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Review

Guidance for clinical management of pathogenic variant carriers at elevated genetic risk for ALS/FTD

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ABSTRACT

There is a growing understanding of the presymptomatic stages of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and nascent efforts aiming to prevent these devastating neurodegenerative diseases have emerged. This progress is attributable, in no small part, to the altruism of people living with pathogenic variants at elevated genetic risk for ALS/FTD via their willingness to participate in natural history studies and disease prevention trials. Increasingly, this community has also highlighted the urgent need to develop paradigms for providing appropriate clinical care for those at elevated risk for ALS and FTD. This manuscript summarises recommendations emanating from a multi-stakeholder Workshop (Malvern, Pennsylvania, 2023) that aimed to develop guidance for at-risk carriers and their treating physicians. Clinical care recommendations span genetic testing (including counselling and sociolegal implications); monitoring for the emergence of early motor, cognitive and behavioural signs of disease; and the use of Food and Drug Administration-approved small molecule drugs and gene-targeting therapies. Lifestyle recommendations focus on exercise, smoking, statin use, supplement use, caffeine intake and head trauma, as well as occupational and environmental exposures. While the evidence base to inform clinical and lifestyle recommendations is limited, this guidance document aims to appraise carriers and clinicians of the issues and best available evidence, and also to define the research agenda that could yield more evidence-informed guidelines.

INTRODUCTION

The study of unaffected people living with pathogenic variants that elevate the risk for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) has informed our understanding of the presymptomatic stage of these related neurodegenerative diseases.[1–5] In turn, this has empowered pioneering trials that aim to delay the onset or even prevent some genetic forms of ALS,[6] with the hope and expectation that similar interventional studies will soon be possible for other forms of genetic ALS and FTD. The success of these endeavours has been built on the foundation of interest and commitment from the community of people living with a pathogenic variant. Increasingly, this community has highlighted the urgent need to develop the best care frameworks for providing appropriate clinical care given current levels of evidence (Box).[7 8] This care includes treatments, but also guidance on clinical monitoring, on legal concerns and on which putative environmental factors to seek out or avoid. These considerations served as the impetus for the hosting of an international workshop (Malvern, Pennsylvania, 21–23 September 2023) that aimed to develop guidance for the clinical management of people at significantly elevated genetic risk for ALS and FTD. We use the term 'guidance' to capture the intent of providing information and advice, rather than clinical practice 'guideline', which would imply the use of a particular methodology.[9] This Workshop brought together people living with a pathogenic variant at risk for ALS/FTD, representatives from patient advocacy groups, an international group of neurologists, neuropsychologists and psychiatrists deeply involved in the care of patients with ALS and FTD and devoted to studying people at elevated risk for these disorders, along with genetic counsellors, ethicists, statisticians, epidemiologists, nurses and representatives from the pharmaceutical industry.

Questions considered by Workshop attendees included:

1. How to incorporate the care needs and preferences of those at elevated genetic risk for ALS and FTD into clinical practice.
2. How to approach predictive genetic counselling and testing, alongside the sociolegal implications of people learning their genetic status especially if this is documented in the medical record.
3. Whether people at elevated genetic risk for ALS and FTD should be treated with therapeutic agents approved by regulatory authorities such as the US Food and Drug Administration (FDA) for patients with clinically manifest ALS/FTD.

4. Whether recommendations can be made to people at elevated risk for ALS and FTD regarding lifestyle, occupational and environmental exposures, physical exercise, smoking, nutrition and management of hyperlipidaemia.
5. How best to evaluate people living with a pathogenic variant for signs of disease, and how frequently these evaluations should be performed.

SURVEY OF CURRENT CLINICAL PRACTICE

To better understand the prevailing opinions and current approach to the care of individuals at elevated genetic risk for ALS/FTD, a short survey soliciting information on evaluation, follow-up and treatment was administered to 150 Northeast ALS Consortium sites prior to the Workshop between May and July of 2023. Responses were received from 71 (47.3%) sites. Of the respondents ~80% were physicians (MDs), ~9% nurse practitioners (NPs) and ~8% nurse coordinators. Respondents reported routinely offering genetic testing to patients affected by ALS (~88%) while ~9% offered testing only to those with a family history. Without genetic testing the identification of at-risk individuals is limited and indeed, most MDs, NPs and coordinators (~64%) reported limited experience with persons at genetic risk for ALS, encountering, on average, ≤10 genetically at-risk individuals in their practice. About 29% of MDs and NPs recommended that these unaffected individuals be re-evaluated only when symptoms become evident. 62% of MDs and NPs recommended regular follow-up, with ~78% of these favouring 6 or 12-month intervals. About 68% of MDs and NPs would perform electromyograms (EMGs) only if symptomatic, and ~55% recommended cognitive testing every 6–12 months. Baseline neurofilament light chain (NfL) levels were recommended by ~57% of MDs and NPs and ~36% would continue monitoring NfL at regular intervals, generally every 6–12 months. Finally, ~72% of MDs and NPs would not offer pharmacological treatment to at risk individuals, while ~15% would offer riluzole, ~5% sodium phenylbutyrate/TUDCA and ~5% edaravone (this survey was conducted prior to the results of the ADORE and PHOENIX trials of oral edaravone and sodium phenylbutyrate/TUDCA, respectively). About 35% of MDs and NPs would offer tofersen only to symptomatic *SOD1* pathogenic variant carriers, while some would treat asymptomatic carriers with an abnormal EMG (10%) or elevated NfL (5%) and only 1% would treat carriers without symptoms and a normal examination, EMG and NfL. While genetic testing is routinely offered to patients with ALS, clinician experience managing at-risk individuals is quite limited, and there is clearly wide variation in practice for monitoring and treating this population. These observations underscore the need for developing guidance to aid clinical practice.

GENETIC COUNSELLING AND TESTING

Unaffected relatives of people with ALS and FTD often inquire about their risk of developing one of these diseases. While the risk to first-degree relatives of people with sporadic ALS is estimated to be fivefold to eightfold compared with the general population[10 11] (in which the cumulative lifetime risk is 1 in 300[12]), the risk is much higher for relatives of patients with familial disease (ie, when there have been multiple affected family members). Considerations for predictive genetic testing ideally begin with construction of a family pedigree and a comprehensive evaluation of an affected individual to determine the genetic basis for ALS/FTD in the family.[13 14] Prior to ordering genetic testing in an affected individual, family concerns and plans for communication of results should be explored, noting the potential implications of positive (and negative) results both for the patient and their relatives. The importance of sharing information with at-risk relatives if a genetic aetiology is found should be emphasised.[14 15] A three-generation family

Community perspective(intentionally written in the first person)

As individuals within families that are affected by genetic ALS or FTD, we have witnessed generations of loved ones die of ALS, FTD or both. As science has advanced and is able to identify the genetic causes of disease in our families, we have chosen to undergo genetic testing and to receive confirmation that we harbour the variants associated with the disease in our families, although we recognise that not everyone wishes to live with this knowledge. Having learnt of our genetic risk, we now face the challenge of considering how to proactively manage our health. We have witnessed the anticipatory fear of a diagnosis steeped in existential dread by our parents, who further had to endure prolonged diagnostic delays even after the emergence of initial symptoms.

Guidance about how to mitigate risk and what steps might be taken to extend functional capacity and maximise disease-free years, would have been valuable for our affected family members and remains, for us, a compelling need. Such advice would facilitate the rational assessment of lifestyle strategies, evaluating their effectiveness in delaying (or even preventing) disease onset or slowing its progression. Moreover, monitoring would enable the medical team to gauge the appropriate timing for referrals to clinical trials or the initiation of therapeutic interventions. While there may be no trials or treatments currently available for all pathogenic variants associated with these diseases, the rapid advancements in the field, driven by the unwavering commitment of scientists and researchers, bring hope for both in the future.

Notwithstanding the foregoing, it is paramount to underscore the need for safeguarding an individual's privacy and protecting personal relationships from unwarranted intrusion. Moreover, maintaining a sense of self-identity is critical. This requires careful consideration of the frequency of diagnostic evaluations to ensure they do not disrupt one's sense of self. The cadence and type of health observations should be tailored to align with the most probable age and phenotype of disease onset associated with the specific genetic variants, whenever this is known. It is vital to recognise that while guidance and care recommendations are indispensable, individuals at elevated risk must be allowed to make informed choices about adopting these recommendations. This decision should be made in the context of genetic counselling services and in partnership with a trusted clinician.

Finally, in the entire endeavour of categorising and solving these genetic diseases, we must protect the humanity and dignity of our communities. Speaking of the masses of individuals with these variants as monoliths with stigmatising language is hurtful, often inaccurate (informed by the lives of achievement of so many of our family members) and counterproductive to the goal of welcoming our genetic community into research and care.

history can assist in identifying at-risk relatives—both close and distant—who could be informed of the genetic finding.[14] A detailed pedigree also informs penetrance, a critical element in determining the risk of developing clinically manifest disease if a pathogenic variant is identified.[16] Clinicians should support further family discussion after the results are provided to the affected individual. This might be accomplished, for example, by inviting family members to join future discussions or providing written materials to distribute to the family.[14 15]

If a genetic cause or genetic risk factor is identified in an affected person, biological relatives may then consider predictive testing. If a genetic cause is not (yet) identifiable, but a strong family history suggests a genetic aetiology, broad predictive testing may be contemplated provided that the unaffected individual understands the limitations of such testing in the absence of an identified variant in an affected family member, most notably the risk of an uninformative negative or uncertain finding. The decision to undergo predictive genetic testing is highly personal and nuanced, with variable reasons for or against, which have been summarised elsewhere.[17 18] There are major potential psychosocial, ethical and legal (eg, insurance) implications that must be explored prior to predictive testing, which should only be performed in the context of genetic counselling, ideally by a genetic counsellor.[14 19 20]

Currently, no guidelines exist for long-term follow-up for people with positive predictive genetic results conferring elevated risk of ALS/FTD spectrum disorders.[21] People who undergo such testing, however, should be offered follow-up that is tailored to their individual needs (eg, mental health therapy, additional genetic counselling, connection to advocacy and other peer support resources). This is true regardless of whether testing reveals a pathogenic variant or not. Those who learn they have not inherited the risk for ALS/FTD may have strong emotional reactions, including for example, survivor's guilt or difficulty adjusting after having lived under the assumption that they were at risk.[18] Additional specialised referral may be necessary for people in whom a pathogenic variant is identified, depending on how the person wishes to act on the risk information. For example, if a person is interested in a clinical evaluation or research participation, then an appropriate referral should be made. If they have an interest in alternative reproductive methods such as in vitro fertilisation with preimplantation genetic testing, it is critical that they are referred to a genetic counsellor and fertility clinic with expertise in the reproductive space. Genetic counselling recommendations are summarised in table 1.

LEGAL CONSIDERATIONS

Legally, the care of people at elevated risk for ALS/FTD spectrum disorders raises questions about privacy, confidentiality and discrimination. Each has different degrees of protection under the law. Privacy protections restrict access

Table 1 Clinical care recommendations

Testing	**Genetic counselling** ► Individuals with a family history of ALS/FTD spectrum disorders who are interested in predictive genetic counselling and testing should first determine whether their affected relative(s) underwent genetic testing; ideally, patients with a genetic aetiology identified for their ALS/FTD should communicate their results to relatives (close and distant) who may be impacted. ► Predictive genetic testing should only occur in the context of genetic counselling (ideally by a genetic counsellor, but if not available, then by another qualified health professional) given emotional and practical considerations that are essential to consider prior to testing. ► People receiving predictive genetic test results should be referred for follow-up that is tailored to their individual needs (eg, mental health counselling, subsequent genetic counselling, clinical evaluation). ► Referral to a genetic counsellor with expertise in the reproductive space is essential if a person would like to consider IVF/PGT or other alternative reproductive methods. ► Carriers of a pathogenic variant at risk for ALS/FTD should be provided with information about available research opportunities. **Sociolegal** ► Protections (and limits of these protections) offered by laws such as GINA and the Affordable Care Act should be discussed early (before information is documented in the medical record). ► Patient access to their medical record (21st Century Cures Act Final Rule) should be factored into decisions about what to document in the medical record and plans made for review of any genetic test results.
Monitoring	**Clinical care paradigms** ► Clinical evaluation of individuals at genetic risk for ALS/FTD should include a history of symptoms (if any), an assessment of what information the individual would like returned from the clinical evaluation and consent regarding disclosure of potential findings; as well as a motor evaluation (including EMG to increase sensitivity) and an assessment for cognitive, language and behavioural impairment and neuropsychiatric symptoms. ► Unaffected carriers should be informed that input from a loved one is helpful in assessing possible symptoms of FTD, but that the impact on relationships of a loved one serving in this capacity is unknown. As such, informant report should only be sought with the explicit consent of people at elevated genetic risk. ► The frequency of evaluations should be tailored to an individual's age, genotype, prodromal manifestations of disease, personal preferences and clinical needs.
Intervention	**FDA-approved therapies** ► As there have been no studies of the efficacy of riluzole or, edaravone in unaffected individuals at genetic risk for ALS/FTD, and only limited evidence that the biological mechanisms targeted by these agents are active during the presymptomatic stage of disease (whether clinically silent or prodromal), we recommend against routine use of these agents in unaffected carriers. ► As there is good a priori biological rationale for believing that therapeutic interventions are more likely to be effective when initiated early, we recommend the initiation of these approved therapies as early as possible following phenoconversion to clinically manifest ALS. **Gene-targeting therapies** ► Outside of ongoing clinical trials or new evidence of efficacy, we do not recommend the use of ASOs in unaffected carriers of pathogenic variants, especially when the toxicity of (long-term) administration of these agents is unknown.

ALS, amyotrophic lateral sclerosis; ASO, antisense oligonucleotide; EMG, electromyogram; FDA, Food and Drug Administration; FTD, frontotemporal dementia; GINA, Genetic Non-Discrimination Act; IVF, in vitro fertilisation; PGT, preimplantation genetic testing.

to an individual's information. Here, we provide details for the USA, but similar provisions and gaps in the law are likely to apply in other countries. In the USA the Genetic Non-Discrimination Act (GINA) precludes employers from asking for genetic information or using genetic information in employment related decisions. Confidentiality protects against unlawful disclosures of information. The Health Insurance Portability and Accountability Act, for example, limits the disclosure of health information without a patient's consent. Evolving legal standards have, however, expanded access to health information. The 21st Century Cures Act, for example, makes health information, including laboratory and genetic test results, available to patients through patient portals, even ahead of receipt of appropriate genetic counselling.[22] Privacy and confidentiality protections may vary depending on state law and may change with legal and policy amendments.

Anti-discrimination protections limit or prohibit the decisions that can be made by a third-party using health information. However, federal and state laws apply in discrete situations and may only provide protections to individuals who qualify under the law. GINA, for example, prohibits employer and health insurance discrimination based on genetic information, with genetic information broadly defined to include information from genetic tests, family history and results of a family member's genetic tests.[23] There are, however, important gaps in protections under GINA, with protections only applying to organisations with more than 15 employees and excluding the military. In the context of insurance, GINA only prevents discrimination by health insurers and does not apply to actions taken by long-term care, life or disability insurers.[24] And while employers cannot request access to an individual's genetic information, this does not prevent employers from accessing the same information through inadvertent disclosures (eg, an employee disclosure of their genetic status to a manager or colleague). While State laws may, in some circumstances, provide additional protections that cover gaps under GINA (eg, Florida law[25]), variations among state laws may impede any general guidelines that can be adopted across the USA.[26] Moreover, protections under GINA no longer apply once a disease manifests. The Americans with Disabilities Act provides some protection to those with manifest disease, but only for those who meet the definition of 'disability' as defined in the Act. The definition of disease manifestation is ill-defined—an individual could meet the definition of 'disease manifestation' if disease pathology (eg, based on a biomarker) appears regardless of symptomatic status,[27] but they might not yet meet the definition of 'disabled'. Thus, while legal mechanisms may extend some protections, critical gaps persist that are relevant to people at genetic risk for ALS and FTD, as well as those with early manifestations of disease.[28] Recommendations relevant to these sociolegal considerations are summarised in table 1.

APPROVED THERAPIES FOR PATIENTS WITH ALS/FTD

Three drugs have been approved for ALS disease modification—riluzole,[29] edaravone[30] and sodium phenylbutyrate/TUDCA[31]—although there is regional geographic variation in approval. However, emerging evidence from recently completed trials calls into questions the efficacy of some of these agents, with sodium phenylbutyrate/TUDCA recently withdrawn from the market.[32 33] Each of these approved drugs is associated with adverse events, but these are generally mild. There are no data to suggest that any of these agents have any beneficial effect during the presymptomatic stage of disease. Currently, there are no approved disease modifying drugs for the treatment of FTD.

In the absence of evidence of efficacy, a biological argument might be made for the use of riluzole presymptomatically given its impact on cortical hyperexcitability, an early feature of ALS,[34 35] including in a very small number of presymptomatic *SOD1* carriers close to phenoconversion.[36] Hyperexcitability testing, however, is not widely available, and the effects of riluzole on cortical excitability are short-lived,[34] raising questions about the rationale for using riluzole during the presymptomatic stage of disease. Currently, there is no biomarker evidence that the pathophysiological processes targeted by edaravone are active during the presymptomatic stage of disease, limiting biological rationale for its use in the genetically at-risk population. New imaging techniques have revealed abnormalities in carriers of some pathogenic variants,[37] but whether these reflect early manifestations of disease or a neurodevelopmental defect, is unclear. As such, MRI findings alone cannot currently be used to justify initiation of therapy.

There have been no studies of these agents in a genetically at-risk population. This, together with incomplete penetrance,[16] no biomarker evidence supporting the activity of relevant disease mechanisms during the presymptomatic stage of disease, and no way to measure the impact of these approved therapies during this stage of disease, we do not recommend their use in the unaffected population at significantly elevated risk. The potential for adverse effects and questions about whether the costs of off-label use of these drugs would be covered by insurance, should also be considered. However, there is good a priori biological rationale for believing that therapeutic interventions are more likely to be effective when initiated early.[38 39] Based on this, combined with the limited available empiric data, we do recommend the early initiation of these approved therapies once patients phenoconvert to clinically manifest ALS, with phenoconversion based on published definitions.[5 40 41]

The FDA has granted accelerated approval to tofersen, an antisense oligonucleotide (ASO) targeting SOD1, for patients with *SOD1*-associated ALS. Tofersen is currently being evaluated, through the ATLAS study, in unaffected carriers of highly penetrant pathogenic *SOD1* variants that are also associated with rapidly progressive disease. In this trial, tofersen is initiated once serum NfL levels rise above a predefined threshold.[6] These eligibility criteria are based on robust data from *Pre-fALS*, a natural history and biomarker study in which serum NfL was found to rise in the 6–12 months prior to phenoconversion to clinically manifest ALS.[3] Tofersen is generally well tolerated, but it may be associated with serious neurological side effects including myelitis and papilloedema.[42] By inference and based on an N of 1 experience in treating a *FUS* pathogenic variant carrier in the prodromal stage of disease (personal communication), the ongoing FUSION study of an ASO targeting FUS enrols both patients with *FUS*-associated ALS and carriers of a pathogenic variant if a rise in serum NfL is found to be associated with ongoing denervation changes on EMG. The treatment of asymptomatic *FUS* people living with a pathogenic variant in this way is somewhat more speculative since the temporal course of NfL in this form of ALS is less well-established. Outside of clinical trials, and pending new evidence of efficacy, we do not recommend the use of ASOs in carriers of other pathogenic variants, especially when the risk of phenoconversion

cannot be predicted and the (long-term) toxicity of these agents is unknown. Recommendations regarding the use of FDA-approved therapies and gene-targeting therapies are summarised in table 1.

METABOLIC CONSIDERATIONS: WEIGHT, DIABETES, DIET, LIPIDS AND STATIN USE

There is evidence that individuals with higher body mass index (BMI) have a lower risk of developing ALS based on several longitudinal observational studies. However, there is some uncertainty about the dose–response[43–45] and the possibility of reverse causation has not been excluded. Further, the biological mechanisms underlying this association remain to be elucidated. Moreover, although presymptomatic BMI was lower among *C9orf72* repeat expansion carriers than among those without repeat expansion, this did not seem to reflect a causal relationship between BMI and the risk of ALS.[46] The association of prior diabetes (and so insulin resistance as an aetiological factor) with ALS risk, has been inconsistent across studies in ALS (reviewed in[47]) and FTD.[48 49] Mendelian randomisation (MR) studies have suggested that genetic liability to higher adiposity[50] is not causally associated with ALS, and that genetic liability to type 2 diabetes has a neuroprotective association with ALS,[51] although type 2 diabetes may represent a risk factor in East Asian populations.[52]

While there are limited data on the relationship between diet and the risk of ALS, one of the most promising areas relates to the intake and plasma levels of polyunsaturated fatty acids (PUFAs), and particularly the n-3 alpha-linolenic acid (ALA). In a large prospective study documenting nearly 1000 ALS cases during follow-up, higher dietary intake of n-3 PUFAs, most notably the 18-carbon, plant-derived ALA,[53] was associated with a markedly lower risk of ALS. This finding was consistent with the results of two previously conducted case–control studies.[54 55] In a follow-up study in the same prospective cohorts, higher prediagnostic plasma levels of ALA were associated with a lower risk of ALS,[56] and among participants in the phase 3 trial of dexpramipexole in ALS, higher plasma levels of ALA at recruitment were associated with longer survival and slower functional decline.[57] While there is no evidence in the population at genetic risk for ALS (or FTD), the available evidence provides strong rationale for a trial of ALA supplementation in the treatment of ALS.

Evidence for a potential role of other nutritional factors is less consistent. A lower ALS risk has been reported among individuals with higher vitamin E intake,[58 59] an important antioxidant, but this finding remains to be confirmed. In contrast, suggestions of potential protective effects of caffeine consumption are not supported by the results of large rigorous longitudinal studies.[60 61]

Studies of lipid profiles have been the subject of more dedicated presymptomatic study, mainly in ALS. The Swedish AMORIS cohort considered prospective data in >600 000 individuals over two decades prior to the development of ALS in a subset of 623.[62] Divergence was noted in levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein B (both generally higher in the ALS group) and high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 (generally lower, maximally 10 years prior to symptom onset, but reversing to higher levels in the few years before diagnosis). Similarly, in the UK Biobank cohort of >500 000 individuals, in which 343 developed ALS,[63] higher HDL cholesterol and apolipoprotein A1 levels were associated with a lower risk of later ALS, with similar prediagnosis trajectories noted for both LDL and HDL cholesterol in data from primary care blood tests.[64] However, a matched case–control study nested in several large US population cohorts observed a higher prediagnostic HDL level as a risk factor for ALS.[65] MR studies in relation to lipids have consistently reported a causal role for higher LDL cholesterol in increased ALS risk.[66–68] No significant divergence of presymptomatic triglyceride levels has been identified.

Meta-analysis of statin use prior to ALS found no evidence of any significant risk association (higher or lower).[69 70] MR analysis has reported a causal effect between statin use and increased risk of ALS,[71] apparently independent of lipid-lowering effects.[72] Intuitively, presymptomatic changes in diabetes or lipid profiles might be expected to influence cardiovascular disease comorbidity. Variably controlled studies have reported reduced premorbid cardiovascular events in those developing ALS.[73–75] In a comparison of apparently sporadic versus familial FTD patients, although postdiagnosis, no significant differences were seen in smoking, hypertension, diabetes or cholesterol.[76] However, significantly higher rates of premorbid heart disease were noted in the apparently sporadic group (20% vs 10%). Overall, however, major confounds are yet to be unpicked to reach a deeper understanding of lipid divergence in the pathway to ALS (and FTD). Results may depend critically on the timing of sampling in relation to symptom onset, with genotype-related factors which will require dedicated cohort studies. Recommendations related to omega 3/ALA intake, statin use, and other interventions for metabolic disease are summarised in table 2.

SMOKING

Smoking has been found to be associated with an increased risk of ALS in most studies that have examined this question, with some suggesting no association, and none suggesting a protective effect.[46 77–81] There are no studies examining the association between smoking and FTD. In a single study of 143 people who developed *C9orf72*-ALS, no causal relationship between smoking and ALS was identified.[46] There is evidence that smoking has no protective effect on the risk of developing ALS or FTD among those without identifiable genetic risk factors or among unaffected *C9orf72* repeat expansion carriers. Given this evidence and the numerous health benefits of not smoking, we recommend that people at genetic risk for ALS/FTD refrain from or stop smoking (table 2).

EXERCISE

Exercise has many positive health benefits as emphasised by guidelines from the Centers for Disease Control and Prevention, National Health Service (UK) and WHO among others. Exercise reduces the risk of common diseases including heart disease, stroke and diabetes.[82] This has two important implications, first it is conceivable that, even without any direct link, ALS may be over-represented in those who regularly exercise because exercise is associated with longevity and ALS is more common in the elderly (ie, survival bias). Moreover, even if ALS risk were to be linked directly to physical exercise, any intervention to reduce exercise would have a significant health cost which needs to be weighed against a measurable protective effect.

Table 2 Lifestyle and environmental exposure recommendations*

	Recommendation	Notes
Omega-3/ALA intake	Ensure adequate intake of omega-3 fatty acids/α-linoleic acid	► There is some preclinical and clinical evidence that consumption of foods high in α-linoleic acid is associated with lower risk of ALS. ► α-linoleic acid is likely safe when used in amounts found in foods, but there is insufficient information to inform the safety of higher doses. ► Foods high in α-linoleic acid include flaxseeds, soybeans, tofu, pumpkin seeds, walnuts, uncooked canola, soybean, walnut and pumpkin seed oil; many of these have high caloric content.
Caffeine intake	No modification recommended	► There is no evidence that caffeine intake has any causal impact on risk for ALS/FTD.
Selenium intake	Consume no more than daily recommended intake	► In studies of the general population, overexposure to inorganic selenium (in water and through diet and dietary supplements) may be associated with higher rates of ALS/FTD.
Statin use	Use as clinically appropriate	► There is no direct evidence that statin use has any causal impact on the risk of ALS/FTD.
Other interventions for metabolic disease	Use as clinically appropriate	► There is some evidence for metabolic differences, in particular some lipid 'divergence' from the general population in those who go on to develop ALS. ► There is no evidence that dietary or (non-statin) pharmacological interventions for metabolic disease impact the risk of ALS/FTD.
Smoking	Do not smoke	► In most studies, including a single study in presymptomatic C9orf72 mutation carriers, smoking is associated with ALS, but evidence for a causal relationship between ALS and smoking is currently lacking. ► There are many proven harms associated with smoking.
Exercise	Follow WHO guidelines on sufficient exercise	► There is no conclusive evidence that (non-professional) exercise impacts the risk of ALS and FTD. ► Exercise has been shown to have physical and mental health benefits.
Head trauma	Minimise head injury	► The evidence linking head injury to ALS is inconclusive. ► This broad recommendation is based on the association between head trauma and chronic traumatic encephalopathy (CTE).
Occupational and environmental exposures	Consider minimising occupational and environmental exposures to fertilisers/pesticides and lead	► In studies in the general population, there is some evidence that exposure to high amounts of fertiliser/pesticides, and lead may be associated with higher risk of ALS. ► However, there is no direct evidence that these environmental exposures impact risk or age of onset of ALS in people at genetic risk.

*Since there is currently limited research on people at elevated genetic risk for ALS/FTD, these recommendations are based almost entirely on studies in the general population.
ALA, alpha-linolenic acid; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia.

For FTD there is emerging observational evidence that physical activity is associated with slowed functional, cognitive and neurodegenerative decline in adults with genetic forms of FTD[83] which is supported by longitudinal associations in blood-based biomarkers.[84] These findings underscore the importance of encouraging people at genetic risk of FTD to follow standard guidance on exercise.

For ALS, there is a wide body of research testing for an association between different types of physical activity and risk of sporadic ALS. Three professional sports (soccer, American football, rugby) have been linked to higher risk,[85 86] leading to the idea that there may be an important exposure which is specific to professional soccer, football and rugby. However, this association has not been consistently found in other types of professional sports or in non-professional soccer,[87] American football and rugby.[88] Of two prospective studies on exercise, one concluded that exercise may be protective for ALS[89] and the other found no overall association between cross-country skiing and ALS.[90]

It is not known what may be driving the association for professional soccer, football and rugby. Hypotheses include repeated head injury, which has been independently linked to risk of ALS,[91] extreme exercise,[92] exposure to environmental toxins[93] or some combination of the above. Given this uncertainty, the extreme exercise involved in professional sports, the lack of evidence of an association between general exercise and risk of ALS, the absence of any adequately powered studies in people at genetic risk of ALS, and the risk of extrapolating from a subset of professional athletes to those at genetic risk of ALS, we recommend that individuals at genetic risk for ALS follow standard exercise guidance (table 2).

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Occupational and environmental exposures are widely researched as potential ALS risk factors in global studies.[94] For many of these potential risk factors, however, epidemiological studies have yielded inconsistent results, possibly due to the effect of biases. As a result, the evidence is insufficient to make recommendations about occupational or environmental exposures, irrespective of whether ALS has an identifiable genetic cause or not.

Of possible occupational exposures, those with very high electromagnetic fields and agricultural pesticide exposure[95–97] show a consistent association with ALS risk, but conflicting results have also been reported. Moreover, the biological plausibility of the association is not entirely clear, risk ratio estimates are generally imprecise due to small sample size, and confounding might have been responsible for these observations. Very limited evidence is available for genetic ALS, where a single study restricted to monozygotic ALS-discordant twins highlighted regular vehicle maintenance and occupational paint usage as potential risks.[98]

For environmental exposures to chemicals, there is epidemiological evidence suggesting a role for excess exposure to the metalloid selenium and to the heavy metal lead, and to some groups of pesticides, despite some risk variability across studies.[99–103] While dietary intake is the most abundant source of selenium, most selenium species in foods are

organic, and generally less toxic than the inorganic forms that may be found in drinking water and occupational environments. Very few studies assessed the potential interaction of these chemicals with ALS-related genetic variants, but those available suggest a role of selenium in disease aetiology[104] and less clearly of copper, iron and manganese.[105 106] Therefore, potential interactions between environmental risk factors and an increased susceptibility for those with greater genetic susceptibility are still to be adequately characterised. Recommendations are summarised in table 2.

Military service is associated with an elevated ALS risk across many, but not all studies,[94 107 108] and while potential causal factors are uncertain, chemical exposure is among proposed hypotheses.[95 109] Nonetheless, no study demonstrates that avoidance of military service prevents ALS onset,[108] and no studies, to our knowledge, on the interaction between military service and ALS genetic risk are published.

In contrast to ALS, the literature on FTD occupational and environmental risk factors is extremely limited,[110] and almost absent in carriers of pathogenic variants. A single study reported possible associations with occupational exposure to aluminium, pesticides and other chemicals (dyes, paints or thinners), some professional sports and long-term use of selenium-containing dietary supplements,[111] but this is an area in need of further research.

CLINICAL CARE PARADIGMS

Understandably, most clinical care guidelines have focused on the needs of patients with clinically manifest ALS or FTD.[112 113] However, those at genetic risk for ALS or FTD have their own clinical needs. For the unaffected population, care should begin with informed consent that includes communication of the risks of medical record documentation and discussion of the issues outlined earlier (see the Genetic counselling and testing and the Legal considerations sections). The availability of support systems should be evaluated, alongside the need for a psychiatric evaluation or counselling/psychotherapy, with a delay in testing if appropriate.

Clinical assessment (summarised in table 1) should include a motor evaluation with an EMG to increase sensitivity in detecting mild motor impairment (MMI). Cognitive, language, behavioural and neuropsychiatric symptoms should be formally assessed in all individuals at risk for FTD. Input from a loved one is helpful in assessing possible symptoms of FTD, especially since a loss of insight may be an early symptom of behavioural variant FTD,[114 115] but such information may not be available or feasible. Unaffected carriers may also have reservations about requesting input from a loved one especially given potential implications for their personal relationship. Carriers should be informed of the value of third-party input and have the option to choose whether to authorise the physician to contact a loved one.

The transition from presymptomatic to early symptomatic illness in familial ALS and FTD can be difficult to recognise.[1 114] Clinical evaluation of (presumptive) presymptomatic individuals should include an appraisal of patient (and family) goals, an interval history including an assessment of what information the individual would like returned from the clinical evaluation, and consent regarding disclosure of potential findings. The clinician may also consider testing relevant biomarkers including neurofilament chain light (NfL), and Alzheimer's disease (AD) biomarkers if AD is on the differential diagnosis.

Beyond an initial assessment, the frequency of evaluations for people at genetic risk will depend on many factors including the individual's age relative to estimated age of onset (even though such estimates are currently very imprecise), genotype, clinical needs (eg, concern over possible symptoms) and presence of any potential early symptoms of ALS or FTD including those suggesting the presence of MMI, mild cognitive impairment (MCI) or mild behavioural impairment (MBI).[114 116 117] Prior to the clinical assessment, the physician should determine whether the carrier wishes to learn about the presence of a potential prodromal syndrome (MMI, MCI, MBI) if this is detected. If information about a prodromal state is to be shared, the uncertainty surrounding the implications of these states, and the extent to which they predict short-term phenoconversion to ALS or FTD, should be communicated. A clinical visit frequency of at least annually allows individuals at risk for ALS or FTD to learn about developments in the field and opportunities to participate in research. Early involvement of a care team and referral to other healthcare providers is often indicated including ALS and FTD specialists, genetic counsellors, mental health professionals, and social workers.

CONCLUSIONS

Considerations around the provision of care to people living with a pathogenic variant at elevated risk for ALS and FTD, are complex. Moreover, there are numerous logistical challenges to developing and implementing an infrastructure to support such care. The optimal path through which unaffected carriers might enter the health system is uncertain and informed consent discussions will need to occur before any information about genetic risk for disease is documented in the medical record (table 1); the Huntington's Disease Society of America, for example, recommends a telephone screening call prior to a visit for genetic testing.[118] The cost of care for unaffected carriers might be borne by health insurance companies, or national healthcare payers systems, but if not then by individuals, with implications of these health economic considerations for access to care. We hope that the foregoing serves as the impetus for developing much-needed new paradigms of clinical care that are fit for the genomic era of medicine and relevant not only to ALS/FTD, but also to other adult-onset genetic disorders.

In addition, the evidence base from which any lifestyle recommendations might be drawn (table 2), is currently extremely limited and is focused on assessing ALS risk in the general population rather than specifically on those at elevated genetic risk. A dedicated and globally cooperative research agenda is needed to develop the knowledge base necessary to assist unaffected carriers in accessing care and guide lifestyle decisions that are most likely to delay or prevent the emergence of clinically manifest ALS or FTD.

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