported by Crook et al., (2022) who conducted a qualitative study into genetic testing experiences in FTD and ALS in Australia. In accordance with the findings of this study, they found a lack of information and support, minimal pre and post-test counselling and inadequate follow up, suggesting that the issues highlighted within this study are not limited to UK predictive testing procedures, but rather are indicative of flaws within fFTD genetic testing process worldwide. Crook et al., (2022) also identified support and information needs for genetic testing in FTD and ALS that overlap with the recommendations derived from the data within this study; including greater clarity of information provided, clearer pathways to access genetic testing and further support, information regarding genetic testing timeframes, a clearly defined follow up plan and procedure, as well as access to psychological support. This provides further support to the recommendations for predictive testing outlined within this thesis and suggests clinical implications reaching outside the boundaries of the UK and NHS healthcare systems.

It is clear from the qualitative data analysed alongside this study, that there is room for improvement within the genetic testing experience. It is important within this era of patient-centred care, and in line with the NHS constitution and values, that this lived-experience is accounted for, and the data used to develop services that serve and support this population appropriately. Many healthcare professionals lack experience and knowledge regarding FTD, therefore, for example when counselling those at-risk, they may lack confidence due to the many complexities discussed above (Crook et al., 2022; White et al., 2020). Therefore, the expert consensus recommendations outlined in this study may provide much-needed clarity on some of the difficult topics and scenarios that may arise when dealing with FTD families. This increased clarity and confidence may, in turn, translate directly into a smoother and more positive

experience for patients which is vital given that this is often a difficult and distressing time. The implementation of this protocol may also help to create a more uniform genetic testing experience across services. Clinicians will also recognise that living at-risk of fFTD, undergoing genetic testing and receiving genetic information, whether positive or negative, is a highly challenging and emotional time for not only the individual themselves, but also their family and loved ones. Therefore, it is imperative that genetics services create a supportive and sensitive, patient-centred environment within which to explore these issues.

2.5.2. Limitations

As with all qualitative research, there are limitations regarding the sample studied. The themes outlined within this study are not necessarily representative of the predictive testing experience across different services. Anecdotally, there is high geographical variability observed regarding predictive testing experience, with some services being well equipped to manage rarer conditions such as fFTD. Therefore, findings may be limited in terms of application across services, however the recommendations remain important in guiding counselling and predictive testing procedures. In addition, the application of the patient perspective recommendations outlined within this study may be limited by healthcare resources, or may simply be difficult to apply e.g., minimisation of administrative issues. One issue that arose when presenting these findings to clinical geneticists, were variants of unknown significance. Many geneticists were uncomfortable carrying out genetic tests where there was a possibility of uncertain findings as they are unable to counsel individuals on what this means, therefore increasing the individual's uncertainty, rather than reducing it. Therefore, while such uncertainty exists, geneticists may be reluctant to implement such recommendations. Therefore, further collaboration with clinical genetics services is required.

2.5.3. Future work

As with the diagnostic testing recommendations in Chapter 1, evaluation will be required to determine whether the implementation of these recommendations within predictive testing clinics leads to an improvement in patient experience, as well as evaluating application across cultural groups and settings. In addition, in order to

address the application of recommendations in a clinical setting further collaboration with clinicians and genetics services will be required. The findings regarding assisted suicide were a novel finding that has not yet been discussed within at-risk FTD, therefore further research will be crucial in understanding this within this group in order to safeguard individuals and ensure suitable support is in place. Further work is needed to integrate tailored psychological support interventions such as that outlined in **Error! Reference source not found.**, within predictive testing services, and reliably identify those individuals who require additional support e.g. using the GPRI*plus* questionnaire as described in **Error! Reference source not found.**. This further work is important to ensure a well-integrated and connected service and reduce the frustration felt by patients with regards to a disconnect between different aspects of their care.

2.5.4. Conclusions

Overall, the predictive testing experiences presents a number of challenges, both from the perspective of healthcare professionals in terms of determining how to manage more difficult predictive testing scenarios, and also from the patient perspective. Data obtained from qualitative interview regarding the predictive testing experience suggested a number of areas in which the patient experience may be improved. These were, management of expectations, accessibility and integration of psychological support, individualisation of the counselling process and management of administrative issues. Recommendations outlined provide additional guidance to that currently used for HD, providing insight and information on important topics to cover when counselling those at-risk of fFTD, and providing signposting to services such as RDS and AFTD that can offer additional support. Findings highlighting the need for psychological support during the predictive testing process support findings reported in Chapter 3 and 4 and suggest that due to current guidelines being designed for HD, this protocol is not followed consistently across services. Therefore, the FTD-specific protocol outlined here has important implications for predictive testing experience in fFTD. The use of these guidelines will hopefully provide improved confidence to those counselling individuals at-risk of fFTD, providing them with the resources required to provide comprehensive counselling. In turn, I hope that this will improve the experience of predictive testing for patients. Future integration of predictive testing with tailored

psychological interventions as outlined in Chapter 5 will also ensure a more well-rounded, informational and supportive experience.

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Appendices

Appendix 1: Genetic Psychosocial Risk Instrument *plus* questionnaire

Genetic Psychosocial Risk Instrument (GPRI) *plus*

[for presymptomatic participants only]

Section 0 – Demographics [not needed if included within main GENFI pack]

Name or GENFI code			
Gender (please circle)	Male/female	**Years in education** e.g. if left at 18 and started at 5 = 13	
Date of birth		GENFI site	
What genetic mutation are you at risk of? ☐ C9orf72 ☐ GRN (Progranulin) ☐ MAPT (Tau) ☐ Other (please specify):			

Section 1 – Living at-risk

1	At what age did you find out that you were at-risk of FTD or a related condition?	

Section 2 – Genetic counselling and presymptomatic genetic testing

1	Have you ever had genetic counselling?	Yes/No		
2	Have you had presymptomatic genetic testing?	Yes/No	If yes, when (number of years and months ago)?	_ _ years _ _ months
3	If Yes to Question 2, how long did you	☐ Less than 6 months		

	consider having genetic testing for before you had the test?	☐ 6 months to 1 year ☐ 1 year to 2 years ☐ 2 years to 3 years ☐ More than 3 years
4a	If Yes to Question 2, did presymptomatic genetic testing show that you were a carrier of the genetic mutation?	☐ Yes – mutation carrier ☐ No – not a mutation carrier ☐ Do not want to share
4b	If No to Question 2, on a scale of 0-100% (where 0 is no risk and 100 is a definite mutation carrier), what do you think your risk is of carrying a mutation? (place a X on the line)	0 _____50_____100 _____

Questions 5 and 6: If you have had presymptomatic testing or you have definitely decided you will have it, answer question 5. If you have decided not to have testing or are undecided on whether to have testing, answer question 6.

5	To what extent were the following reasons important in your decision to have presymptomatic testing?	Not at all	A little	Somewhat	Very	Extremely
	Relieving uncertainty	1	2	3	4	5
	General planning for the future	1	2	3	4	5
	Being able to inform my children about their risks	1	2	3	4	5
	Being able to make arrangements for my future care	1	2	3	4	5
	To relieve anxiety	1	2	3	4	5
	To alter the medical care I currently receive	1	2	3	4	5
	To confirm the feeling that I already	1	2	3	4	5

	have the disease					
	Planning a family	1	2	3	4	5
	Curiosity	1	2	3	4	5
	Other (please state):	1	2	3	4	5
6	To what extent were the following reasons important in your decision to not have presymptomatic testing?	Not at all	A little	Somew hat	Very	Extreme ly
	The results would be too difficult to handle	1	2	3	4	5
	The results would not alter my medical care	1	2	3	4	5
	The results would not affect my future planning	1	2	3	4	5
	There is nothing that can be done anyway	1	2	3	4	5
	It would make me worry about my children's risks of developing FTD	1	2	3	4	5
	I would not be able to continue enjoying life	1	2	3	4	5
	The results could change how people treat me	1	2	3	4	5
	I would just be preoccupied with the signs of onset of the disease	1	2	3	4	5
	Insurance companies can misuse my information	1	2	3	4	5
	Other (please state):	1	2	3	4	5

7	Do you have children?	Yes/No

Section 3 – Mental and physical health

1a	Have you had emotional problems in the past?		Yes No				
1b	Have you ever had any diagnosed mental health problems?		Yes – previous Yes – ongoing No				
1c	If the answer to Question 1b is yes, what diagnosis was made? Select all that apply (if more than one).		Depression Anxiety Other (please state):				
1d	Since finding out that you were at risk of FTD, have you had emotional problems that have led to you having thoughts about suicide?		Yes – currently Yes – more than 6 months ago Yes – more than 1 year ago No Prefer not to answer				
1e	In the past month:		Not at all	Hardly ever	Sometimes	Often	Almost all the time
		Have you felt generally sad	1	2	3	4	5
		Have you felt generally nervous and anxious	1	2	3	4	5
2	Has being aware of your at-risk status changed your mental health (please circle a number)?		Changed for the worse			Not changed	Changed for the better
			1	2	3	4	5	6	7

3	If you have had presymptomatic genetic testing, has that changed your mental health (please circle either N/A or a number)?		N/A (i.e. you have not had presymptomatic genetic testing)						
			Changed for the worse			Not changed	Changed for the better		
			1	2	3	4	5	6	7
4	To what extent do you currently agree with the following statements:		Not applicable	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	
	If I learn that I have a genetic mutation, I believe that:	I will have more problems in my life	0	1	2	3	4	5	
		I will change plans for my career/ profession	0	1	2	3	4	5	
		I will have difficulties in my family relationships	0	1	2	3	4	5	
	The disease for which I am at risk is *currently* causing a significant disruption in my family life		0	1	2	3	4	5	
	I am worried that my test result will impact on my relationship with my significant other (or future partner)		0	1	2	3	4	5	
	I am worried about talking to my children (young or adult) about the heritable nature of the disease		0	1	2	3	4	5	
	My worries about the disease affect my daily mood		0	1	2	3	4	5	

	I often find myself worrying or preoccupied with my risk of getting the disease	0	1	2	3	4	5
	I am concerned about my risk of getting the disease, however this concern interferes minimally with my everyday life	0	1	2	3	4	5
	I feel guilty that I might pass on the disease risk to my children	0	1	2	3	4	5
5	Have you taken care of a very ill parent or another close family member (e.g. sibling)	Yes/No	If yes, was the illness they suffered from FTD/related condition such as MND?				Yes/No
6	Have you lost a close family member (e.g. parent/sibling) to FTD (or related disorders such as MND)?	Yes/No					
7	Have you had counselling with a counsellor and/or mental health professional in the past?	Yes/No					
8	Are you currently seeing a counsellor and/or mental health professional about any emotional concerns?	Yes/No					

Section 4 – Support during the at-risk period

1	Have you had any support during the at-risk period?	No Yes (please state what):
2	If you have accessed support (or attempted to), how easy was it to get?	1 (Extremely easy) – 2 – 3 – 4 – 5 – 6 – 7 (Extremely difficult)
3	If you have accessed support, how much have you benefited from it?	1 (Hugely) – 2 – 3 – 4 – 5 – 6 – 7 (Not at all)

GAD-7

Over the **last 2 weeks**, how often have you been bothered by the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Feeling nervous, anxious or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Worrying too much about different things	0	1	2	3
4	Trouble relaxing	0	1	2	3
5	Being so restless that it is hard to sit still	0	1	2	3
6	Becoming easily annoyed or irritable	0	1	2	3
7	Feeling afraid as if something awful might happen	0	1	2	3

PHQ-9

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself – or that you are a failure or have let yourself	0	1	2	3

	or your family down				
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

Appendix 2: Semi-structured interview schedule

Questions	Follow up/Prompts
1. How did you find out about being at-risk of FTD?	• E.g. Were you told by a family member or did you find out when someone became symptomatic • How old were you?
2. What was it like for you when you found out that you were at risk?	• How did you feel about it at the time? • (If say it was difficult) How did you adjust to the information? • How long did this take?
3. Has your experience changed since then?	• How?
4. How do you think your life has been affected by finding out about your risk?	• Have you done anything differently that you might not have done if you weren't at-risk?
5. Have you had any support?	• (if so) what support have you had? • How did you find this support? • Did you feel any different due to the support? • Did you do anything differently as a result of this support?
6. Is there any other support that you think would have made a difference?	• E.g. guidance around adjusting to your risk of FTD
7. What kinds of things, if any, may have got in the way of you receiving or accessing support?	• (If they don't bring up) do you have thoughts about how to overcome these? • (if so) please tell me them?
8. What kind of things, if any, helped you to get support?	• E.g. did you find support on the internet or via GP/research team etc?
9. Is there anything else that you think would have helped you?	• What might this look like? • How do you think this would have

	changed things for you?
(depending on whether had genetic testing) And lastly/finally… 10. What sort of support do you think other people in your situation would find most useful?	
If had genetic testing:	
11. What was going through the genetic testing process like?	• What sorts of feelings did you have along the way?
12. Did things change immediately after you found out your result?	• How so?
And lastly/finally… 13. How has this changed in the time since you found out your result?	
Debrief	
14. Is there anything you want to mention that we haven't covered?	
15. How was it having this interview?	
16. Any feedback for future interviews?	
17. Is there anything you weren't asked but thought you should have been?	

Appendix 3: Distribution of qualitative themes across participant groups

Table 4- A table to show distribution of themes and subthemes by genetic status for the feelings and experiences living at-risk of fFTD

Theme	P1	P2	P3	P4	P5	P6	P7	P8	P9	P 10	P
1. The reaction to learning about risk or status – *'it's like ups and downs all the time'*											
a) Attitude to 50% risk – 'it's 50-50 – I might have it, but I might not…'											
b) Dealing with a lot while also trying to process status											
c) Seeing symptoms in family causes concern for self – 'I was totally scared that it was something that could affect me'											
d) Strategies for adjustment											
2. The journey to finding out about your risk											
a) Finding out about risk was a gradually evolving process											
b) Finding out that you are at-risk - Predicting the future											

c) Found out when parent diagnosed											
d) Suspected a genetic cause											
3. The value of information - 'I'm a bit more in control if I've got the knowledge'											
4. Coping											
a) Avoidance – burying the risk in the sand											
b) Planning											
c) Talking											
5. How risk influences life											
a) Effect on individual											
i) Having children											
ii) Importance of time											
iii) Risk factors into decisions											
iv) Risk is always in mind											
b) Effect on relationships – non-romantic											
c) Effect on relationships – romantic											

6. The *'whirlwind'* of emotions experienced throughout the at-risk journey											
a) negative											
i) Anger											
ii) Fear											
iii) Frustration											
v) General negative psychological response											
vi) Helplessness											
vii) Isolation – 'it's almost like you're left out at sea'											
viii)Low mood											
ix) Participant visibly emotional											
x) Shock											
xi) Survivor guilt											
xii) Uncertainty											
xiii)Worry & anxiety											
b) Positive											
i) Hope											

ii) Positivity											
iii) Relief											

Table 5 - A table to show distribution of themes and subthemes by mutation status for support needs while living at-risk of fFTD

Theme	P1	P2	P3	P4	P5	P6	P7	P8	P9	P 10	P
1. The presence or absence of support											
a) Lack of support											
2. The types of support received											
a) Psychological therapy											
3. Support is *'paramount'* - The impact of support											
4. 'I didn't know where to go to get proper support that actually understood' - Barriers to accessing support											
a) Accessibility											
b) 'You don't want to bring people down about talking about it - it's quite miserable'											

c) Individual attitudes – 'lots of people would rather saw their leg off than see a therapist'											
d) Lack of understanding											
e) Time											
5. Facilitators for support											
a) Utility of being online											
6. Support wanted											
a) Professional support											
b) Better coordination, timing and accessibility of support											
c) Peer support											
d) Knowledge and information											
e) Didn't feel needed support											
f) Safe space to explore feelings											
7. The importance of understanding the specific difficulties – 'I couldn't face talking to people that didn't know											

what I was talking about.'											
a) Research support											
b) Peer support groups											
c) General peer support											
d) Supportive partner											
e) Supportive family											

Appendix 10: FTD genetic testing protocol Delphi consensus round 1 – Question 1 percentage of responses for each item

	All	All <50 years	All <60 years	All <x years (please include age in 2nd column)		Those with a strong family history (defined as modified Goldman 1 or 2)	Those with a family history (defined as modified Goldman score 1, 2 or 3)	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)
bvFTD	42%	25%	33%	17%	60/65	27%	27%	45%
FTD-ALS	67%	17%	33%	17%	any/65	27%	27%	36%
nfvPPA	25%	33%	33%	8%	any	27%	45%	55%
svPPA	8%	42%	25%	8%	60	45%	45%	45%
lvPPA (AD biomarkers unknown)	8%	50%	17%	8%	60	36%	45%	36%
lvPPA (AD biomarkers positive)	0%	33%	33%	8%	60	36%	18%	27%
lvPPA (AD biomarkers negative)	25%	33%	25%	17%	60/65	18%	27%	45%
PPA-NOS	17%	33%	33%	17%	60/65	27%	27%	36%
CBS	8%	50%	17%	8%	60	45%	45%	45%

PSP	0%	42%	17%	8%	60	64%	36%	36%
bvFTD/PPA overlap	42%	25%	33%	17%	60/65	27%	36%	36%
CBS/PPA overlap	17%	42%	25%	8%	60	36%	36%	55%
Late-onset psychosis (including schizophrenia)	17%	8%	17%	8%	60	55%	18%	0%

Appendix 11: FTD genetic testing protocol Delphi consensus round 2 – Question 1 percentage of responses for each item

Phenotype	**All**	**All <60 years**	**All <50 years**	**Those with a strong family history (defined as modified Goldman 1 or 2)**	**Those with a family history (defined as modified Goldman score 1, 2 or 3)**	**Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)**
bvFTD	83%	0%	-	-	-	13%
FTD-ALS	92%	0%	-	-	-	4%
nfvPPA	42%	0%	0%	0%	13%	25%
svPPA	17%	0%	0%	9%	9%	39%
lvPPA (AD biomarkers unknown)	9%	4%	0%	4%	30%	22%
lvPPA (AD biomarkers positive)	0%	17%	0%	39%	4%	0%
lvPPA (AD biomarkers negative)	46%	4%	-	-	4%	25%
PPA-NOS	54%	4%	-	4%	0%	21%
CBS	18%	0%	0%	18%	9%	36%

PSP	9%	0%	0%	35%	4%	22%
bvFTD/PPA overlap	70%	0%	-	-	4%	9%
CBS/PPA overlap	26%	0%	0%	9%	9%	35%
Late-onset psychosis (including schizophrenia)	5%	-	-	73%	9%	14%

Appendix 12: FTD genetic testing protocol round 2 question 1 – percentage of responses for additional combined options

	Goldman score of 1-3.5 **AND** <60 yrs	Goldman score of 1-3.5 **OR** <60 yrs	Goldman score of 1-3.5 **AND** <50 yrs	Goldman score of 1-3.5 **OR** <50 yrs	Goldman score of 1-3 **AND** <60 yrs	Goldman score of 1-3 **AND** <50 yrs	Goldman score of 1-3 **OR** <60 yrs	Goldman score of 1-3 **OR** <50 yrs	Goldman score of 1-2 **AND** <60 yrs	Goldman score of 1-2 **OR** <60 yrs	Goldman score of 1-2 **AND** <50 yrs	Goldman score of 1-2 **OR** <50 yrs
bvFTD	0%	4%	-	-	-	-	-	-	-	-	-	-
FTD-ALS	0%	4%	-	-	-	-	-	-	-	-	-	-
nfvPPA	4%	8%	0%	0%	4%	0%	0%	4%	-	-	-	-
svPPA	0%	9%	0%	4%	4%	0%	4%	4%	-	-	-	-
lvPPA (AD biomarkers unknown)	-	-	-	-	9%	-	22%	-	-	-	-	-
lvPPA (AD biomarkers positive)	-	-	-	-	-	-	-	-	22%	17%	-	-
lvPPA (AD biomarkers	8%	8%	-	-	-	-	-	-	-	-	-	-

negative)												
PPA-NOS	13%	4%	-	-	-	-	-	-	-	-	-	-
CBS	-	-	0%	5%	-	-	-	-	-	-	0%	14%
PSP	0%	4%	0%	4%	-	-	-	-	4%	9%	0%	9%
bvFTD/PPA overlap	0%	4%	-	-	-	-	-	-	-	-	-	-
CBS/PPA overlap	9%	9%	0%	4%	-	-	-	-	-	-	-	-
Late-onset psychosis (including schizophrenia)	-	-	-	-	-	-	-	-	-	-	-	-

Appendix 13: FTD genetic testing protocol round 3 question 1 – percentage of responses for each item

	All	All <50 years	All <60 years	Those with a strong family history (defined as modified Goldman 1 or 2) at any age				Those with a family history (defined as modified Goldman score 1, 2 or 3) at any age	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5) at any age		
				At any age	AND <60 yrs	OR <60 yrs	OR <50 yrs		At any age	AND <60 yrs	OR <60 yrs
bvFTD											
FTD-ALS											
nfvPPA	76%							4%	20%		
svPPA	16%			0%				8%	72%		4%
lvPPA (AD biomarkers unknown)								60%	20%		4%
lvPPA (AD biomarkers			12%	64%	12%	12%					

positive)											
lvPPA (AD biomarkers negative)	80%							8%		8%	4%
PPA-NOS	80%								20%	0%	
CBS	8%			16%					76%		
PSP	4%			64%		4%	4%		24%		
bvFTD/PPA overlap											
CBS/PPA overlap	20%			8%				0%	60%	4%	8%
Late-onset psychosis (including schizophrenia)											

Appendix 14: FTD genetic testing protocol results rounds 1-3 questions 2-4, percentage of responses for each item

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Round 1	Round 2	Round 3
No – they should have predictive testing instead of non-predictive testing	23%	8%	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	25%	20%	12%
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	37%	52%	64%
Other – please comment: - An individualised approach should be considered for each person according to their needs; on many occasions this will require predictive counselling	12% 4%	20%	24%

3. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

	Round 1	Round 2	Round 3
No – should use current guidelines – progranulin levels are not helpful	10%	5%	
Yes – a low blood or CSF level should be considered definitively pathogenic	19%	14%	
Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	62%	82%	
Yes – a low CSF (but not blood) level should be	5%		

considered definitively pathogenic			
Yes – a low CSF (but not blood) should be considered supportive of pathogenicity but not definitive	5%		
Other – please comment	0%		

4. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.	Round 1	Round 2	Round 3
Do not offer predictive testing at all	4%		
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	0%		
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	70%	85%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	22%	15%	
Other – please comment	4%		

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing	Round 1	Round 2	Round 3
Do not offer predictive testing at all	7%		
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	4%		
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	50%	81%	

Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	29%	15%	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	11%	4%	
Store a sample from the affected only if the relative has a strong family history of FTD (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	0%		
Other – please comment	4%		

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from an affected relative.	Round 1	Round 2	Round 3
Do not offer predictive testing at all	14%	4%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	0%		
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive	43%	84%	

testing			
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	32%	12%	
Other – please comment	11%		

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member	Round 1	Round 2	Round 3
Do not offer predictive testing at all	78%	88%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	11%	12%	
Other – please comment	11%		

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD	Round 1	Round 2	Round 3
Do not offer predictive testing at all	18%	12%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	4%		
Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for	61%	88%	

C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP			
Other – please comment	18%		

Appendix 15: FTD genetic testing protocol Delphi round 1 questionnaire

FTD genetics protocol Delphi consensus

1. What would you consider your specialist interest to be?

Neurologist with interest in FTD	
Neurologist with interest in neurogenetics	
Psychiatrist with interest in FTD	
Psychiatrist with interest in neurogenetics	
Clinical geneticist with interest in neurogenetics	
Other (please state):	

2. When would you recommend offering diagnostic testing for the following diagnoses? (Tick one or more boxes)

	All	All <50 years	All <60 years	All <x years (please include age in 2nd column)		Those with a strong family history (defined as modified Goldman 1 or 2)	Those with a family history (defined as modified Goldman score 1, 2 or 3)	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)
bvFTD								
FTD-ALS								
nfvPPA								

svPPA								
lvPPA (AD biomarkers unknown)								
lvPPA (AD biomarkers positive)								
lvPPA (AD biomarkers negative)								
PPA-NOS								
CBS								
PSP								
bvFTD/PPA overlap								
CBS/PPA overlap								
Late-onset psychosis (including schizophrenia)								

Please add any comments you have

Note:

Modified Goldman score =

1 - autosomal dominant family history

2 - familial aggregation of three of more family members with dementia (including FTD/PSP/CBS/ALS)

3/3.5 - one other first degree relative with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family i.e. <65, and 3.5 if onset above 65

4 - no or unknown family history.

3. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

No – they should have predictive testing instead of non-predictive testing	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	
Other – please comment	

4. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

No – should use current guidelines – progranulin levels are not helpful	
Yes – a low blood or CSF level should be considered definitively pathogenic	

Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	
Yes – a low CSF (but not blood) level should be considered definitively pathogenic	
Yes – a low CSF (but not blood) should be considered supportive of pathogenicity but not definitive	
Other – please comment	

5. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	
Other – please comment	

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	
Store a sample from the affected only if the relative has a strong family history of FTD (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	
Other – please comment	

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from an affected relative.	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive testing	
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	
Other – please comment	

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Other – please comment	

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP	
Other – please comment	

Appendix 16: FTD genetic testing protocol Delphi round 2 questionnaire

FTD genetics protocol Delphi consensus

1. When would you recommend offering diagnostic testing for the following diagnoses? Tick only 1 box for each diagnosis. The percentage of respondents who selected each option is shown in brackets (%).

Note:

Modified Goldman score =

1 - autosomal dominant family history

2 - familial aggregation of three of more family members with dementia (including FTD/PSP/CBS/ALS)

3/3.5 - one other first degree relative with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family i.e. <65, and 3.5 if onset above 65

4 - no or unknown family history.

bvFTD

☐ All (62%)
☐ Goldman score of 1-3.5 **(at any age) (**31%)
☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)

FTD-ALS

☐ All (77%)

☐ Goldman score of 1-3.5 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (12%)

☐ Goldman score of 1-3.5 (19%) **AND** <60 yrs (12%)
☐ Goldman score of 1-3.5 (19%) **OR** <60 yrs (12%)

nfvPPA
☐All (38%)
☐ Goldman score of 1-3.5 **(at any age)** (27%)
☐ Goldman score of 1-3 **(at any age)** (23%)
☐ All <60 yrs **(any family history)** (19%)
☐ All <50 yrs **(any family history)** (12%)
☐ Goldman score of 1-2 **(at any age)** (12%)

☐ Goldman score of 1-3.5 (27%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (27%) **AND** <50 yrs (12%)
☐ Goldman score of 1-3.5 (27%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3.5 (27%) **OR** <50 yrs (12%)
☐ Goldman score of 1-3 (23%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3 (23%) **AND** <50 yrs (12%)
☐ Goldman score of 1-3 (23%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3 (23%) **OR** <50 yrs (12%)

svPPA
☐All (19%)
☐ Goldman score of 1-3.5 **(at any age)** (31%)
☐ Goldman score of 1-3 **(at any age)** (27%)
☐ All <50 yrs **(any family history)** (19%)
☐ Goldman score of 1-2 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3 (27%) **AND** <50 yrs (19%)
☐ Goldman score of 1-3 (27%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3 (27%) **OR** <50 yrs (19%)
☐ Goldman score of 1-3 (27%) **OR** <60 yrs (19%)

lvPPA (AD biomarkers unknown)
☐ Goldman score of 1-3 **(at any age)** (31%)
☐ Goldman score of 1-3.5 **(at any age)** (23%)
☐ All <60 yrs **(any family history)** (23%)
☐ Goldman score of 1-2 (**at any age) (**19%)
☐ All (19%)
☐ All <50 yrs **(any family history)** (15%)

☐ Goldman score of 1-3 (31%) **AND** <60 yrs (23%)
☐ Goldman score of 1-3 (31%) **OR** <60 yrs (23%)

lvPPA (AD biomarkers positive)
☐ Goldman score of 1-2 **(at any age)** (31%)
☐ All <60 yrs **(any family history)** (27%)
☐ Goldman score of 1-3.5 **(at any age)** (23%)
☐ All <50 yrs **(any family history)** (15%)
☐ Goldman score of 1-3 **(at any age)** (12%)
☐ All (12%)

☐ Goldman score of 1-2 (31%) **AND** <60 yrs (27%)
☐ Goldman score of 1-2 (31%) **OR** <60 yrs (27%)

lvPPA (AD biomarkers negative)

☐ All (35%)

☐ Goldman score of 1-3.5 **(at any age)** (35%)

☐ Goldman score of 1-3 **(at any age)** (19%)

☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (35%) **AND** <60 yrs (19%)

☐ Goldman score of 1-3.5 (35%) **OR** <60 yrs (19%)

PPA-NOS

☐ All (31%)

☐ Goldman score of 1-3.5 **(at any age)** (27%)

☐ All <60 yrs **(any family history)** (27%)

☐ Goldman score of 1-3 **(at any age)** (19%)

☐ Goldman score of 1-2 **(at any age)** (15%)

☐ Goldman score of 1-3.5 (27%) **AND** <60 yrs (27%)

☐ Goldman score of 1-3.5 (27%) **OR** <60 yrs (27%)

CBS

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-2 **(at any age)** (27%)

☐ All <50 yrs **(any family history)** (23%)

☐ Goldman score of 1-3 **(at any age)** (23%)

☐ All (23%)

☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (23%)

☐ Goldman score of 1-2 (27%) **AND** <50 yrs (23%)

☐ Goldman score of 1-2 (27%) **OR** <50 yrs (23%)

PSP

☐ Goldman score of 1-2 **(at any age)** (35%)

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-3 **(at any age)** (27%)

☐ All <60 yrs **(any family history)** (23%)

☐ All <50 yrs **(any family history)** (23%)

☐ All (12%)

☐ Goldman score of 1-2 (35%) **AND** <60 yrs (23%)

☐ Goldman score of 1-2 (35%) **AND** <50 yrs (29%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (29%)

☐ Goldman score of 1-2 (35%) **OR** <60 yrs (23%)

☐ Goldman score of 1-2 (35%) **OR** <50 yrs (29%)

☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (29%)

bvFTD/PPA overlap

☐ All (54%)

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-3 **(at any age)** (12%)

☐ All <60 yrs **(any family history)** (23%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (23%)

CBS/PPA overlap

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ All (23%)

☐ Goldman score of 1-3 **(at any age)** (23%)

☐ Goldman score of 1-2 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (19%)
☐ All <50 yrs **(any family history)** (15%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (15%)
☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (15%)

Late-onset psychosis (including schizophrenia)
☐ Goldman score of 1-2 **(at any age)** (35%)
☐ Goldman score of 1-3.5 **(at any age)** (19%)
☐ Goldman score of 1-3 **(at any age) (**12%)
☐ All (12%)

For the following questions the percentage of respondents that selected each answer in the previous round is displayed. The answer you selected is highlighted in yellow (if still available – those options selected by less than 10% of respondents have been removed). Please re-answer these questions.

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Previous answers	Current answer
No – they should have predictive testing instead of non-predictive testing	28%	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	28%	

Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	36%	
An individualised approach should be considered for each person according to their needs; on many occasions this will require predictive counselling	~16% (taken from 'other')	

3. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

	Previous answers	Current answer
No – should use current guidelines – progranulin levels are not helpful	10%	
Yes – a low blood or CSF level should be considered definitively pathogenic	19%	
Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	62%	

4. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.		
	Previous answers	Current answer
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	70%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to	22%	

ascertain whether a mutation is present and then offer predictive testing		

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing		
	Previous answers	Current answer
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	50%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	29%	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	11%	

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from a non-living affected relative. The family are in agreement with testing.

	Previous answers	Current answer
Do not offer predictive testing at all	14%	
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive testing	43%	
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	32%	

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member		
	Previous answers	Current answer
Do not offer predictive testing at all	78%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	11%	

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD. E.g. only fixed tissue available, no DNA has been able to be extracted.		
	Previous answers	Current answer
Do not offer predictive testing at all	18%	

Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP	61%	

Appendix 17: FTD genetic testing protocol Delphi round 3 questionnaire

FTD genetics protocol Delphi consensus – round 3

Please re-answer these questions based on the new information provided, the percentage of respondents who selected each option in the previous round is shown and your previous answers are highlighted in yellow (if still available).

1. When would you recommend offering diagnostic testing for the following diagnoses? Tick only 1 box for each diagnosis.

nfvPPA		
	Consensus from previous round	Current answer
All	42%	
Goldman score of 1-3.5 (at any age)	25%	
Goldman score of 1-3 (at any age)	13%	
svPPA		
	Consensus from previous round	Current answer
All	17%	
Goldman score of 1-3.5 (at any age)	39%	
Goldman score of 1-3 (at any age)	9%	
Goldman score of 1-2 (at any age)	9%	
Goldman score of 1-3.5 OR <60 yrs	9%	
lvPPA (AD biomarkers unknown)		
	Consensus from previous round	Current answer
Goldman score of 1-3 (at any age)	30%	
Goldman score of 1-3.5 (at any age)	22%	
Goldman score of 1-3 OR <60 yrs	22%	

lvPPA (AD biomarkers positive)		
	Consensus from previous round	Current answer
Goldman score of 1-2 (at any age)	39%	
All <60 yrs (any family history)	17%	
Goldman score of 1-2 AND <60 yrs	22%	
Goldman score of 1-2 OR <60 yrs	17%	
lvPPA (AD biomarkers negative)		
	Consensus from previous round	Current answer
All	46%	
Goldman score of 1-3.5 (at any age)	25%	
Goldman score of 1-3.5 AND <60 yrs	8%	
Goldman score of 1-3.5 OR <60 yrs	8%	
PPA-NOS		
	Consensus from previous round	Current answer
All	54%	
Goldman score of 1-3.5 (at any age)	21%	
Goldman score of 1-3.5 AND <60 yrs	13%	
CBS		
	Consensus from previous round	Current answer
Goldman score of 1-3.5 (at any age)	36%	
Goldman score of 1-2 (at any age)	18%	
All	18%	
PSP		
	Consensus from previous round	Current answer

Goldman score of 1-2 (at any age)	35%	
Goldman score of 1-3.5 (at any age)	22%	
All	9%	
Goldman score of 1-2 OR <60 yrs	9%	
Goldman score of 1-2 OR <50 yrs	9%	
CBS/PPA overlap		
	Consensus from previous round	Current answer
Goldman score of 1-3.5 (at any age)	35%	
All	26%	
Goldman score of 1-3 (at any age)	9%	
Goldman score of 1-2 (at any age)	9%	
Goldman score of 1-3.5 AND <60 yrs	9%	
Goldman score of 1-3.5 OR <60 yrs	9%	

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Consensus from previous round	Current answer
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	20%	
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	52%	
An individualised approach should be considered for each person according to their needs; on many	20%	

occasions this will require predictive counselling		

Appendix 18: Amendments to MacLeod's HD predictive testing recommendations

	HD REC	HD COM	FTD REC	FTD COM	Change
1.	All persons who may wish to take the test should be given up to date, relevant information in order to make an informed voluntary decision.	The highest standards of counselling should be available in each country. It is recommended that informed consent for the test be documented with the signature of the person to be tested and the professional responsible for the counselling as a standard medical practice.			
2	Access to the test				
2	The decision to take the test is the sole choice of the person concerned. No requests from	The person must choose freely to be tested and not be coerced by family, friends, (potential)			

	third parties, be they family or otherwise, should be considered.	partners, physicians, insurance companies, employers, governments, etc.			
2.1	It is recommended that the minimum age of testing be 18 years. Minors at risk requesting the test should have access to genetic counselling, support and information including discussion of all their options for dealing with being at risk.	Testing for the purpose of adoption should not be permitted, since the child to be adopted cannot decide for him/herself whether he/she wants to be tested. It is essential, however, that the child should be informed about his/her at-risk status.			
2.2	Each participant should be able to take the test independently	Each national lay organization should use its influence with government			

	of his/her financial situation.	departments, public and private health insurers, etc, to reach this goal.			
2.3	Persons should not be discriminated against in any way as a result of genetic testing for Huntington's disease (see also REC 5.3.5).		Persons should not be discriminated against in any way as a result of genetic testing for **Frontotemporal dementia or related syndromes**		Changed wording – HD to FTD
2.4	Extreme care should be exercised when testing would provide information about another person who has not requested the test	This will arise when an individual(s) at 25% risk request(s) testing with full knowledge that his/her parent does not want to know his/her status. Every effort should be made by the			

		counsellors and the individuals concerned to come to a satisfactory solution of this conflict.			
2.5	For participants with evidence of a serious psychiatric condition, it may be advisable that testing is delayed and support services put into place.				
2.6	Testing for HD should not form part of a routine blood investigation without the specific permission of the subject.	Such a specific permission should in principle also be required for symptomatic persons.	Testing for **FTD** should not form part of a routine blood investigation without the specific permission of the subject.		Changed wording – HD to FTD

2.7	Ownership of the test results remains with the person who requested the test. Legal ownership of the stored DNA remains with the person from whom the blood was taken.	The consent form should address this issue. Local legal opinions may be helpful.			
2.8	All laboratories are expected to comply with the Organization for Economic Co-operation and Development (OECD) Guidelines for Quality Assurance in Molecular Testing by providing and practicing genetic testing under a quality assurance	At-risk individuals, family members and the lay organizations can enquire about the quality standards of the laboratory, including, for example, its certification and accreditation status. The lay organizations can also assist persons who want to be or have been tested with their enquiries and			

	framework, meet rigorous standards of accuracy, participating in external quality assessment (EQA) schemes and working towards certification and accreditation.	concerns.			
2.8.1	Laboratories should be cognizant of the limitations of the methodologies used (including, e.g. the possibility of missing a very large expansion, the risk of error that might lead to a non-carrier result if an affected relative has not been		Laboratories should be cognizant of the limitations of the methodologies used, and should indicate these clearly in reports issued, along with margins of error.		Minor amendment to the existing statement removing additional information.

	tested), and should indicate these clearly in reports issued, along with margins of error.				
2.9	The counsellors should be specifically trained in counselling methods and form part of a multidisciplinary team	Such a multidisciplinary team should consist, for example, of a clinical geneticist, genetic counsellor or social worker, neurologist, psychiatrist or psychologist.			
			There should be a minimisation of administrative issues wherever possible to make predictive testing more accessible to those living at-risk who may also be caregivers etc.		Added based on data from this study
3	Support during the test process				
3.	The participant should be encouraged to select a	This should be assessed on an individual basis and the presence			

	companion to accompany him/her throughout all the different stages: the pre-test, the taking of the test, the delivery of the results and the post-test stage.	of a companion may not be appropriate or required in all cases.			
3.1	The counselling unit should plan with the participant a follow up protocol which provides support during the pre- and post-test stages, whether or not a person chooses to be accompanied by a companion.	Wherever possible, support should be available close to the person's community, and on a remote basis, by phone or telehealth where necessary.			
			Access to counselling		

			and/or specialist psychological support should be available in tandem with predictive testing for FTD. There should be clarity regarding how to access this support and participants should be informed of this at the beginning of the predictive testing process.		
4	Recommendation on communication of information				
	Testing and counselling should be provided by genetic counselling units knowledgeable about molecular	Often the test will be conducted at a site different from the counselling centre. If no lay organization exists in the country, the centre should	Testing and counselling should be provided by genetic counselling units knowledgeable about molecular genetic issues in	If no lay organization exists in the country, contacts can be made with a lay organization of a neighbouring country or: - GENFI/ALLFTD - RDS	HD changed to FTD and information regarding lay organisations added

	genetic issues in Huntington's disease. These centres should work in close collaboration with the lay organization(s) of the country.	contact the IHA.	**FTD**. These centres should work in close collaboration with the lay organization(s) of the country.	- AFTD	
4.1	The laboratory performing the test should not communicate the final results to the counselling team until very close to the time the results are given to the participant.	The aim is to protect the participant from the possibility of counselling bias at any time (see also COM 5.2.6).			
4.2	As a rule, members of the counselling team or the technical staff should not communicate any information	Only in the most exceptional circumstances (e.g. prolonged coma or death) may information about the test result, if so			

	concerning the test and its results to third parties without the explicit permission of the person tested.	requested, be provided to family members whose risk is affected by the result.			
4.3	Neither the counselling centre nor the test laboratory should establish direct contact with a relative whose DNA may be needed for the purpose of the test without permission of the participant and of the relative. All precautions should be taken when approaching such a relative.				

4.4	Care should be taken regarding access to clinical reports of the test results.	Consent of the participant should be sought before sending a letter to any physician involved in their care (e.g. family doctor, neurologist, or hospital physician). The possible benefits and drawbacks of sending the result to such physicians should be discussed. These benefits include: post-test support, future clinical care including identification and support around the onset of symptoms, and their symptomatic treatment. The risks include: potential discrimination in			

		economic, social and medical domains, should their medical files be accessed by third parties. In general, it is good clinical practice for the counselling team to suggest that other physicians involved in the participant's care be kept informed about the test and the result. If the participant objects, his/her view should be respected except in the most exceptional of circumstances. If consent is given by the person tested for the test result to be communicated it should be			

		accompanied by a full explanation of the meaning of that result.			
5	Essential information - 'Essential information' means information which is absolutely vital to the whole test procedure. General information:				
5.1		This information should be both written and oral and be provided by the team responsible for the test service.			
5.1.1	On Huntington's disease, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, reproductive	It must be pointed out that at this time no proven prevention, treatment that slows disease progression, or cure is available.	On **FTD**, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, reproductive options, availability of treatment, etc.		HD changed to FTD

	options, availability of treatment, etc.				
5.1.2	On the implications of non-paternity (and nonmaternity).	Genetic testing may show, or suggest, that the putative parent is not the biological parent; this aspect should be drawn to the attention of the participant and discussed. With the presently available techniques of in vitro fertilization, etc., even occasional non-maternity may occur.	On the implications of non-paternity (and nonmaternity).	Genetic testing may show, or suggest, that the putative parent is not the biological parent; this aspect should be drawn to the attention of the participant and discussed.	Minor amendment removing additional information.
5.1.3	On lay organizations, including their documentation on HD, their addresses for help and social	If no lay organization exists in the country, contacts can be made with the IHA or lay organization of a neighbouring	On lay organizations, including their documentation on **FTD**, their addresses for help and social	If no lay organisation exists in the country, contacts can be made with a lay organisation of a neighbouring country or: - GENFI/ALLFTD	HD changed to FTD and information added regarding FTD lay organisations

	contacts, etc.	country.	contacts, etc.	- RDS - AFTD	
5.1.4.	Psychosocial support and counselling must be available before the test procedure commences.	Lay organizations should be mentioned as an additional source of support and information.			
			9. Predictive testing and genetic counselling should be tailored to the individual wherever possible: a. During the first genetic counselling session, a timeline for future appointments should be agreed with the patient, for some it may be appropriate to have fewer sessions or a shorter period between appointments due to other time-sensitive issues such as PGD. Therefore, it is important to assess on a case-by-case basis. b. As above, the length of the 'cooling off' period should be discussed and agreed with the patient, again to minimise		

			frustration. For some a shorter cooling off period may be appropriate if they have communicated certainty on their decision throughout the counselling process, while those who remain undecided may request a longer period to make their final decision. The content of genetic counselling should be tailored to the individual's knowledgebase. The counsellor should assess the patient's baseline knowledge and what they would like to understand through the counselling process. For some, it may be pertinent to cover the basic elements FTD psychoeducation and heritability, such as possible phenotypes and potential age at onset. Others may already be well-read on such information and prefer a higher-level of understanding, with the guidance of a professional who may be able to help them understand more complex issues		
5.2 – Information pertaining to the test					
5.2.1	How the test is done.				

5.2.2	Possible need for DNA from an affected family member and the possible problems arising from this.	Asking an affected person, who may be unaware of or unwilling to acknowledge his/her symptoms, to contribute a blood sample may be an invasion of privacy.			
5.2.3	The limitations of the test (error rate, uncertain predictive interpretation of some CAG repeat numbers, etc).		The limitations of the test (error rate, uncertain interpretation of some repeat numbers, variants of unknown significance etc).		HD testing limitations changed to include FTD testing limitations
5.2.4	The counsellor must explain that, although the genetic mutation has been found, at the present time only limited useful	The correlation between CAG repeat size and mean age of onset could be discussed, but it is important to point out the wide confidence	The counsellor must explain that, although the genetic mutation has been found, at the present time only limited useful	- Age at onset cannot be accurately predicted for GRN or C9orf72 however mean family age at onset is correlated with age at onset	Limits regarding usefulness of test included specifically for FTD

	information can be given about age at onset or about the kind of symptoms, their severity, or the rate of progression.	intervals. A specific repeat size is usually associated with a wide range of age at onset; current mathematical models of age of onset have not been validated for clinical practice.	information can be given about age at onset or about the kind of symptoms, their severity, or the rate of progression.	in MAPT - Age related penetrance can be seen in GRN (and to a lesser extent in C9orf72) see Moore et al. (2020) - Phenotype can't be predicted but common phenotypes seen for the relevant mutation should be explained e.g. C9orf72 and FTD-ALS	
5.2.5	Pre-test genetic counselling should mention all possible test outcomes, including intermediate and reduced penetrance results, which may be prone to repeat instability and	There is at present insufficient information regarding clinical implications of intermediate alleles for future generations.	Pre-test genetic counselling should mention all possible test outcomes, including intermediate repeat expansions and variants of unknown significance where	- The possibility of an intermediate repeat expansion should be discussed in relation to C9orf72, however care should be taken as to how this is interpreted. To date there is insufficient evidence to	Intermediate expansions and variants of unknown significance discussed in FTD

	may expand into higher repeat ranges upon transmission to future generations. However, there is insufficient information regarding the magnitude of the risk of expansion for future generations.		appropriate.	interpret intermediate expansions - Variants of unknown significance should be discussed where appropriate in GRN	
5.2.6	The predictive test indicates whether someone has or has not inherited the gene mutation, but it does not make a clinical diagnosis of HD if the gene expansion is present.	Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of HD; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather,	The predictive test indicates whether someone has or has not inherited the gene mutation, but it does not make a clinical diagnosis of **FTD** if the gene expansion is present.	Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of **FTD**; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather, they should be offered additional pre	HD changed to FTD

		they should be offered additional pre and post test support.		and post-test support.	
5.2.7	Pre-test counselling should also outline information on post-test counselling and options for future research participation and care.				
			10. Management of expectations a. Expected timelines and waiting times should be clearly communicated to patients wherever possible to minimise frustration. Patients should be fully informed regarding the purpose and procedures involved in genetic counselling. There should be transparency regarding the support available throughout the genetic counselling process.		

5.3 Information on consequences					
5.3.1	For the person him/herself.	Most participants will adjust to their predictive test result. Some individuals may, however, experience difficulty coping with any of the possible results in the short or long term (including a result in the normal range). Additional counselling should be offered to those at risk of having difficulties with coping (e.g. individuals with a history of psychiatric illness).			
5.3.2	For the spouse/partner and children.	If the participant is not accompanied by his/her spouse/partner			

		during the counselling sessions, there should be particular discussion about the potential impact of the test result on the spouse/partner. It is possible that the genetic test result and/or family history will impact the participants' current or future family members' eligibility for insurance, employment, legal care of and access to children, and adoption.			
5.3.3	For the affected parent and his/her spouse.	The feelings of the affected parent, who may well become aware of the results, must			

		be taken into account.			
5.3.4	For the other members of the participant's family.	Whatever information is obtained, it may influence the feelings of and the relationship with others, with a potential for discrimination in the family. This may include: disrupted patterns of behaviour and interaction, such as communication changes and feelings of altered sense of membership.			
5.3.5	Potential socioeconomic consequences, including employment, insurance, legal care of and access to				

	children, adoption eligibility, social security, data security and other problems which may occur as a consequence of disclosing the test result or family history.				
5.4 Information on alternatives the participant can adopt					
5.4.1	Not to take the test for the time being.				
5.4.2	To deposit DNA for research.				
5.4.3	To deposit DNA for possible future use by family and self.				
5.4.4	DNA deposited under 5.4 above would be made available to the donor's				

	family members at their request after the death of the donor if it is essential to obtain an informative result.				
5.4.5	In the case of DNA deposited under 5.4.2 and/or 5.4.3 above, the unit collecting the DNA must provide a written declaration that samples will not be used for purposes other than specified in the said declaration with the exception of the provisions of 5.4.4.				
6 - Important preliminary investigations					

6.1	It is important to verify that the diagnosis of HD in the person's family is correct.		It is important to verify that the diagnosis of **FTD** in the person's family is correct.	However, many family histories may be complex with varied presentations or misdiagnoses. Relevant diagnoses should be used in support of the family history, rather than creating a barrier to predictive testing. e.g. late-onset psychiatric diagnoses, broad diagnoses of 'dementia'	Changed HD to FTD and added information regarding ambiguous family history in fFTD.
6.2	Neurological examinations (if possible) and psychological appraisal are considered important to establish a baseline evaluation of each person. This however is not a requirement for participation in predictive	Refusal to undergo these and other additional examinations will not justify the withholding of the test from participants.			

	testing.				
7 Reproductive options					
7.0.1	Preconception counselling should be available to couples where one partner is at risk of HD or is a carrier of the HD gene expansion.	The importance of preconception counselling is stressed, because of the timeframe in making a decision about testing during an ongoing pregnancy. Moreover, such preparation may help to decrease the simultaneous requests for presymptomatic and prenatal diagnosis; a very stressful situation due to the limited time available and the potential for consecutive adverse outcomes.	Preconception counselling should be available to couples where one partner is at risk of **FTD** or is a carrier of the **FTD** gene expansion.	The importance of preconception counselling is stressed, because of the timeframe in making a decision about testing during an ongoing pregnancy. Moreover, such preparation may help to decrease the simultaneous requests for presymptomatic and prenatal diagnosis; a very stressful situation due to the limited time available and the potential for consecutive adverse outcomes.	HD changed to FTD
7.0.2	Preconception				

	counselling should include discussion around the range of reproductive options available. These options may include proceeding with a pregnancy without testing, prenatal diagnosis (PND) preimplantation genetic diagnosis (PGD), donor insemination and adoption.				
7.1					
7.1.1	Couples should be made aware of all the options available to them in	Careful pre-test counselling by an informed professional is necessary in order to ensure	Couples should be made aware of all the options available to them in pregnancy,	Careful pre-test counselling by an informed professional is necessary in order to ensure that the (future) pregnant woman and her	Removal of irrelevant HD-specific information.

	pregnancy, including the possibility of prenatal testing.	that the (future) pregnant woman and her partner are fully aware of the consequences of prenatal testing. All possible test outcomes (full expansion, reduced penetrance, intermediate and normal alleles) should be made clear to the couple. It is preferable for the counselling to take place in a specialized (prenatal or genetics) centre.	including the possibility of prenatal testing.	partner are fully aware of the consequences of prenatal testing. All possible test outcomes should be made clear to the couple. It is preferable for the counselling to take place in a specialized (prenatal or genetics) centre.	
7.1.2	Direct prenatal testing for the HD mutation is usually only performed if the parent at risk has already		Direct prenatal testing for **FTD mutations are** usually only performed if the parent at risk has already		HD mutation changed to FTD mutations

	been tested. For a possible exception see 7.1.6.		been tested. For a possible exception see 7.1.6.		
7.1.3	PND for an individual with a reduced penetrance allele of the HD gene is justified.				
7.1.4	PND for an individual with an intermediate allele of the HD gene is justified.	There is insufficient information regarding the magnitude of the risk of CAG repeat expansion of intermediate alleles in the transmission to offspring. The risk of expansion into the full penetrance range is small, but may vary with the CAG size of the intermediate allele and the ethnicity			

		of the individual.			
7.1.5	Exclusion PND should be available as an option for couples where the at-risk parent does not want to know his/her genetic status. The pros and cons of this procedure, however, should be discussed in detail during counselling.	The major advantage of exclusion PND is that it allows the possibility of a prenatal test where the at-risk parent does not wish to have a predictive test but where the couple is clear they do not wish to have a child at risk of HD. The disadvantage is that the couple may end up terminating an unaffected pregnancy where the at-risk parent is not a mutation carrier.	Exclusion PND should be available as an option for couples where the at-risk parent does not want to know his/her genetic status. The pros and cons of this procedure, however, should be discussed in detail during counselling.	The major advantage of exclusion PND is that it allows the possibility of a prenatal test where the at-risk parent does not wish to have a predictive test but where the couple is clear they do not wish to have a child at risk of **FTD**. The disadvantage is that the couple may end up terminating an unaffected pregnancy where the at-risk parent is not a mutation carrier.	HD changed to FTD
7.1.6	Direct prenatal testing of the fetus where one of the parents is at risk but	The only advantage of this approach is that, in the case of a normal result in			

	prefers not to know his/her carrier status should be considered where the couple requests this in pregnancy.	the fetus, the parent at risk still does not know his/her carrier status, preserving his/her wish not to know. However, in the case of identifying the gene mutation in the fetus, the carrier status of the parent at risk will be disclosed. The possibility of this adverse outcome should be clearly outlined and the couple adequately prepared for such an eventuality, before agreeing with this test proposal.			
7.1.7	The couple requesting prenatal testing must be clearly informed that if	This is in line with the recommendation not to test minors. The child's	The couple requesting prenatal testing must be clearly informed that if	This is in line with the recommendation not to test minors. The child's autonomy regarding his/her future right to	Gene expansion changed to gene mutation to

	they intend to complete the pregnancy whether the fetus is a carrier of the gene expansion or not, there is no valid reason for performing the test.	autonomy regarding his/her future right to decide whether or not to undergo a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result. The limiting of the couple's autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect. Also, there is a small, but not negligible risk of spontaneous abortion related to the procedure.	they intend to complete the pregnancy whether the foetus is a carrier of the **gene mutation or expansion** or not, there is no valid reason for performing the test.	decide whether or not to undergo a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result. The limiting of the couple's autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect. Also, there is a small, but not negligible risk of spontaneous abortion related to the procedure.	expansion

7.1.8	It is not recommended to terminate the pregnancy of a fetus on the basis of an intermediate allele result.	An allele in the intermediate range is not associated with HD symptoms. Although an intermediate allele can expand into a reduced penetrant or full penetrant allele in future generations, this fact per se is not a reason for a pregnancy termination.			
7.2 Preimplantation genetic diagnosis					
		Preimplantation Genetic Diagnosis (PGD) in association with IVF is a reproductive option for people at risk of passing on a genetic condition. The different types of PGD for HD and		Preimplantation Genetic Diagnosis (PGD) in association with IVF is a reproductive option for people at risk of passing on a genetic condition. The different types of PGD for **FTD** and the different situations where PGD may be an option will be outlined in the following specific	HD changed to FTD

		the different situations where PGD may be an option will be outlined in the following specific recommendations regarding PGD for HD.		recommendations regarding PGD for **FTD**.	
7.2.1	It is recommended to offer PGD to an asymptomatic carrier of the HD gene expansion (36 or more repeats) and his/her partner if there is access to this technology in the country where genetic counselling is being provided.	In general, PGD is offered to people at risk of passing on a serious genetic condition. The risk of expansion of an intermediate allele to a reduced penetrant or full penetrant allele is not exactly known, but is low. Participants with an intermediate allele requesting PGD should be offered genetic counselling.	It is recommended to offer PGD to those with an asymptomatic carrier of an **FTD gene mutation or expansion** and his/her partner if there is access to this technology in the country where genetic counselling is being provided.	In general, PGD is offered to people at risk of passing on a serious genetic condition.	HD gene expansion changed to FTD gene mutation or expansion and irrelevant HD-specific information has been removed.

7.2.2	Exclusion PGD should be available for couples at high risk for offspring with HD.	The major advantage of exclusion PGD is that it enables prospective parents to avoid the transmission of the HD mutation, while at the same time respecting the atrisk person's wish not to know. The counselling should explicitly address the impact of the parent's remaining uncertainty about his/her own genetic status upon the welfare of the future child(ren).	Exclusion PGD should be available for couples at 50% risk of inheriting an FTD mutation or expansion.	The major advantage of exclusion PGD is that it enables prospective parents to avoid the transmission of the **FTD mutation/expansion**, while at the same time respecting the at-risk person's wish not to know. The counselling should explicitly address the impact of the parent's remaining uncertainty about his/her own genetic status upon the welfare of the future child(ren).	HD risk changed to statistic for FTD and HD mutation changed to FTD mutation/ expansion
7.2.3	Non-disclosure PGD should be discouraged.	Non-disclosure PGD raises troubling practical and ethical issues. First, in			

		practice it will be extremely difficult to preserve the participant's wish not to know. Second, the procedure creates difficult situations where reproductive physicians would be obliged both to offer more IVF/PGD cycles and to perform a sham transfer while the risk of having a child with HD will be (practically) zero.			
7.2.4	Couples where one partner is already symptomatic should have access to counselling for PGD. Psychosocial counselling on	Being symptomatic is not a priori an exclusion criterion for PGD. Special attention should be given to the effects of the symptoms of HD upon the future	Couples where one partner is already symptomatic should have access to counselling for PGD. Psychosocial counselling on	Being symptomatic is not a priori an exclusion criterion for PGD. Special attention should be given to the effects of the symptoms of **FTD** upon the future child's welfare. The condition and coping skills of the partner are crucially	HD changed to FTD

	the impact upon a child of growing up with a parent with HD in general and exploration of the potential effects in the specific case is an important aspect of the PGD procedure.	child's welfare. The condition and coping skills of the partner are crucially important in this regard. A case-by-case approach does optimal justice to couples where one partner faces the personal burden of HD in her/himself, while being aware of the ramifications for future children.	the impact upon a child of growing up with a parent with **FTD** in general and exploration of the potential effects in the specific case is an important aspect of the PGD procedure.	important in this regard. A case-by-case approach does optimal justice to couples where one partner faces the personal burden of **FTD** in her/himself, while being aware of the ramifications for future children.	
7.2.5	Only embryos with two normal HD alleles should be transferred.		Only embryos with two normal alleles should be transferred.		HD removed
8 The test and delivery of results					
8.1	Excluding exceptional circumstances there should be a minimum	Such an interval is necessary to give the person sufficient time to assimilate the pre-	A conversation should be had with the participant regarding their		Added information regarding individualising the 'cooling

	interval of one month between the giving of the pre-test information and the decision whether or not to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the participant's request.	test information in order to make an informed decision. During this interval, specialists from the test centre must be available. Prenatal testing may represent an exception, as it is important to complete testing procedures as early as possible during the pregnancy.	preferred 'cooling off period'. Other circumstances may be at play which the counsellor should pay mind to. Should the participant request a shorter waiting period than recommended (<1 month), the counsellor should explain the reasoning behind this and help the participant to understand how this can be beneficial to them, while accounting for their personal circumstances. Excluding exceptional		off' period

			circumstances (**e.g. where other care depends on this information – like PGD)** there should be a minimum interval of one month between the giving of the pre-test information and the decision whether or not to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the participant's		

			request.		
8.2	The result of the predictive test should be delivered as soon as reasonably possible after completion of the test, on a date agreed upon in advance between the centre, the counsellor, and the person.				
8.3	The manner in which results will be delivered should be discussed between the counselling team and the person.		The manner in which results will be delivered should be discussed between the counselling team and the person.	Delivery of results: a. A rapport should be built during the counselling process so that genetic counsellors can	Added comment based on data from this study.

				understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result	

				they may receive. b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up and additional support if needed. If not already in progress, patients should be offered psychological support.	
8.4	The participant has the right to decide at any time that the				

	result shall not be given to him/her.				
8.5	The results of the test should be given personally by the counsellor to the person and his/her companion. In geographically remote areas the result session may be arranged by prior agreement with a clinician known locally to the participant No result should ever be given by telephone or by mail. The counsellor must have sufficient time to discuss any questions				

	with the person.				
8.6	All post-test provisions (see Section 9) must be available from the time the test results are given.				
			Delivery of results: a. A rapport should be built during the counselling process so that genetic counsellors can understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result they may receive. b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up		Added based on data from this study

			and additional support if needed. c. If not already in progress, patients should be offered psychological support.		
9 Post test counselling					
9.1	The frequency and the form of the post-test counselling should be discussed between the team and the participant before the performance of the test, but the participant has the right to modify the planned programme. Although the intensity and frequency will vary from person to person, post-				

	test counselling must be available at all times.				
9.2	The counsellor should have contact with the person within the first week after delivery of the results, regardless of the test result.				
9.3	If there has been no further contact within one month of the delivery of the test result, the counsellor should initiate the follow up.				
9.4	It is essential that post-test counselling is made available regardless of the person's				

	financial situation.				
9.5	During post-test contact specific information on followup options, including (if applicable) participation in clinical research studies, can be provided. The nature of emerging prodromal signs of pre-motor manifest mutation carriers and their management possibilities (if available) could be discussed.	Information should be provided on: • specialist centres providing clinical care for HD • provision for regular follow up after the test • option of participation in observational studies (e.g. REGISTRY, Enrol-HD) • option of participating in future clinical trials • there is a pre-motor stage of HD that results in symptoms and signs likely reflecting HD-induced brain changes ('prodromal' signs) • prodromal signs and	During post-test contact specific information on follow-up options, including (if applicable) participation in clinical research studies, can be provided. Referral to a cognitive neurologist may be discussed should there be concerns regarding symptom onset.	Information should be provided on: - specialist centres providing clinical care for **FTD** - provision for regular follow up after the test - option of participation in observational studies **(e.g. GENFI/ALLFTD)** - option of participating in future clinical trials - Participation in research is entirely voluntary and the standard of follow up care provided will be unaffected by whether or not the individual chooses to take	Changed HD to FTD and added GENFI and ALLFTD study information

		symptoms might respond to symptomatic pharmacotherapy, even if no reliable data on this point are available at present. Participation in research is entirely voluntary and the standard of follow up care provided will be unaffected by whether or not the individual chooses to take part.		part.	
9.6	Ideally, information in Section 9.5 should be raised during the pre-test counselling.				
9.7	The lay organization has an				

	important role to play in the post-test period. The information and support that it can provide should always be offered to the participant regardless of whether he or she belongs to that organization.				
			Follow-up should be considered a priority At least one follow-up appointment should be scheduled during the final genetic counselling session or following the delivery of the genetic result. Follow appointments should be in-person wherever possible, however video or phone appointments may also be suitable. If a patient does not attend their follow up appointment, contact should be made via email or letter to provide contact details for follow up support.		Added based on data from this study

			Connect to support and research Regardless of test outcome, patients should be connected to available research studies e.g. GENFI (UK, Europe and Canada) and ALLFTD (US), genetic counsellors or geneticists may refer patients directly to the study, or provide contact details for the patient to self-refer. Regardless of test outcome, patients should be linked to appropriate support services e.g. Rare Dementia Support (UK) and AFTD (US). Regardless of test outcome, patients should be provided information on how to access further psychological support if necessary.	Added based on data from this study