Patient and relative experiences and decision-making about genetic testing and counseling for familial ALS and FTD: a systematic scoping review

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Abstract:

Genetic testing and counseling is an emerging part of care for patients with Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and their families. This scoping review aimed to map patients' and relatives' experiences of genetic testing and counseling for familial ALS and FTD and the factors influencing their decision to proceed with testing or counseling. Informed by the Joanna Briggs Institute methodology, five databases were systematically searched. Thirty studies from 39 references were included. A descriptive numerical summary analysis and narrative synthesis was conducted. Mostly positive diagnostic testing experiences were reported, but issues arose due to progressive disease and discordant results. Predictive testing impacted at-risk relatives, regardless of the result received, and psychosocial sequelae ranged from relief to guilt, worry or contemplating suicide. Four reproductive testing experiences were reported. Personal, familial and practical factors, and the lived experience of disease, informed decision-making. Greater uncertainty and complexity may be faced in familial ALS/FTD than in other late-onset neurodegenerative diseases due to clinical and genetic heterogeneity, and testing limitations. Genetic counseling models of care should consider this difference to ensure that individuals with, or at risk of, ALS/FTD are effectively managed. Implications for research and practice are discussed.

Keywords: genetic testing; genetic counseling; lived experience, decision-making

Introduction

Genetic testing, and the genetic counseling that accompanies it, is emerging as part of the multidisciplinary care of patients with the two neurodegenerative conditions Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)[1]. In order to provide client-centered care for patients and their relatives, a thorough understanding of genetic testing and counseling experiences, and factors that informed decision-making, is required.

Genetic testing in familial ALS (fALS) and FTD (fFTD) can occur in three different clinical testing scenarios: diagnostic, predictive and reproductive (Box 1). As results of genetic testing do not currently alter a patient's disease management, benefits of genetic testing mainly relate to the potential familial and psychological implications. Genetic counseling is an essential aspect of any decision-making regarding testing for fALS and fFTD genes, providing educational and emotional support to patients and families[2].

Recent recommendations[1,3-7] suggest all individuals with ALS or FTD should be offered genetic counseling and diagnostic testing given up to 10% of individuals with apparently sporadic ALS (sALS) and FTD (sFTD) also have pathogenic variants[1,8,9]. Despite this recommendation, a recent ALS clinician survey demonstrated that genetic testing and counseling was not consistently offered[10]. Although not all patients and relatives wish to undergo genetic testing or counseling[6,11-16], further interest is expected in future with the emergence of genotype-driven therapies[17-20]. Therefore, it is timely to review the literature on fALS/fFTD genetic testing and counseling to inform future practices.

This scoping review of the literature aimed to map the nature and characteristics of patients' and relatives' experiences of genetic testing and counseling for fALS and fFTD and the factors that informed their decision to proceed with testing and/or counseling. The findings will inform the future management of individuals with, or at risk of, ALS or FTD.

Methods

The Joanna Briggs Institute methodology for scoping reviews guided the review process[21].

Eligibility criteria

The inclusion and exclusion criteria were developed using the population, concept and context (PCC) elements[21] (Supplemental Digital Content 1). Each element was broadly defined to widely map the existing evidence[21]. The population were adults from families with, or at risk of, ALS or FTD. The concept was genetic testing and counseling experiences and decision-making. The context was broadly defined to include published literature, case studies, and particular gray literature (i.e. informally published literature such as conference abstracts or dissertations), reported since 1993 (the year when the first gene associated with ALS/FTD was reported)[22].

Search strategy

The three-step search method was used[21]: once keywords were developed, a search was undertaken across the CINAHL, MEDLINE, PsycINFO, EMBASE, and ProQuest Health and Medicine databases. The search combined terms for genetic testing and counseling with terms for ALS and FTD, and limited the publication date from 1 January 1993 (see full search strategy, Supplemental Digital Content 2). Further references were identified from backward-searching reference lists of included studies and forward-searching on Web of Science. Corresponding authors were contacted by email when full-texts were not readily available. References were excluded if corresponding authors were unresponsive after at least two attempts. The search was re-run before the final analysis on 29 October 2020.

Study selection

After de-duplication, and piloting the inclusion criteria, title and abstract, and full-text screening proceeded (Figure 1). AC completed 100% of title and abstract and full-text screening, while ER conducted 10% and 20%, respectively. All disagreements were

resolved through discussion. After title and abstract and full-text screening, inter-rater reliability demonstrated a level of agreement of 95.0% and 93.75%, respectively, and strong agreement using the prevalence-adjusted bias-adjusted kappa (PABAK=0.900 and 0.875)[23,24].

Data extraction and synthesis

AC completed data charting (i.e. data extraction), then ER verified and validated each item. A descriptive numerical summary analysis and narrative synthesis was conducted[21,25,26], with data items related to the scoping review aims mapped and summarized into key topic areas.

Results

Study characteristics

Thirty-nine references from 30 studies were included (Table 1; see complete data extraction in Supplemental Digital Content 3). The majority (26/39) were journal articles, followed by published conference posters or presentations (12/39); one was a dissertation. Thirteen studies (from 22 references) focused on ALS only, 13 on FTD only, and four on ALS and FTD (ALS-FTD). No relevant studies on fALS/fFTD genes associated with X-linked or autosomal recessive inheritance were identified. Fifteen studies (from 20 references) originated from the United States of America (USA). Study types included case series (n=14), quantitative surveys (n=11), case reports (n=7) and qualitative studies (n=5). Seven studies used more than one study type. Thirteen studies directly ascertained patients' or relatives' opinions[6,11,12,16,17,27-41]. The remainder were informed by clinician observation. The included population consisted of affected individuals, at-risk individuals, and other related or unrelated family members. Eleven

studies included only a single person or family with, or at risk of, ALS/FTD[34,42-51]. The total number of included patients, families and at-risk relatives was not calculated due to missing information or differences in defining familial and sporadic disease.

Narrative synthesis

Findings from the narrative synthesis are summarized under two topics: experiences of genetic testing and counseling, and the decision to proceed.

Experiences of genetic testing and counseling

Twenty-four studies from 33 references reported experiences of testing and counseling. The experiences are divided between diagnostic testing, predictive testing, and reproductive testing or family planning.

Diagnostic testing. Eight ALS[6,11,12,27,31,32,39,42,46,47,50], four FTD[44,51-53] and four ALS-FTD[41,43,45,48] studies reported experiences of diagnostic testing. In one national survey from the United States of America (USA), most of the 105 ALS patients who underwent diagnostic testing were positive about their experience and satisfied with the pre-test discussion, explanation of results and implications, and emotional support provided[6,11,12], and indicated the results were useful to them and their families[6]. Results were mostly disclosed during an office visit (65.1%) by a physician (69.4%)[6,12]. Experiences did not differ if they tested positive or negative, had fALS or sALS, or met a genetic counselor[6,11,12]. The six respondents who had a generally negative experience of testing reported that they were not informed or could not recall their results[6,11]; this issue was reported in two ALS patient surveys in the USA [6,11,12,31]. Some relatives recalled receiving inadequate support at results disclosure in an Australian qualitative study[27,39,41]. No studies directly ascertained patient or relative experiences of diagnostic

testing for fFTD.

Study authors deemed some diagnostic testing experiences as problematic for patients or relatives in studies across the USA, United Kingdom (UK), Australia and Italy. Issues arose with FTD patients' capacity to consent[48,53] or ALS patients' communication abilities[50] due to disease progression. Some relatives became responsible for consenting to genetic testing on the patient's behalf[43,48,50,53] and notifying relatives about a genetic finding[32]. Patients or relatives were faced with decisions about storing DNA for future use[43,47,48,50], sharing results after death[47], and consenting to autopsy[43] or testing, at the time[48] or in future[43,50,51]. These issues were further complicated when relatives disagreed[43,53], or there were risks of breaching confidentiality[53]. Discordant (or inconsistent) results also complicated experiences. Result discordance occurred between affected relatives in a family due to reduced penetrance alleles[44,46] or phenocopies[44,45,47,52]. In one case, discordance also occurred between laboratory reports for a patient due to varying *C9orf72* repeat length and interpretation[42], causing unnecessary distress as the disease progressed[41] and resulting in uncertainty regarding the implications of the result for the patient and their relatives[41,42].

Predictive testing. Four ALS[27-29,32,33,37-39,54,55], five FTD[16,30,36,44,49] and one ALS-FTD[41] study reported at-risk relatives' experiences of predictive testing across the USA, UK, Australia and Spain.

Three ALS studies reported on the testing and counseling process[27,32,33,54,55]. Although the predictive testing protocol was considered useful in one qualitative study, some, who had already decided to test, thought it was too lengthy[27]. One study randomized participants into receiving results by telephone or in person, and all were comfortable with their allocated group[33]. Those who received their positive results by telephone did not believe it would have been easier to learn results in person[33]. One

study noted confusion over whether predictive testing results from research would be provided[32].

At-risk relatives' responses after receiving predictive testing results varied, and this was reported in four FTD[16,30,36,49], three ALS[28,29,33,37-39] and one ALS-FTD[41] study. Several who tested positive felt unsettled or frantic, particularly in the short term[33,37-39]. Some worried about informing children[33,39,41]. Others worried about developing ALS[33,37-39], planning suicide or euthanasia before becoming dependent on others[33]. Some reported positive changes in their lives, as the result confirmed their suspicion, and results would inform future planning[33]. One made significant life changes by changing their view on marriage, leaving their job, and moving home to be with family[33]. No lost or changed employment, relationship or financial changes were reported in another study[49]. Those who received negative results reported feeling guilty[28,29,33,37-39], relieved, grateful, and that they could get back to living their lives[33]. Individuals who assumed they would test positive found their joy was hard to maintain, feeling unprepared for the possibility of living a long and healthy life[33,37-39].

In two studies, anxiety levels decreased from pre-testing, with post-testing levels similar to the general population[30,49]. Some still experienced anxiety or depression[30]. Another study reported increased depression but decreased anxiety levels in those who had completed testing (regardless of their result), compared to those who were untested[36]. Minor regrets of undergoing testing were noted in a qualitative study; two individuals wondered whether they would have been better not to know[37-39]. No studies reported psychiatric hospitalizations, suicide attempts, or major regrets of undergoing testing. However, follow up was absent in three concerning cases: one individual who was distressed with results requested no further contact from researchers[16], and two

individuals who had tested negative but had indicated "planning for suicide" as a reason to be tested were not followed up[30].

In one qualitative study from the USA, 14/20 participants elected to learn their results from predictive testing; several only told relatives their results if they were negative[33]. Others chose not to discuss results as they saw no benefit without a cure, wanted to give their children the option of making their own decision about clarifying their risk, or were worried it could alter relationships or beliefs[33]. One Australian qualitative study participant only realized the importance of sharing results with children after a genetic counseling consultation[39,41]. One case report outlined the possible issue when individuals at 25% risk wish to proceed with predictive testing, and the intervening relative does not, risking revealing the relative's obligate carrier status[44].

Reproductive testing or family planning. Four ALS[28,29,32,37,39,40,46] and two FTD[15,35] studies referred to reproductive testing or family planning experiences across Australia, the USA, UK and the Netherlands. Overall the published use of prenatal diagnosis (PND) and pre-implantation genetic testing (PGT) was low, with two single PND[15,37,39] and PGT[39,40,46] experiences, and no exclusion/non-disclosure experiences reported. No studies ascertained the uptake rate of PND or PGT. In one PGT case, 12 embryos were produced in the first IVF round, yet only four were available for implantation[46]. In the other, a relative underwent PGT three times without success, then elected to conceive naturally[39,40]. Other reported family planning decisions included choosing to have children regardless of the possible risks[28,29,32], choosing not to have children or more children[28,29,32], sterilization[35], and adoption[29]. No references reported using a donor embryo or gamete. Some made decisions based on a possible risk to children rather than a definite 50% risk, as predictive testing was not available when the decision was made, or they had elected not to undergo predictive testing[28,29,32]. In one qualitative study from

the USA, although some experienced conflicting thoughts at the time, none of the ten fALS at-risk individuals regretted their decision[29].

The decision to proceed

Twenty-six studies from 35 references reported on factors informing the decision to access genetic testing or counseling. Diagnostic and predictive testing are jointly reported due to extensive cross-over between decision-making for these testing types. Reproductive testing or family planning, followed by the psychological burden of familial disease are then reported.

Diagnostic or predictive testing. Several factors informed decision-making regarding accessing diagnostic or predictive testing and counseling (Table 2). It is important to note that in seven studies from five countries, some patients and relatives were unaware of the availability of genetic testing or counseling in ALS[6,11,12,14,27,31,56] and FTD[13,57], and therefore were not given the option to decide for themselves. For example, almost half of the respondents in an ALS patient survey did not know that diagnostic (and predictive) testing was available[12]. Once informed, 82.7% believed it should be offered to all ALS patients[12]. Overall, diagnostic testing was more likely to be offered to individuals with ALS or FTD if they saw a genetic counselor[6,11,12], were diagnosed under age 50[12], or at a younger age[57], lived in certain Canadian provinces[56], had more substantial FTD family history[57] or had a family history of ALS, compared to those with no family history[6,12,13] or a family history of dementia only[12].

Reproductive testing or family planning. Three ALS[27-29,32,37-40], one FTD[35], and one ALS-FTD[41] study, from Australia, the Netherlands and the USA, outlined factors that informed decision-making regarding family planning and reproductive testing (Table 3).

Two qualitative fALS studies demonstrated that at-risk individuals were enthusiastic about PGT[29,37-40]. However, many were unsure whether they would have used it anyway[29]. Other individuals questioned some clinicians' capacity to provide non-directive genetic counseling, feeling pressured to undergo PGT or not have children due to fALS[27,37,39-41].

The psychological burden of familial disease. Thirteen studies reported at-risk individuals burdened by their lived experience of fALS[28,29,32,33,40,43,45] and/or fFTD[15,30,35,36,43-45,49,52], which impacted on testing decision-making. Lived experiences may have included losing one or multiple close relatives to the disease[33] or being a carer[15,33]. Some at-risk individuals felt distressed if they were made aware of the familial disease as children[32], ashamed due to the behavior of a relative with FTD[15], or guilty if they had distanced themselves from an affected relative[32]. The lived experience may have resulted in difficulty making decisions about receiving genetic results[15,43] or led to assumptions about a high[15,30,32,33] or low[30,32,35] perceived risk of developing the disease or carrying a pathogenic variant. Without undergoing predictive testing, some at-risk individuals were preoccupied with symptoms[15,30,33,35]; one moved into a single-story dwelling just in case they carried the pathogenic variant and developed disease in future[33]. Others experienced difficulty planning for the future, investing in friendships or relationships[15,28,29,35,43]. Individuals were more likely to choose not to have children or undergo reproductive testing if they had a more extensive lived experience of disease[28,29,40] (Table 3).

The presence of psychiatric symptoms in at-risk relatives also informed decision-making regarding predictive testing[33]. Psychiatric symptoms may be present either due to lived experiences[33,44,45,52], the psychiatric phenotype that can be seen in certain pathogenic variant carriers[33,45,52], or unknown reasons[43]. Five studies

demonstrated that at-risk individuals experienced increased anxiety[30,32,35,36,49] or depression[30,32,35] levels over the general population[30,32] and intrusive thoughts or sleeping difficulties[32]. In one survey, 53% of fFTD at-risk individuals (some of whom had completed testing) suggested additional support may be beneficial, including further information about fFTD, support groups, counseling, and future planning[36].

In contrast, a small number of individuals believed that their lived experience did not influence[35] or had a positive impact[29,32,33] on their life. They felt empowered[32], were able to prioritize and plan their future[29], appreciated life[29], had stronger relationships[29] or had found ways to honor their relatives[33].

Discussion

The primary aim of this scoping review was to map the nature and characteristics of individuals' experiences of genetic testing and counseling for fALS and fFTD and the factors that informed their decision to proceed with testing or counseling. Thirty studies from 39 references were included. Despite the clinical and genetic overlap between ALS and FTD, only four studies focused on combined ALS-FTD families. Mostly positive experiences around diagnostic testing were reported. Still, some complex issues arose due to progressive disease and discordant or uncertain results, impacting the patient and family. Direct experiences of diagnostic testing in FTD and preferences for pre- and post-test counseling and result disclosure, such as appointment length or format, were not ascertained. Few direct experiences of the predictive testing process were identified. Both positive and negative impacts of predictive testing results on at-risk relatives were reported, regardless of the result received. Although various family planning decisions were reported, only four single reproductive testing experiences were identified, and research is lacking on the uptake of PGT and PND. Personal and familial factors informed the decision to proceed with genetic testing and counseling, as

did practical factors, given some were unaware of testing availability. The lived experience of disease had negative psychological consequences for some at-risk individuals, impacting on testing decision-making and other aspects of their life. Some unique findings specific to fALS and fFTD compared with other (adult-, or) late-onset neurodegenerative diseases (LONDs) are identified, which has implications for research and practice.

Given the possible familial impacts of diagnostic testing, due to both familial risks and progressive disease, a family-centered approach is supported[43,48,50,53,58]. While relatives may become responsible for making time-dependent decisions about testing or communicating results in other LONDs[59], fALS/fFTD genetic testing may be further complicated by certain disease characteristics. ALS and FTD are clinically and genetically heterogeneous conditions and familial cases may demonstrate result discordance between affected relatives[44,45,47,52,60] or laboratory reports[41,42], oligogenic inheritance[61-64], reduced penetrance[44,46,65,66] and phenotypic variation[66-68]. These characteristics lead to greater uncertainty regarding the meaning of results for patients and relatives[28,49]. Clinicians must be aware of the limitations of our understanding of fALS/fFTD and communicate these to clients as part of pre-test counseling to ensure informed decision-making[42]. As receipt and recollection of results was an issue for some patients, clear and supportive communication, perhaps in verbal and written format, is likely necessary for a satisfactory testing experience[5]. The involvement of an additional family member or support person may also help with test recall and understanding even in the absence of cognitive impairment[7] or a positive result[58]. Like HD diagnostic testing guidelines[58], it may be impossible to make strict recommendations for diagnostic testing in ALS and FTD, given the presence of a

variety and complexity of clinical situations. Instead, a checklist of discussion items before and after diagnostic testing may be useful[58].

No catastrophic events from predictive testing were reported. However, three of the included cases were lost to follow up[16,30] and similar to studies of patients with HD, few long-term outcomes were reported[69]. The removal of uncertainty that comes with having a predictive test can be beneficial, with decreased anxiety post-testing in some LOND cohorts, regardless of the result received[30,36,49,70]. However, perhaps distinct from other LONDs, residual uncertainty may remain in fALS/fFTD pathogenic variant carriers, given variable penetrance and expressivity[3]. Depression and suicidal behavior may also be induced or worsen after predictive testing for LONDs[36], particularly at specific time points in the illness trajectory[69-73] or due to the psychiatric phenotype within certain kindreds[45,74,75]. The issues raised here support a multidisciplinary, person-centered care approach to pre- and post-test predictive test counseling as recommended by the HD protocol[76] and recent ALS guidelines[77]. Counseling should ensure an autonomous and informed decision is being made[45,76], that family communication and support is explored[4,33,44,76], and post-test support is provided regardless of whether the result is positive or negative[30,33,76,78]. Telephone or telehealth appointments may be of benefit, as has been demonstrated by the continued emergence of telehealth in healthcare[79,80]. Novel approaches to support after testing have been trialed recently in HD[81], and this may be an area of future investigation for fALS/fFTD.

Similar to HD[78,82], decisions about whether to proceed with diagnostic and predictive testing were informed by shared personal, familial and practical factors. The commonly reported reason for and against proceeding with testing across the studies was related to implications for others, further supporting a person and family-centered counseling approach. The second most common reason against testing is that no

preventative options are currently available for pathogenic variant carriers. It is important to note that there may be increased testing uptake if current treatment trials are successful[17,82]. Still, some may decide not to be tested, as demonstrated by other, more treatable LONDs[83], so non-directive counseling remains essential. Although ALS patients are highly interested in genetic testing[12], FTD patients' or relatives' interest in diagnostic testing is mostly unknown. The findings support the recommendation that diagnostic testing is routinely discussed or offered[1,7], but current practices for offering testing vary. Consistent with a recent systematic review[84], clinicians may need additional support, time, knowledge or guidance. Diagnostic testing and counseling consensus guidelines may provide some support to address this issue[10,85].

Access to reproductive testing or family planning options was a commonly reported reason to proceed with diagnostic or predictive testing. Yet, similar to other LONDs, the published use of reproductive testing was low[15,46,86], reproductive decisions were sometimes made long before the availability of genetic testing[28,29,32,35,87]. Individuals generally did not regret the decision made[29,59,88]. The two cases presented demonstrate that PGT can limit the number of embryos available for implantation, and there is no guarantee of a successful pregnancy. Family planning decisions that prevent pathogenic variants from being inherited by future generations will also not address all parental concerns, given future children may still have an affected parent and be burdened by the lived experience of disease[28,29,32,87]. Qualitative experiences demonstrated the need to ensure one's reproductive autonomy is respected[46]. Therefore, non-directive counseling, commonly involving both members of a couple[87], about reproductive testing and family planning options, including limitations, is important.

Like other LONDs, at-risk individuals may be burdened by their lived experience, spending time anticipating disease onset long before they know their testing

result, which impacts many aspects of their lives[15,30,33,35,78,89,90], including family planning[28,29,87]. Regardless of whether the disease is familial, the impact of being a carer or close relative of a patient with ALS/FTD is widely reported[91-94]. As most ALS/FTD clinics are focused on the care of patients and their carers, at-risk individuals may fall outside the current medical system[32] unless they seek genetic counseling or testing or are caring for a relative. More emotional, educational and practical support may be necessary. An online resource, similar to one that has been trialed for individuals at risk of HD to support informed decision-making and provide information about support options and research opportunities[95], may assist. However, a targeted psychosocial intervention that can further address the issues arising from lived experience may be necessary[36]. At-risk relatives who have more recently discovered their risk (e.g., if a pathogenic variant is confirmed in an apparently sporadic ALS/FTD patient) will have different needs than those with extensive lived experience, and this further justifies the need for a client-centered approach to care[45,58]. Genetic counselors are specially trained health professionals who are well placed to provide counseling, information and support, although they are not accessible worldwide[96].

Limitations

Limitations exist regarding the included references and scoping review methodology. Only studies published in English were included. Additional publication and reporting biases were minimized by including specific gray literature. Several references[16,35,49] also included families with other LONDs, and as a result, data extracted from three studies were incomplete. Few studies focused on those who declined or deferred testing. Half of the studies were from the USA. Most studies were informed by clinician observation rather than patient/ relative opinions. Eleven references were single individual and family case reports. Experiences and decision-making factors may have

been reported in one or more individuals, and this was clarified in the results, where known. Differences between sporadic and familial cases were hard to determine, given the mixed definitions of familial and sporadic disease across the included studies[6,12,17,31,32,57]. No rating of the quality of evidence is provided in a scoping review, and the implications for research and practice cannot be graded.

Conclusions

Patient and relative experiences of genetic testing and counseling for fALS and fFTD, and factors that informed their decision to proceed were varied and inconsistent across the included studies. Individuals with, or at risk of, ALS/FTD pathogenic gene variants uniquely face more uncertainty and complexity than other late-onset neurodegenerative diseases due to clinical and genetic heterogeneity as well as genetic testing limitations, further complicating clinical practice. Genetic counseling models of care in ALS/FTD should consider these differences to other late-onset neurodegenerative diseases to ensure adequate care is provided. The findings are particularly critical as genetic testing becomes a more routine aspect of ALS and FTD management.

Implications for research. Areas of future research in familial ALS and FTD include:

- Experiences and decision-making in:
    - ALS-FTD combined families
    - Diagnostic testing for fFTD
    - Reproductive genetic testing and family planning in general
- Preferences for diagnostic, predictive and reproductive testing and counseling (e.g. pre- and post-test discussions, results disclosure, appointment format and timing)

- Development and evaluation of clinician consensus guidelines/checklists for genetic testing discussions, including minimum discussion points pre- and post-testing
- Development and evaluation of support resources for at-risk individuals regardless of whether they decide to proceed with genetic testing and counseling, including online support resources, a targeted psychosocial intervention or other novel approach to support post-testing
- The psychosocial impacts of genetic testing and counselling, assessed using patient reported outcome measures and longitudinal studies
- Consensus definitions of familial and sporadic disease (including the option of additional patient categories)[97-99]

Implications for practice. The following may be necessary when providing genetic testing (and associated counseling) to ALS/FTD patients and relatives:

- A supportive, client-centered counseling process that is informed by the lived experience of disease, the perceived utility of genetic results, and assessment of risk factors for a negative response to testing, and which facilitates family communication and access to personal support resources
- Discussions regarding the possible complex implications of fALS and fFTD genetic test results, to ensure an informed decision is made, given limitations to our current knowledge may result in residual uncertainty
- A clear process for relaying results and their implications (e.g. both verbal and written format), and clear communication regarding whether research results will be disclosed
- Provision of further support, as necessary, regardless of the result received

- Emotional, educational and practical support for at-risk individuals who are undecided or are not seeking genetic testing
- For diagnostic testing, offering testing as an option for all ALS and FTD patients (where resources allow), allowing adequate time to facilitate family-centered counseling, ideally in conjunction with a support person/family member
- For predictive testing, a flexible, multidisciplinary, person-centered care approach to pre- and post-test counseling as recommended by the HD protocol[76]
- For reproductive testing and family planning, non-directive counseling about the options available, including their limitations

Summary of figures and tables

List of Supplemental Digital Content

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Box 1 Definitions of key terms used throughout this manuscript

Genetic counseling is 'the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease'[2].
Diagnostic testing is an initial search for pathogenic variants (or mutations) in an ALS or FTD patient. Identifying a pathogenic variant in a patient provides blood relatives with the option to discover their own risk (through predictive testing) and/or consider family planning options.
Predictive testing (also referred to as presymptomatic testing) identifies whether an individual has inherited a pathogenic variant previously identified in a relative. It can help determine a relative's future risk of disease but cannot accurately predict if, when, or how it will develop. Test results are either positive (familial pathogenic variant confirmed) or negative (familial pathogenic variant not detected).
Family planning options include choosing to conceive children naturally (and having up to a 50% chance they may have inherited the pathogenic variant), choosing not to have children, or opting to have children while ensuring the risk is not inherited (for example, by using a donor's sperm, egg or embryo, or undergoing reproductive genetic testing).
Reproductive genetic testing includes pre-implantation genetic testing (PGT, through *in vitro* fertilisation, IVF) or prenatal diagnosis (PND, through chorionic villus sampling or amniocentesis, with an expectation of terminating the pregnancy should the pathogenic variant be confirmed). At-risk individuals who do not wish to know their carrier status from predictive testing can undergo PGT or PND with exclusion or non-disclosure.

Figure 1 PRISMA flow chart[100]

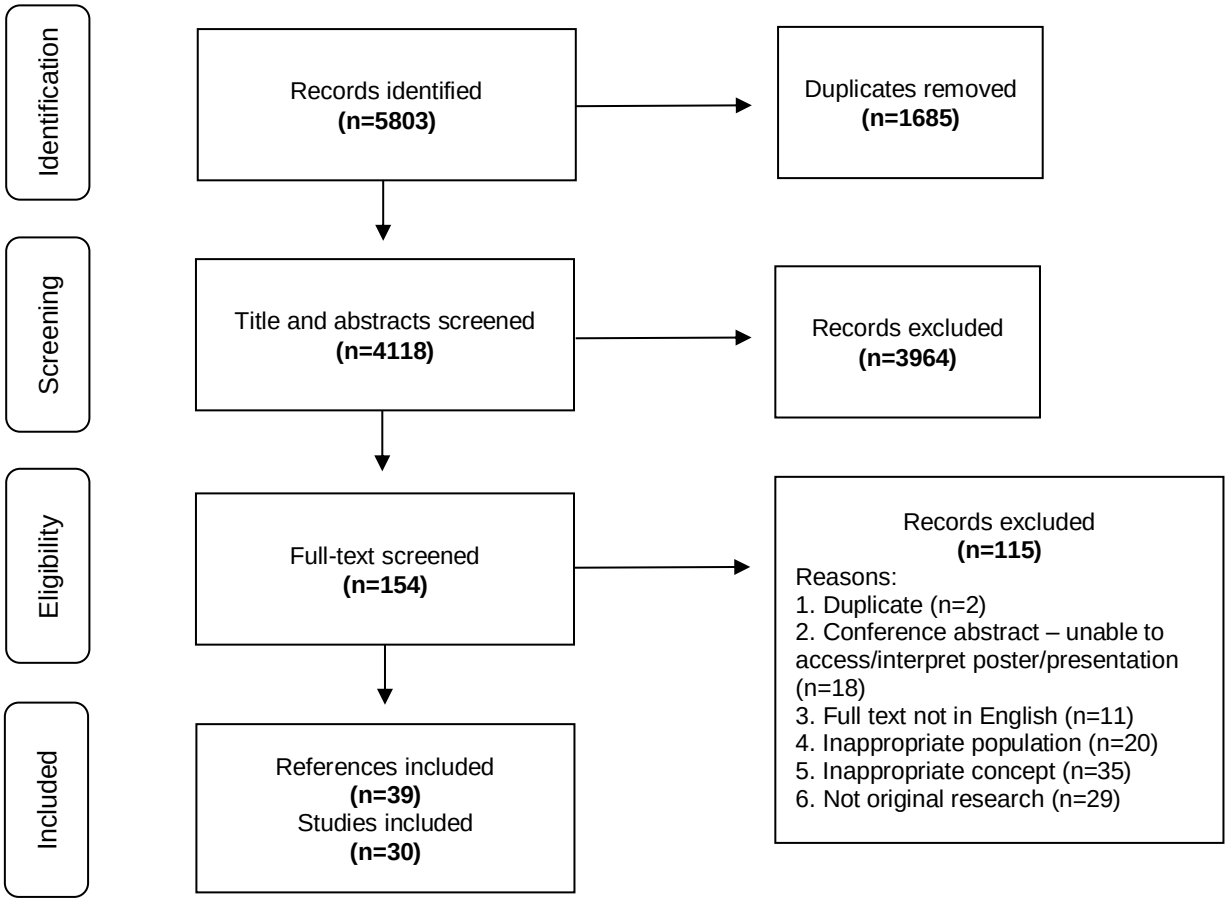

Table 1 Study Characteristics

Characteristics	Number of studies	Number of references	References
Condition/ gene investigated[a,b]			
Amyotrophic lateral sclerosis (ALS) only	13	22	6,11,12,14,17,27-29,31-33,37-40,42,46,47,50,54-56
- *SOD1*	5	13	6,11,12,17,27,33,37-40,46,54,55
- *C9orf72*	3	9	6,11,12,27,37-40,42
- *TARDBP*	1	1	47
- Unknown/not stated	11	19	6,11,12,14,17,27-29,31,32,37-40,47,50,54-56
Frontotemporal dementia (FTD) only	13	13	13,15,16,30,34-36,44,49,51-53,57
- *MAPT*	5	5	15,16,34,49,52
- *VCP*	1	1	30
- *PGRN*	2	2	44,57
- *C9orf72*	1	1	57
- Unknown/not stated	7	7	13,15,35,36,51-53
ALS and FTD (ALS-FTD)	4	4	41,43,45,48
- *C9orf72*	3	3	41,43,45
- *TARDBP*	1	1	41
- ALS Parkinsonism dementia complex	1	1	48
Main author location			
United States of America	15	20	6,11,12,16,17,28-34,43-45,50-52,54,55
Australia	4	8	27,37-42,53
Italy	3	3	47,48,57
The Netherlands	2	2	15,35
Canada	2	2	13,56
France	1	1	14
United Kingdom	2	2	36,46
Spain	1	1	49
Study type[b]			
Case series	14	15	13-16,41,45,46,49,51-57
Survey	11	13	6,11,12,14,16,17,30-32,34-36,42
Case report	7	7	15,42-44,47,48,50
Qualitative	5	10	27-29,32,33,35,37-40
[a]Only data on conditions of interest extracted, [b]some references included multiple categories			

Table 2 Factors informing decision-making regarding diagnostic and predictive testing

Factors that increased the likelihood of accessing genetic testing or counseling	Number of studies[a]		Testing type and references			Factors that decreased the likelihood of accessing genetic testing or counseling	Number of studies[a]		Testing type and references		
	ALS	FTD	Diagnostic testing	Predictive testing	Unspecified testing type		ALS	FTD	Diagnostic testing	Predictive testing	Unspecified testing type
Wishing to inform risk for relatives, and/or help others	6	8	31,43,48	28-30,33-36,49,52,55	27,37-39	Worry about how others may cope with the result including adverse emotional, social and financial effects, damaging relationships and burdening family members	5	6	12,43	15,32-36,43,52	27
Wishing to benefit research	3	6	31,48,52	17,33-35,48,55	27	Belief that result wouldn't alter medical care and nothing can be done, and/or would only consider testing when a treatment or other preventative options become available for pathogenic variant carriers	4	4	43,47	32,34,36,43,51	27,37-39
Wishing to inform reproductive decision-making	4	4		30,32,34,36,46,49,55	27,37-39	Worry about coping if results indicate pathogenic variant is present (e.g., anxiety, stress, frustration, anger, becoming depressed and self-centered, regretting decision, worry about developing disease/ symptoms, guilt for passing onto children)	2	5		32-36,52	27
Belief that knowing results will provide time to plan for one's future, e.g., Change life priorities, travel, career, financial, lifestyle or retirement planning	3	4		30,32-36,55	27,37-39	Do not believe ALS is running in the family or that they are a pathogenic variant carrier or do not understand dominant inheritance pattern	3	1	12,31	32,44	
Hoping to relieve uncertainty	2	5		15,30,33-36	27	Concerns regarding ability to get insurance coverage and insurance discrimination	3	2	12	32,34,36	27
Belief that knowing is better than not knowing, and/or that knowing will decrease one's anxiety	3	4		28-30,33,34,36,49,55	37-39	Fear of survivor guilt if found not to have pathogenic variant	3	0		28,29,32,33	
Hoping to explain the cause of disease or confirm possible symptoms	3	1	31,52	27-29		Belief that result is positive (has pathogenic variant) and/or that familial disease is already on the mind	1	2		33,34,36	
Wishing to have the time to be psychologically prepared for future onset of disease	2	0		32	27	Difficulty accessing testing due to cost or logistical reasons (e.g., accessing appropriate, competent or supportive health professionals)	3	0	12		27,37-39,41
Having a family history of ALS or being classified as fALS	2	0	6,11,12,14			Already had children before testing available	1	1		33,51	

Hoping to learn one did not have the pathogenic variant	2	0		[32]	[27]	Belief that life is in God's hands so not important to know or feelings of guilt over tampering with nature	1	1		[32,34]	
Hoping to satisfy curiosity	1	2		[30,36]	[27]	Limited perceived benefits of knowing result	1	1		[34]	[27,39]
Wishing to proceed only if children requested it	1	1	[47]	[51]		Unable to predict onset or disease phenotype	1	0			[27]
Wishing to be eligible for clinical trials or treatment in future	1	1	[31]	[49]		Wishing to maintain hope	1	0		[33]	
Testing arranged as part of a research study	1	1		[30,33,54,55]		Afraid of loss of employment	0	1		[34]	
Belief that one has a perceived personal responsibility or moral obligation to find out	1	0			[27,39]	Don't want disease to influence life one way or another	0	1		[34]	
Belief that disease is caused by genetics	1	0	[31]			Fear of feeling 'flawed' by having the gene	1	0		[32]	
Wishing to liberate self from oppressive and restrictive family	0	1		[15]		Afraid of losing a sense of control	0	1		[34]	
To inform planning for suicide	0	1		[30]		Lack of support from relatives to pursue testing	0	1		[15]	
To relieve pressure from other relatives to have testing	0	1		[34]		Worry about possible changes in how people will treat them depending on the results	0	1		[36]	
To confirm gut feeling	0	1		[36]							
[a]Studies of ALS –FTD are included in both columns											

Table 3 Factors informing reproductive genetic testing and family planning decisions

Factors related to the decision to conceive naturally without intervention	**Factors related to undergoing reproductive genetic testing**	**Factors related to deciding against having children**
Knowledge that symptoms usually do not emerge until middle age, and thus the person could have a full, productive life regardless of disease[28,29,32,37,40]	Wishing to prevent the condition being inherited by the next generation[28,29,32,37,39,40]	
Belief that there are riskier possibilities that a child might encounter before ALS/FTD[28,29,32,35]	Wishing to protect a partner from being burdened by more than one ALS diagnosis in the immediate family[37,39,40]	Not wanting a child to experience the death of a parent at a young age[28,29,32]
Wishing to have the opportunity to be a parent[28,29,37]		Not wanting a child to be burdened as a caretaker[32]
Hope that a cure would be available in their child's lifetime[28,29]	Greater lived experience of disease: having many affected relatives, extensive ALS and caretaking experience, having experienced early parental death or seeing ALS as an inevitable tragedy[28,29,40]	
Wishing to make a statement about the value of the life of the relative with ALS[32]	Costs as a barrier to accessing reproductive genetic testing[40]	
Hope that PGT would be available in their child's lifetime[32]	Moral beliefs related to PGT or PND[40]	
	Doctors unaware of the option of reproductive genetic testing[37-39]	

Supplemental Digital Content 1 Selection criteria

Inclusion	**Exclusion**
Population	
• Adults (≥18 years old) from families with, or at risk of, ALS and/or FTD[a]	• Individuals at risk of childhood-onset motor neuron diseases (e.g., spinal muscular atrophy) • Population of interest not reported separately to other populations
Concept	
• Individuals' experiences of genetic testing or counseling for familial ALS and/or FTD pathogenic gene variants including: o Genetic counseling o Before, during and after diagnostic, predictive and reproductive genetic testing o Decision-making factors: attitudes, intentions, barriers and facilitators o Outcomes of genetic testing or counseling on individuals and their family/ support network o Family planning o Lived experience of familial ALS or FTD	• Research genetic testing, where the result is never disclosed to the individual • Laboratory methods of genetic testing • Genotype-phenotype or variant incidence data without information on individual experience of genetic testing or counseling
Context	
• Any healthcare setting worldwide • Original research of any study design or methodology • Published journal articles, conference abstracts, theses and dissertations, government or support association reports • Published after 1 January 1993[b], in the English language	• Full text/ presentation not available in English • Full conference presentation (poster or slides) not available
[a]**FTD** includes frontotemporal (lobar) dementia/degeneration, pallido-ponto-nigral degeneration, Pick's disease; **ALS** includes Amyotrophic Lateral Sclerosis, Motor Neurone Disease, and Lou Gehrig's disease (see all search terms in Supplemental Digital Content 2) [b]1993 was chosen because it was the year when the first gene associated with ALS/FTD was reported[22]	

Supplemental Digital Content 2 Full search strategy

General search terms	Subject headings and results				
	Medline (all subheadings included) – 9/5/19	*Embase: Excerpta Medica (all subheadings included) – 9/5/19*	*CINAHL – 9/5/19*	*PsycINFO – 9/5/19*	*Proquest health and medical (Source type: conference papers & proceedings; Dissertations & Theses; Government & Official Publications) – 9/5/19*
1. Genetic counsel*	Genetic Counseling/ Genetic counsel*.tw.	genetic counselling/ Genetic counsel*.tw.	TI genetic counsel* OR AB genetic counsel* (MH "Genetic Counseling")	TI genetic counsel* OR AB genetic counsel* DE "Genetic Counseling"	(ti(genetic counsel*) OR ab(genetic counsel*)) OR mesh.Exact("Genetic Counseling") OR mainsubject.Exact("genetic counseling" OR "genetic counselling")
2. Genetic testing : Gene* test OR Genetic test* OR gene test*	(gene* test or genetic test* or gene test*).tw. Genetic Testing/	(gene* test or genetic test* or gene test*).tw.	TI gene* test OR AB gene* test OR TI genetic test* OR AB genetic test* OR TI gene test* OR AB gene test*	TI gene* test OR AB gene* test OR TI genetic test* OR AB genetic test* OR TI gene test* OR AB gene test* DE "Genetic Testing"	(ab(gene* test) OR ab(genetic test*) OR ab(gene test*) OR ti(gene* test) OR ti(genetic test*) OR ti(gene test*)) OR mesh.Exact("Genetic Testing") OR mainsubject.Exact("genetic testing" OR "genetic tests" OR "genetic test")
3. Genetic screening: Gene* screen OR genetic screen* OR gene screen*	(gene* screen or genetic screen* or gene screen*).tw.	(gene* screen or genetic screen* or gene screen*).tw. Genetic screening/	TI gene* screen OR AB gene* screen OR TI genetic screen* OR AB genetic screen* OR TI gene screen* OR AB gene screen* (MH "Genetic Screening")	TI gene* screen OR AB gene* screen OR TI genetic screen* OR AB genetic screen* OR TI gene screen* OR AB gene screen*	(ab(gene* screen) OR ab(genetic screen*) OR ab(gene screen*) OR ti(gene* screen) OR ti(genetic screen*) OR ti(gene screen*)) OR mesh.Exact("Genetic Screening") OR mainsubject.Exact("genetic screening")
4. Amyotrophic Lateral Sclerosis	Amyotrophic Lateral Sclerosis/ Amyotrophic Lateral Sclerosis.tw.	amyotrophic lateral sclerosis/ Amyotrophic Lateral Sclerosis.tw.	TI amyotrophic lateral sclerosis OR AB amyotrophic lateral sclerosis (MH "Amyotrophic Lateral Sclerosis")	TI amyotrophic lateral sclerosis OR AB amyotrophic lateral sclerosis DE "Amyotrophic Lateral Sclerosis"	(ab(Amyotrophic Lateral Sclerosis) OR ti(Amyotrophic Lateral Sclerosis)) OR mesh.Exact("Amyotrophic Lateral Sclerosis") OR mainsubject.Exact("amyotrophic lateral sclerosis")
5. motor neuron* disease	Motor Neuron Disease/ motor neuron* disease.tw.	motor neuron disease/ motor neuron* disease.tw.	(MH "Motor Neuron Diseases") TI motor neuron* disease OR AB motor neuron* disease	TI motor neuron* disease OR AB motor neuron* disease	(ab(motor neuron* disease) OR ti(motor neuron* disease)) OR mesh.Exact("Motor Neuron Disease") OR mainsubject.Exact("motor neuron disease")
6. lou gehrig* disease	lou gehrig* disease.tw.	lou gehrig* disease.tw.	TI lou gehrig* disease OR AB lou gehrig* disease	TI lou gehrig* disease OR AB lou gehrig* disease	ab(lou gehrig* disease) OR ti(lou gehrig* disease)
7. Frontotemporal Dementia	Frontotemporal Dementia/ Frontotemporal Dementia.tw.	frontotemporal dementia/ Frontotemporal Dementia.tw.	(MH "Frontotemporal Dementia") TI frontotemporal dementia OR AB frontotemporal dementia	TI frontotemporal dementia OR AB frontotemporal dementia	(ab(frontotemporal dementia) OR ti(frontotemporal dementia)) OR mesh.Exact("Frontotemporal Dementia") OR mainsubject.Exact("frontotemporal dementia")

8. Frontotemporal Lobar Degeneration	Frontotemporal Lobar Degeneration/ Frontotemporal Lobar Degeneration.tw.	Frontotemporal Lobar Degeneration.tw.	(MH "Frontotemporal Lobar Degeneration") TI frontotemporal lobar degeneration OR AB frontotemporal lobar degeneration	TI frontotemporal lobar degeneration OR AB frontotemporal lobar degeneration	(ti(frontotemporal lobar degeneration) OR ab(frontotemporal lobar degeneration)) OR mesh.Exact("Frontotemporal Lobar Degeneration") OR mainsubject.Exact("frontotemporal lobar degeneration")
9. Dementia	DEMENTIA/ Dementia.tw.	Dementia/ Dementia.tw.	(MH "Dementia") TI dementia OR AB dementia	DE "Dementia" TI dementia OR AB dementia	(ab(dementia) OR ti(dementia)) OR mesh.Exact("Dementia") OR mainsubject.Exact("dementia")
10. semantic dementia	Semantic dementia.tw.	Semantic dementia/ Semantic dementia.tw.	TI semantic dementia OR AB semantic dementia	DE "Semantic Dementia" TI semantic dementia OR AB semantic dementia	(ab(semantic dementia) OR ti(semantic dementia)) OR mainsubject.Exact("semantic dementia")
11. presenile dementia	Presenile dementia.tw.	Presenile dementia/ Presenile dementia.tw.	(MH "Dementia, Presenile") TI presenile dementia OR AB presenile dementia	DE "Presenile Dementia" TI presenile dementia OR AB presenile dementia	ab(presenile dementia) OR ti(presenile dementia)
12. Pick* disease	"Pick Disease of the Brain"/ Pick* disease.tw.	Pick* disease.tw.	(MH "Pick Disease of the Brain") TI pick* disease OR AB pick* disease	DE "Picks Disease" TI pick* disease OR AB pick* disease	(ab(pick* disease) OR ti(pick* disease)) OR mesh.Exact("Pick Disease of the Brain") OR mainsubject.Exact("pick disease of the brain")
13. Pick* dementia	Pick* dementia.tw.	Pick presenile dementia/ Pick* dementia.tw.	TI pick* dementia OR AB pick* dementia	TI pick* dementia OR AB pick* dementia	ab(pick* dementia) OR ti(pick* dementia)
14. Tauopath*	Tauopathies/ Tauopath*.tw.	Tauopathy/ Tauopath*.tw.	TI tauopath* OR AB tauopath*	TI tauopath* OR AB tauopath*	(ab(tauopath*) OR ti(tauopath*)) OR mesh.Exact("Tauopathies") OR mainsubject.Exact("tauopathies")
15. Pallidopontonigral degeneration	Pallidopontonigral degeneration.tw.	Pallidopontonigral degeneration.tw.	TI Pallidopontonigral degeneration OR AB Pallidopontonigral degeneration	TI Pallidopontonigral degeneration OR AB Pallidopontonigral degeneration	ti(Pallidopontonigral degeneration) OR ab(Pallidopontonigral degeneration)
16. pallido ponto nigral degeneration	pallido ponto nigral degeneration.tw.	pallido ponto nigral degeneration.tw.	TI Pallido ponto nigral degeneration OR AB Pallido ponto nigral degeneration	TI Pallido ponto nigral degeneration OR AB Pallido ponto nigral degeneration	ti(Pallido ponto nigral degeneration) OR ab(Pallido ponto nigral degeneration)
17. 1 or 2 or 3					
18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16					
19. 17 and 18					
20. 19 and year 1993-present					
*Denotes truncations of key terms to broaden the search and include various word endings and spellings.					

Supplemental Digital Content 3 Summary of included references

Study number	Reference, location and format	Study details	Relevant participant details[a]	Aims/objectives	Main findings relevant for the scoping review[a]
1	1 Tibben et al. 1997[35] The Netherlands Journal article	Quantitative survey (adapted self-reported psychological and attitude questionnaires; attitude questionnaire adopted from the Dutch Huntington Presymptomatic Programme) Qualitative in-depth interview	43 individuals at 50% risk from 3 fFTD families (hereditary Pick disease) who had previously participated in genetic research (86% response rate) (21 individuals at risk of AD not included)	Assess acceptability of presymptomatic testing, ability to cope with being at risk, and the influence of the disease upon a variety of areas of life Assess attitudes towards presymptomatic testing	68% would consider testing when it became clinically available, 20% would not take the test, 13% were still uncertain 45% first heard about their personal risk of disease during this study, 68% believed their risk was ≤50%, 18% believed their risk was >70% 32 provided reasons for pursuing testing: to further basic research (42%), informing children (50%), future planning (29%), and relieving uncertainty (46%) 40 detailed the expected impacts of a positive presymptomatic test result: increasing problems for spouses (55%) and children (43%), will allow planning own future (40%) and future of family (35%), will increase my problems (40%), will cause me to become depressed (23%) 40 mentioned the impact on life of being at 50% risk: preoccupation with symptoms (60%), restriction in planning the future (53%), anxiety/ depression/ uncertainty (60%) 20% would consider termination of pregnancy if at increased risk for hereditary pick disease
2	2 McRae et al. 2001[34] USA Journal article	Survey with space for comments sent at time of forwarding letter to inform individuals about discovery of *MAPT* pathogenic variant Survey returned anonymously	20 at-risk individuals from 1 fFTD family with the *MAPT*-related disorder, pallido-ponto-nigral degeneration, who had participated in a genetic research study (30% response rate)	Determine the proportion of individuals who would consider genetic testing, and explore the reasons for pursuing or not pursuing such testing Provide family members with information about how others may respond to the opportunity for testing	10 (50%) would consider genetic testing now, 15% were unsure, 35% would not (unclear if those considering testing actually proceeded with it) 11 (55%) would consider testing in future, 30% were unsure, 10% would not Frequently cited reasons to proceed: collaborate with research (70%), know if children are at risk (45%), reduce uncertainty about the future (35%), to help future planning (30-35%) Frequently cited reason not to proceed: life enjoyed more fully by not knowing (50%), afraid of positive result (30%), concerned about implications for family (30%), worry that a positive result would increase anger and frustration (30%)

3	3 Steinbart et al. 2001[16] USA Journal article	Consecutive case series Survey including demographics, psychosocial assessment tools and questions about attitudes and impact of results, IES and HADS	251 letters mailed out to advise previous research participants of availability of genetic testing after participation in research, resulting in 58 (23.10%) enquiries, 21 (8.4%) deciding to proceed with genetic counseling and testing Of the 21, 11 completed survey: 5 were at 50% risk of inheriting fFTD from 2 families with *MAPT* pathogenic variant (16 individuals from AD families not included)	Evaluate the impact of genetic counseling and DNA testing for FTD with parkinsonism linked to chromosome 17 and familial AD on the lives of individuals at 50% risk who underwent DNA testing	All participants had an affected parent One fFTD at-risk individual who had positive test results was distressed with the result and requested no further evaluation or contact from study personnel (additional data not extracted as results were combined with data from AD families)
4	4 Fanos et al. 2004[32] USA Journal article	Qualitative semi-structured interviews Quantitative survey (anxiety and depression scales derived from Hopkins checklist, choosing correct risk percentages) Administered by telephone	25 at-risk individuals from 10 fALS families at the Forbes Norris MDA/ALS Research Center	Assess interest in presymptomatic testing, understanding of medical aspects and genetics of fALS, and perception of presymptomatic status in fALS	24% understood the fALS inheritance pattern, 64% understood incomplete penetrance 60% would have gene testing for themselves (main reasons: hoping to learn they did not have the pathogenic variant; seeking information to alter priorities; ensuring time to accomplish goals; providing time for psychological preparation; influencing reproductive decisions) 20% would not want to know (main reasons: belief there are no preventive measures; concerns of insurance discrimination; wish to avoid guilt of passing on the gene, not having the gene or tampering with nature; wish to avoid worry of developing ALS; fear of feeling ''flawed'' by having the gene) 20% were ambivalent (carefully weighed pros and cons and were reluctant to make a decision) Many were unsure whether they would receive research results Anxiety and depression levels were significantly higher than those in community adults; 50% had moderate anxiety over developing ALS 24% avoided having families because of worry of having affected offspring
5	5 Goldman et al. 2004[52] USA Journal article	Non-consecutive case series	4 families with or at risk of fFTD	Enable physicians to recognize hereditary patterns and genetic concerns of FTD families and understand genetic counseling strategies	Patient 1: presented for a second opinion leading to clarification of diagnosis of AD to FTD. Main genetic counseling issues: clarifying stress could not cause condition, risks for children, and variable presentation of fFTD in the form of early-onset psychologic conditions

					Patient 2: a man diagnosed with late-stage FTD and manifesting symptoms of ALS. Main genetic counseling issue raised: family history evaluation was complicated in all cases by extensive drug and/or antisocial or psychiatric histories, including pedophilia, arson, domestic abuse, bipolar disease, personality changes, abusive behaviors, suicide, and depression Patient 3: a woman with a family history significant for a *MAPT* mutation and 2 first cousins with autopsy-confirmed FTD. Main genetic counseling issues raised: variable phenotype and family history of alcoholism complicated risk assessment and patient elected not to proceed due to concerns about adverse emotional, social, and financial effects Patient 4: a woman who was referred for evaluation of possible FTD because of progressive word-finding difficulty. Genetic counseling issue raised: problem likely caused by worry due to family history
6	6 Williamson and LaRusse 2004[51] USA Journal article	Non-consecutive case series	1 family including 3 siblings (2 with FTD, 1 without), and their spouses, who participated in a research study, and their children (3 other cases not included)	Share our experience working with families with familial neurodegenerative disease, the genetic counseling process, and the major issues that need attention in the genetic counseling setting	Genetic counseling helped at-risk relatives to decide whether to use autopsy tissue from deceased relative to confirm a *MAPT* pathogenic variant: results not considered useful as they had children, but would reconsider this if treatment options became available or if their children expressed a desire to have the information
7	7 Molinuevo et al. 2005[49] Spain Journal article	Non-consecutive case series	1 individual at 50% risk of family *MAPT* pathogenic variant then confirmed to carry family pathogenic variant, followed up for 27 months (8 from early-onset AD and FFI families not included)	Describe the main reasons healthy family descendants of three families affected with early-onset familial AD, fFTD, and FFI received counseling, their initial psychological response after disclosing of predictive test results, and their posterior emotional evolution	All participants stated their main interest was to receive early treatment when needed in the future; secondary reasons were to decrease anxiety, decide regarding family planning, and inform their children. No employment, marital status, or financial changes were made For the *MAPT* carrier, when receiving the diagnosis, he became upset and then quickly tried to brighten up. His anxiety decreased from clinically relevant values to non-relevant, and he never developed depression. He regularly visits a psychiatrist, although he is not taking any pharmacological treatment and has not made any life changes
8	8 Benatar et al. 2006[17]	Quantitative survey by telephone (family pedigrees constructed, attitudes towards genetic testing and	173 individuals interviewed from 132 families, recruited through advertising, 16 families excluded due to unknown inheritance	Evaluate the feasibility of a clinical trial designed to delay or prevent the onset of disease amongst subjects at risk for fALS	96% would be willing to undergo genetic testing, 64% would want to know the results 78% would be willing to participate in a clinical trial designed to delay the onset of disease

	USA Journal article	willingness to participate in a clinical trial ascertained)	116 fALS families demonstrating autosomal dominant inheritance (5544 people): 1557 were members of 25 different *SOD1* positive families. Population included 516 ALS patients (169 from *SOD1* positive families) and 1056 "definitely" or "probably" at-risk individuals (335 from *SOD1* families)		
9	9 Goldman et al. 2007[44] USA Journal article	Case report	1 case-based compilation of several families with *PGRN* pathogenic variants	Describe the genetics of the FTD spectrum and aid in the genetic counseling of individuals who may carry pathogenic variants	Variable phenotype can be present within families in terms of symptoms and age of onset. Possible differential diagnoses include depression and Parkinson's disease Potential for conflicting interests and family secrets within the family. Importance of ensuring at-risk individuals aware of predictive testing protocol, above possible issues, and ambiguity of testing
10	10 Riedijk et al. 2009[15] The Netherlands Journal article	Consecutive case series Case study	100-180 individuals from 3 fFTD families and at 50% risk of *MAPT* 1 case example of an individual with impaired separation-individuation 13 requested genetic counseling between 1999 and 2002 for *MAPT*, 6 requested genetic testing. Acceptance of genetic counseling between 7 and 17% 1 underwent PND *A*n additional 13 individuals counseled between 2003 and 2008 (unknown how many completed testing)	Unclear. Assumed objectives: Report predictive testing uptake and outcomes between 1999-2008 Present a case study and propose the idea of separation-individuation	Important motivation for testing for 5/6: resolving unbearable uncertainty Observation by clinicians who have counseled all counselees: all counselees reported experiencing clear opposition to genetic testing from relatives. Some consciously used the genetic test to liberate themselves from their oppressive and restrictive family: genetic testing would either enable an independent, disease-free life or anticipation of a future disease without the additional burden of problematic family dynamics Separation-individuation in individuals from FTD families may be impaired by family cohesion that becomes too strong in the face of a threatening illness, leading to enmeshment; growing up with an FTD-affected parent may lead to inadequate separation-individuation, and; preoccupation with the future disease may cause at-risk individuals to refrain from separating from the nuclear family
11	11 Dayani 2011[31] USA Dissertation	Survey (completed online or on paper, only in English)	65 patients with ALS surveyed (patient chart reviewed to confirm the diagnosis) Recruitment through clinics and support associations	Evaluate the attitudes and beliefs of individuals with ALS regarding causes of ALS, genetics and genetics testing	23% (13/56) of the sALS and 50% (2/4) of the fALS cohort had genetic testing recommended to them. Of those, all fALS and 85% of sALS underwent testing (1 sALS and 1 fALS- mutation positive) 58% were interested in speaking with a health professional regarding ALS and genetics after completing the survey

12	12 Fanos et al. 2011[33] USA Journal article	Qualitative semi-structured interviews by telephone	20 randomly selected individuals at 50% risk of fALS (*SOD1*), who are part of the pre-familial ALS study (pre-fALS)	Explore participants' decision whether to learn results of presymptomatic testing or not Understand the psychosocial impact of these decisions Assess preferences for receiving results by telephone or in person	14 chose to learn results, 3 who chose non-disclosure were reconsidering and believed they might have made a different decision if they had received more counseling prior Major reasons to learn results: for children; freedom from living with ambiguity; reduction of anxiety; desire to make appropriate lifestyle decisions Major reasons not to learn results: belief they are gene positive, fear or worry about every symptom Varying impact of positive and negative result, informed by pre-existing risk perception and lived experience Three of those who were mutation positive received results by phone: although all experienced difficulty receiving the news, none thought receiving results in person would have helped Of the 14 who chose to learn results, 7 preferred in person, 4 by telephone, 3 no preference
	13 Benatar and Wuu 2012[54] USA Journal article	Consecutive case series (narrative review not extracted)	>160 fALS at-risk individuals consented to pre-fALS, 60 enrolled in study >430 fALS pedigrees ascertained, with genetic cause identified in ~100	Present the rationale for studying presymptomatic ALS, summarize the early evidence supporting the existence of a presymptomatic phase of the disease, and discuss the challenges of studying presymptomatic ALS and how one might approach these challenges	5 enrolled participants converted from presymptomatic to manifest disease Of the consented: 15% known gene positive, 70% chose disclosure of results, 15% chose non-disclosure
	14 Benatar et al. 2016[55] USA Journal article	Consecutive case series	Pre-fALS cohort (as of February 2016: 113 enrolled, 273 provided consent to participate, 48 excluded, 20 in early stage of screening	Highlight clinically relevant aspects of the genetic complexity of ALS Present an approach to predictive testing that we have developed and refined over the last 8 years in the pre-fALS study	317 genetic counseling sessions held with 161 individuals at 50% fALS risk who were consented to the pre-fALS study: 5/25 of gene result known group had *ad hoc* counseling sessions (due to the absence or inadequacy of prior genetic counseling), for the gene result unknown groups: 11 had pre-decision counseling sessions, 156 had pre-test sessions, 145 had post-test sessions Additional 75 post-test counseling sessions for 63 individuals with ALS
13	15 Fong et al. 2012[43] USA Journal article	Case report	1 family – a wife with suspected FTD and a brother with ALS, a husband reluctant to consider testing, a son interested in considering diagnostic genetic testing and a daughter who had attempted suicide previously	Describe genetic counseling considerations for individuals at risk for a *C9orf72* repeat expansion	Main genetic counseling issues raised: husband reluctant to consent to clinical diagnostic genetic testing for his wife. Genetic counseling encouraged son to communicate with his father about the value of diagnostic testing as well as consider autopsy planning or DNA banking to confirm the clinical diagnosis and access testing posthumously. Counseling also led to

					discussions regarding communicating with relatives, possible reactions to the information and an exploration of implications of accessing predictive testing if available in the future The family subsequently enrolled the patient in a research protocol. An expansion in *C9orf72* was detected and confirmed clinically. The result awaits disclosure because the family remains undecided about whether to learn the information
14	16 Holley et al. 2012[29] USA Conference presentation (available on YouTube) 17 Hartzfeld et al. 2015[28] USA Journal article	Semi-structured qualitative interviews	10 individuals at 50% risk for fALS 396 individuals met inclusion criteria and were approached: 44 responded, 22 excluded, 12 did not respond in timely manner Recruited from North-Western neurologic diseases registry	To learn how fALS influences reproductive decisions, the potential influence of others, factors considered during the decision-making process, and participants ' overall experience regarding reproductive choices	Three had no children, 6 had biological children, 1 had adopted, all did not know their genetic status at time of reproductive decision-making. One had three children before having a tubal ligation due to risk of ALS. Time of decision making ranged from 3-30 years prior Four had pursued clinical testing, all after having children Those who had children believed that regardless of the disease, life is productive; Compared ALS relatively favorably to other diseases; always planned on having children; and, hoped for a cure Those who chose not to have children had extensive experience with ALS and caretaking, saw ALS as an inevitable tragedy, and avoided serious relationships. Children experiencing death was a primary concern.
15	18 Smith et al. 2014[50] USA Journal article	Case report	1 ALS patient with family history of Huntington's disease (HD, likely at 50% risk)	Present lessons learned and considerations for other clinical genetics professionals who are presented with similar challenging issues	Genetic counseling challenges: counseling a man with a fatal condition at risk of another fatal condition, complex risk information, the personal and familial implications, family beliefs and secrecy, and the patient's inability to communicate verbally or through writing due to disease progression (wife facilitated communication and direct communication limited to yes/ no questions) DNA banking preserved patient and his wife's right not to learn his HD genetic status during a stressful time of disease progression, while providing the option for relatives to learn this information in the future
16	19 Mandich et al. 2015[47] Italy Journal article	Case report	2 siblings with ALS	Report two siblings with discordant molecular results which consequently raised several issues in patient/ relative counseling Highlight the need to explore the complexity and pitfalls in genetic	The brother underwent clinical testing and carried a *TARDBP* mutation; the sister did not carry a mutation in any of the 7 genes tested in a research study The sister was considered likely sporadic and a phenocopy. She had not listed anyone to share results

				testing and counseling of ALS patients, and the unexpected consequences for relatives	from research with on the consent form, which raised issues for the family after her death
17	20 Surampalli et al. 2015[30] USA Journal article	Survey pre-test and 1 year post-test: demographics, risk perception, perception of symptoms, perceived risks and benefits of testing, HADS, Likert scales	144 individuals at 50% risk of *VCP* pathogenic variant who had participated in a gene discovery study were sent letter informing them about availability of genetic testing and forwarded a survey, 42 returned to sender 33/102 participated in genetic counseling and testing (by phone or in person, 32.3%) and 29 completed baseline questionnaire No questionnaires returned from individuals declining testing 20 completed post-test HADS questionnaire including 13/18 who tested positive	Assess uptake and decision making for predictive genetic testing and the impact on psychological wellbeing	Mean risk perception at baseline was 50.1% (range 0-100%) Reasons for testing: being able to make arrangements for future care, general planning for the future, relieving uncertainty, informing children and satisfying curiosity At baseline, 7/29 had diagnostic levels of anxiety, 2/29 had borderline levels. All 9 had improvements one year following testing. One person who tested negative had high anxiety after testing Depression levels were increased in 1/20 after testing Three participants mentioned planning for suicide was a factor in their decision to choose testing. Two out of three tested negative. The remaining participant was clinically anxious at baseline and was referred for appropriate psychological treatment and follow up counseling. HADS scores decreased to the normal range
18	21 Marin et al. 2016[14] France Journal article	Multicenter observational study/ consecutive case series Patient-administered survey	376 ALS patients from 6 French ALS referral centers: 200 prevalent cases (diagnosed between 2003-2009), 176 incident (diagnosed since start of project) No refusal to participate in observational study, 80% response rate from anonymized questionnaires	Evaluate the extent to which the 2005 recommendations of the European Federation of Neurological Sciences (EFNS) on the multidisciplinary management of ALS are followed in clinical practice	Twenty (5.3%) had a family history of ALS; 17 (85%) had a *SOD1* gene mutation investigated Amongst sporadic ALS patients, 3/356 had a *SOD1* gene mutation investigated Amongst patients with *SOD1* mutation, 4/15 first-degree adult relatives accepted and performed genetic testing Genetic counselor or geneticist not mentioned in any of the clinics
19	22 Crook et al. 2017[27] Australia Conference poster 23 Crook et al. 2018[39] Australia Conference presentation 24	In-depth qualitative interviews by phone or email, analyzed thematically	28 participants from 20 fALS families including ALS patients, at-risk individuals who are pathogenic variant positive, pathogenic variant negative, pathogenic variant unknown, and spouses of affected patients 33 participants from 24 fALS families (with SOD1, C9orf72 or other genes involved) including 4 ALS patients, 4 spouses, 15 at-risk individuals who had undergone predictive testing (9 mutation positive, 6 mutation negative)	Assess the experiences and impact of genetic testing and fALS on the patient and their family, and identify information and support needs Understand how individuals from fALS families decide whether to have genetic counseling, testing and pursue reproductive options Assess and identify information and support needs	(Results combined here but referenced separately in the results) Reasons for pursuing genetic testing: to inform children or family planning, to benefit research, to be prepared for future onset of disease, to change life priorities and plan for the future, hoping for a negative result, to reduce feelings of uncertainty, belief that knowing was better than not knowing, curiosity, already convinced they are mutation positive or have possible symptoms of disease, perceived personal responsibility or moral obligation to find out Reasons against pursuing genetic testing: no useful preventative options available for mutation carriers,

	Crook et al. 2019[37] Australia Conference presentation		and 10 who had declined predictive testing (and 1 AR gene carrier - data not extracted)		unable to predict onset or disease phenotype, limited perceived benefits of knowing result, concern regarding psychological response to result, concerns regarding implications on insurance, perceived costs, difficulty accessing genetic testing, others opposed to testing The process of predictive genetic testing and counseling was helpful for some to work through their decision-making. Some who had the test wondered whether they made the right decision to find out. Those who tested negative experienced a different burden, such as survivor guilt. Most participants were positive about reproductive genetic testing; their lived experience of ALS often influenced this. Some felt strongly that reproductive genetic testing should be more accessible to fALS families. Others felt the variability in disease age of onset provided hope that mutation carriers could still fully experience parenthood Some patients and relatives experienced difficulty gaining accurate information or support from their health professionals. Patient and family-focused care was deemed important (Factors that informed genetic testing decision-making reported but not clear whether they increased or decreased likelihood of testing, extracted where possible)
	25 Crook et al. 2019[38] Australia Conference poster				
	26 Crook et al. 2019[40] Australia Conference poster	In-depth qualitative interviews by phone or email, analyzed thematically Health economic analysis (not extracted)		Explore experiences of fALS families, and decision-making about reproductive genetic testing options Review the cost-effectiveness of providing funding for first degree relatives of FALS index patients to access reproductive genetic testing, which can reduce incidence of ALS in future generations (not extracted)	
20	27 Goldman et al. 2017[45] USA Journal article	Non-consecutive case series	1 individual at 50% risk of *C9orf72* (2 other cases not included)	Discuss three case histories that demonstrate the confluence of psychiatric and neurodegenerative disease Highlight the added complexity that such cases bring to predictive genetic counseling and offer suggestions for how to approach them	Individual at 50% risk, had one year history of unexplained psychiatric symptoms, causing much distress. Elected to proceed with testing whilst being aware of limitations (result would not change management, would not necessarily explain current disease). Confirmed to carry repeat expansion, accepted result without distress, found it comforting to have a possible explanation, did not focus on future risk of developing ALS or FTD
21	28 Lee and Porteous 2017[46] United Kingdom Journal article	Non-consecutive case series	1 individual at 50% risk of *SOD1* I113T variant: variable penetrance allele (2 other cases not included)	Review genetic testing and reproductive choice in neurological disorders Use case examples to illustrate the way families are counseled and discuss the ethical implications of reproductive technologies	Elected to proceed with testing to inform family planning Once variant confirmed, elected to undergo reproductive testing. PGT round 1 produced 12 embryos, 5 carried high-risk haplotype. 4 with low-risk haplotype had developed sufficiently for implantation

22	29 Mantero et al. 2017[48] Italy Journal article	Case report	1 patient with apparently sporadic ALS, FTD and Parkinson's disease (ALS-PDC)	Describe a patient presenting with sporadic ALS-PDC in whom most common pathogenic variants associated with ALS and FTD have been excluded Discuss the ethical, psychological and practical issues that arose	Family decision to proceed with testing: children keen to undergo presymptomatic testing should mutation be confirmed. Also interested in research programs. Results given to patient and children. Further testing permitted on stored DNA sample even after patient's death
23	30 Sexton et al. 2017[53] Australia Conference poster	Non-consecutive case series	2 FTD patients (2 early-onset AD patients not included)	Use case examples to highlight ethical and practical consent issues in dementia	Case 1: patient lacked capacity to consent, no POA and husband unwilling to participate. Active non-disclosure by sister who had mental health issues. Genetics team facilitated referral for sister to neuropsychiatry and social work, continued to attempt to engage husband. Genetic counseling and DNA storage arranged for relatives without breaching confidentiality Case 2: POA overseas. Patient able to understand purpose of test and articulate motivations for testing. No in-person contact with POA to discuss consent and family impact - unclear of POA's understanding of utility of testing. Facilitated consent with POA, requested case worker and proband also sign consent
24	31 Wagner et al. 2017[11] USA Conference poster 32 Wagner et al. 2018[6] USA Journal article 33 Wagner et al. 2017[12] USA Journal article	Anonymous online survey (survey monkey) including Likert scales	449 ALS patients enrolled in a national ALS registry (Agency for Toxic Substances and Disease registry), survey link emailed in a one-time email announcement (8% response rate)	Study patient access, attitudes and experience with ALS genetic testing among patients enrolled in a US ALS registry. Examine factors associated with increased access to and positive attitude towards testing Make suggestions for clinical practice	Genetic testing was offered to 156/449 (34.7%: 68.9% of total fALS respondents, 27.5% total sALS respondents, p=.00001) and 105/156 (67.3%) completed testing: 50/105 (47.6%) underwent clinical testing, 31/105 (29.5%) research testing, 24/105 (22.9%) were not sure. 21/75 (28%) recalled receiving a positive result. 65.0 % who had a mutation detected indicated an understanding of the typical autosomal dominant inheritance of ALS mutations and recalled discussing the chance that their children could also develop ALS Most indicated that genetic testing results were useful to them (70.8%) and their families (62.5%) with 83.3% agreeing that other persons with ALS should consider genetic testing. The lowest test satisfaction scores were observed in items related to implications for relatives, including "My doctor/care team explained what my result means for my children/family members," and "the results of my genetic testing were useful to my family members." 6.2% had negative/ neutral mean test experience scores - each reported they were not told or could not recall their test result

					No differences in test experience scores or attitudes were observed between those who received positive or negative genetic test results (p=0.98), nor those with fALS or sALS (p=0.51), or those who saw a genetic counselor, compared to those who did not (p=0.14). Those with a family history of ALS were more likely to report a favorable attitude towards genetic testing (p=0.0003), as were respondents who saw a genetic counselor (p=0.02) compared to those who did not see a genetic counselor Those with fALS were more likely to have seen a genetic counselor than those with sALS (p=.0082) The following were more likely to be offered genetic testing: the 12.5% who had contact with a genetic counselor (p=.00001), those with a family history of ALS (compared to dementia) (p=0.00001), those diagnosed <50 (p=0.02). Once offered, genetic testing was more likely completed in those who reported a family history of ALS (p=0.05) Results were disclosed by a physician (69.4%), genetic counselor (25.9%), "other" provider (8.2%), nurse (5.9%), and/or nurse practitioner (4.7%). Results disclosure took place during an office visit (65.1%), by letter (37.4%), or phone (16.9%; multiple answers permitted) 82.7 % believed that genetic testing should be offered to all patients with ALS, 77.5 % would have genetic testing if offered Cost was the main detractor for 52% of respondents who were offered genetic testing but declined
25	34 Fostinelli et al. 2018[57] Italy Journal article	Consecutive case series	402 FTD pedigrees assessed and compared with mutation detection rate results for GRN, *C9orf72* and MAPT Patients offered genetic counseling and test results at time of consenting to study	Further validate FTD pedigree classification criteria as a tool to support genetic test decisions in clinical settings	55 families carried pathogenic mutations (13.7%): 38 GRN, 14 *C9orf72*, 3 MAPT Mutation identification rate: high family history (74%, p<0.001), medium family history (15.4%), low family history (9.7%), apparent sporadic (1.3%) and unknown significance cases (5.6%) Rate of requesting genetic counseling: high family history (42%), medium family history (26.9%), low family history (17.7%), apparent sporadic (5.1%) and unknown significance cases (0%). Apparent sporadic patients requesting counseling were significantly younger than the sporadic patients that did not request it (p=0.001)

26	35 Hodgkinson-Brechenmacher et al. 2018[56] Canada Conference poster	Non-consecutive case series	Unique data on 1400 ALS patients, 1140 with complete data, from 12 ALS multidisciplinary clinics	Unclear. Assumed aim: provide an overview of demographic, genetic, treatment and outcomes data of the Canadian neuromuscular disease registry to highlight the issues present and improve standard of care	Uptake of genetic testing by province differs ($p<0.001$). Genetic testing by year of diagnosis not significant
27	36 Taiwo and Okeke 2018[13] Canada Conference poster	Consecutive case series	13 patients dx with FTD from January 2015-December 2017	Review the proportion of newly diagnosed FTD patients in a consultative service who undergo genetic testing Identify any factors associated with uptake of genetic testing	2 had a family history of ALS, 4 had family history of suspected AD, 3 had a family history of Parkinsonism and 3 had a family history of suspected FTD 1 patient (7.69%) agreed to undergo genetic testing, *C9orf72* mutation confirmed Genetic counseling and testing required a trip to a major city for the assessment. The presence of a social support network, severity of illness, underlying psychiatric illness, age and educational level did not impact the decision to pursue/ forego genetic counseling
28	37 Crook et al. 2019[41] Australia Conference poster and presentation	Non-consecutive case series: includes case examples from study 19 and 28	3 families with or at risk of fALS or fFTD (1 due to TARDBP, one due to C9orf72, and another who has a C9orf72 intermediate expansion)	Highlight the complex genetics and counseling issues that arise in familial ALS and FTD Provide an outline of the planned PhD project that aims to better meet the needs of ALS and FTD patients, their families and health providers (not extracted)	Main genetic counseling issues raised: genetic testing can be appropriately conducted outside of a clinical genetics unit, but challenging cases benefit from genetic counselor input. Health professionals may require further education about the complexities of genetic testing decision-making, and referral pathways should be improved; inconsistent results between laboratories can occur, and therefore the limitations of our current knowledge should be discussed pre-test to ensure informed decision-making
29	38 Crook et al. 2019[42] Australia Journal article	Case report Survey of laboratories	1 ALS patient with *C9orf72* intermediate expansion Survey of 13 genetic testing laboratories	Highlight current limitations to analyzing and interpreting *C9orf72* expansion test results Describe how this resulted in discordant reports of pathogenicity between testing laboratories that confounded the genetic counseling process	Discordant reports of *C9orf72* repeat expansion length and interpretation reported in a patient with ALS diagnosed at age 38 13 laboratories demonstrated that repeat size considered pathogenic range: >23 to >699 hexanucleotide repeats Possible psychological or legal risks of incorrectly interpreting pathogenicity outlined
30	39 Greaves et al. 2019[36] United Kingdom Conference poster	Survey including assessments of anxiety and depression (GAD7, PHQ-9), and rating the importance of reasons to have predictive testing (Likert scale)	38 individuals at-risk of fFTD recruited from the GENetic Frontotemporal dementia Initiative (GENFI): 20 had completed predictive testing (17 known mutation carriers, 3 known non-carriers), 18 had not	Assess the psychological impact of living at risk of FTD compared with knowledge of genetic status and decision making around predictive genetic testing	18% had a current, and 21% had a previous diagnosis of an ongoing mental health problem Untested individuals had higher anxiety scores than those tested Those who knew their mutation status scored higher for depressive symptoms than those who were untested

					Those who underwent testing highly rated 'relieving uncertainty' and 'relieving anxiety' as reasons for undergoing testing. Those who were untested rated these as less important Untested participants rated 'worrying about children's risks' highest, followed by being 'preoccupied with onset': 3.06 (1.20) and 'wouldn't alter medical care' 34% had accessed support, 53% would like more support suggesting they would benefit from talking to someone who understands about FTD and their genetic risk and the problems associated with it, more access to support groups, specific counseling for the genetic diagnosis in particular, and advice on positive planning for the future and making the most of life

[a]Data that is combined with other conditions not extracted

KEY: AD= Alzheimer's disease; ALS= amyotrophic lateral sclerosis; ALS-PDC= ALS parkinsonism-dementia complex; At-risk individuals= individuals who are asymptomatic for disease; fALS= familial ALS; fALS-FTD: familial ALS and FTD, FFI= fatal familial insomnia; fFTD= familial FTD; FTD= frontotemporal dementia; GAD7= general anxiety disorder scale; HADS= hospital anxiety and depression scale; IES= impact of events scale; patients= individuals symptomatic of disease; PGT= pre-implantation genetic testing with IVF; PHQ-9= patient health questionnaire depression module; PND= prenatal diagnosis; POA= power of attorney; pre-fALS= a longitudinal study of individuals potentially at risk for developing fALS; USA= United States of America