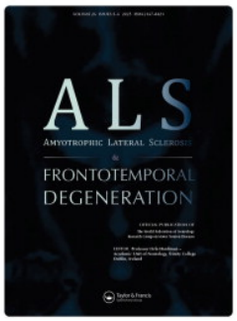

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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REVIEW ARTICLE

The use of genetic testing in amyotrophic lateral sclerosis (ALS): a practical approach

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Abstract

Amyotrophic lateral sclerosis (ALS) is a rare and fatal neurodegenerative disease thought to be precipitated by genetic, environment and lifestyle factors. In the UK, whole genome sequencing has become available to all people living with ALS, regardless of their family history or age of onset of disease. However, there is currently no formal guidance on how to deliver genetic counseling and testing in busy mainstream clinics. This article offers practical suggestions to clinicians who may wish or need to discuss genomic testing. As more clinical trials and targeted gene therapies develop, it is likely that conversations will evolve, reflecting the dynamic nature of this important and complex field.

Keywords: *Genomic testing, diagnostic, MND, ALS, genetic counseling, mainstream clinics*

Introduction

For most clinicians, the diagnosis of amyotrophic lateral sclerosis (ALS), the commonest form of motor neuron disease (MND), is particularly challenging to deliver (1). The diagnosis is overwhelmingly a clinical one and can be made confidently on that basis alone (2). ALS remains incurable despite advances in the understanding of the biology associated with the disease. Riluzole remains the only approved treatment in most countries, having demonstrated a 38% survival extension at 12 months compared to placebo (3), though the absolute and modest benefit to an individual patient is not discernible.

The causes of ALS are complex, and it is recognized that genetics, environment, and lifestyle factors are all important. With the advent of promising gene-targeted therapy and trials for people with ALS, diagnostic genomic testing is becoming part of routine care, requiring neurologists to be upskilled to facilitate testing discussions and adjustment. In England, whole genome sequencing (WGS) is now mainstreamed as part of the NHS genomic medicine strategy. A recent published

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survey showed that neurologists recognized the need for more skills to deliver WGS (4). In this article, we aim to provide practical guidance around delivering genetic counseling and arranging WGS in busy neurology clinics.

The genetic basis of ALS

Historically, ALS was categorized into familial (5–10%) and sporadic (90%) forms based on whether affected relatives were identified in a pedigree (1). Individuals with a positive family history had a higher risk of inheriting the disease. Although this distinction may be useful for genetic counseling, it is an artificial one, since evidence shows that up to 21% of sporadic cases will harbor pathogenic variants in the same genes detected in familial cases (5,6).

It is worth noting that having a positive family can have a wide range of interpretations (7) and may be the result of chance in a condition with 1 in 300 lifetime prevalence (8,9). It may also be difficult to confirm a positive family history because of limited family history being available, together with the small size of some pedigrees and the possibility that relatives may die before manifesting any symptoms. Furthermore, pleiotropy, variable expressivity as well as the highly variable penetrance amongst carriers of pathogenic gene variants (10–12), can reduce the likelihood of identifying a positive family history.

Genetic studies have revealed more than 40 genes linked to ALS with variants in *C9orf72*, *SOD1*, *FUS*, and *TARDBP* being the commonest genetic causes. Most in these genes cause a dominant phenotype but rarely some recessive forms have been reported, for example in *SOD1* p.D91A linked ALS. Additionally, X-linked inheritance can be seen with UBQLN2 pathogenic variants (13,14).

Whole genome sequencing (WGS) for ALS

In England, WGS should be made available to all ALS patients according to the National Genomic Test Directory (15). The test uses whole genome sequencing and short tandem repeats (STR) testing for repeat expansions usually found in *C9ofr72*. Diagnostic WGS can be offered to individuals symptomatic of ALS to search for any underlying pathogenic variants, regardless of their family history. The R58 Adult-onset Neurodegenerative Disorder Testing Criteria stipulate that symptom must include a) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic or neuropathologic examination, AND b) evidence of upper motor neuron (UMN) degeneration by clinical examination, AND c) progressive course, AND d) no evidence of other etiology (15). Importantly, current practice is that WGS is only indicated where no previous pathogenic variant has been identified in the family. If a preexisting familial pathogenic variant is already known (e.g. in an affected parent or sibling), then targeted genetic testing of that specific variant is all that would be routinely undertaken.

"Diagnostic" genetic testing in this regard refers to the fact that the test is undertaken in someone already affected and diagnosed with ALS. The genetic test itself does not play any role in determining if ALS is clinically present or not. This contrasts with a predictive test where people at risk of developing ALS, on account of a pathogenic variant identified in a family member, have the option to test. Currently, predictive test counseling is commonly modeled on the protocol for Huntington's disease and recommendations for pre and post-test counseling support (16). There have been calls to establish predictive test protocols specific to ALS due to the unique clinical and genetic features of the condition (17,18)

In England, the current NHS R58 test (version 6) reports on genetic variants in a panel of 120 genes, including the *C9orf72* gene. This includes ALS linked genes and genes associated with other neurodegenerative phenotypes (parkinsonism, dementias, rare neurological disorders). Single nucleotide variants and short tandem repeats (STRs) in relevant genes will be reported if they meet the laboratory's reporting criteria (19) (Table 2).

The introduction of whole genome sequencing in mainstream clinics has created opportunities to provide patients and their families with more "tangible" biological markers of their disease. This information can shed light into certain clinical features the patient may manifest, e.g. frontotemporal dementia or parkinsonism with *C9orf72* expansions or a slower disease course with some of the *SOD1* pathogenic variants. Confirming the presence of a genetic cause can also facilitate access to novel treatments like Tofersen for *SOD1*-related ALS; to access reproductive genetics as well as the opportunity to join natural history studies or therapeutic clinical trials. Identifying a pathogenic genetic variant also allows other relatives to discuss the option of predictive testing, to access reproductive genetics and to join relevant research studies.

Genomic testing in neurology clinics

In England, WGS can be offered to all people living with ALS. The National Neurosciences Advisory Group (NNAG) has recently identified WGS as a priority and developed the "Optimal Clinical Pathway for Adults: Neurogenetics". This guidance sets out what good care looks like (20).

However, this topic remains difficult because of the complexities of genetics in ALS and the clinical context in which this topic is being discussed.

Genetic testing conversations in ALS clinics can be emotionally charged, particularly as these typically take place in the early stages of receiving a clinical diagnosis, when by necessity there is a focus on addressing the many physical and psychosocial needs of people living with ALS and their families. Consequently, it may prove challenging to provide adequate pretest genetic counseling in this setting, since patients require sufficient time and information available to make well-informed decisions with regards to the pros and cons of WGS and to understand the implications of receiving a result for themselves and their relatives. Communication with other family members should be encouraged, and involving the clinical genetics services early may be helpful (21,22).

In addition to the need to explain what DNA and genes are, an introduction to genetic testing, with patients, needs to include the areas of uncertainty that may arise from testing including limits of our current understanding. Some patients may need more explanations about this uncertainty, related to the variable pattern of inheritance, variable penetrance and expressivity, pleiotropy, and the oligogenic basis in some ALS cases (Table 1). All these factors are important in ALS genetics but can be highly complex to explain, especially as our understanding of this field is actively evolving and changing over time.

Since WGS remains an option rather than mandatory, it is preferred to give patients and families time to reflect on the information shared and to clarify that testing can be discussed and activated at subsequent visits. It is also important to highlight that genetics laboratories can offer DNA storage as a clinical service and patients need to be made aware of this as an option. This allows for the possibility of banking a sample that can be activated at the request of the person with ALS or a close relative after their death.

When the results become available, individuals with a pathogenic or likely pathogenic variant need to understand that the genetic result may not predict prognosis. The genetic risk to other family members needs to be clarified and guidance provided on how to access genetic counseling. Identifying actionable variants in families opens the option of predictive testing for presymptomatic family members. There are also options in relation to starting a family, including preimplantation testing and prenatal diagnosis. During this stage of the conversation, neurologists can also direct patients to appropriate research studies.

Furthermore, it is helpful to clarify that a normal result does not exclude a genetic form of ALS and for those with uncertain results, variants may not be contributing to ALS. Moreover, there should be discussion that periodic review of results may be suitable, and the significance of results could change over time. In the event of an unexpected or unclear result, a referral to clinical genetics may be indicated for further discussion and explanation of the result and to consider whether any additional investigations or familial studies may be helpful.

Motivation to test

Individuals with ALS have different motivations to either consent to or decline WGS and this can change over time. They can consent to WGS to seek answers to why ALS occurred and better understand their condition. Others hope to participate in a treatment trial, or in the case of *SOD1* variants, active treatment, although only a small proportion of patients currently will be eligible. Others have altruistic reasons by wanting to contribute to greater understanding of ALS and to help with research. Sometimes individuals want to have clarity about genetic status looking for

Table 1. Glossary table of some of the terms relevant to genetic counseling and testing discussions.

Genetic terminology	Basic explanation
Alleles	A variant of the nucleotide sequence (the building blocks of DNA) at a particular gene location.
Heterozygous	When an individual has two different versions (alleles) of a gene.
Homozygous	When an individual has two identical versions (alleles) of a gene.
Monogenic disorder	A condition that is caused by pathogenic variants in a specific single gene.
Autosomal recessive disorder	A monogenic disorder that can only occur in individuals with two disease-causing alleles.
Autosomal dominant disorder	A monogenic disorder where a single disease-causing allele is sufficient to cause the condition. Individuals can inherit this from either an affected mother or an affected father. Sometimes, the disease-causing allele can occur *de novo* which means it is seen for the first time in the affected person and cannot be found in either parent.
Oligogenic disorder	Caused or modified by changes in a small number of genes.
Genotype	The combination of alleles in an individual at a specific gene location.
Phenotype	An observable characteristic about an individual, which may be determined by the genotype.
Penetrance	The proportion of individuals carrying a genotype who also develop the disease phenotype.
Expressivity	The extent to which a disease phenotype is expressed in individuals. Variable expressivity is when the same genotype can present with different degrees of severity.
Pleiotropy	The potential for a genotype to associate with different phenotypes.

Table 2. Possible outcomes of WGS and their implications for people living with ALS and their families (ACGS best practice guidelines).

Classification of genomic variant	Explanatory note	Implications
Pathogenic	Very high likelihood that the variant is causative of the disorder. >99% certainty that the variant is pathogenic	May have implications for the affected individual and their relatives
Likely pathogenic	High likelihood that the variant is causative of the disorder. >90% certainty that the variant is pathogenic	May have implications for the affected individual and their relatives
Variant of uncertain significance (VUS)	Any variant that cannot be classified as likely pathogenic or likely benign. Further testing or investigations could be undertaken to re-classify the variant as likely pathogenic e.g. parental testing or mRNA analysis	Unclear significance at the time of reporting but may have future implications for the affected individual and their relatives. This result cannot be used for predictive or reproductive testing.
No variant identified	No pathogenic or likely pathogenic variants identified in ALS linked genes	No genetic cause found in the selected genes. Does not exclude a genetic cause to the disease.
Additional pathogenic variants (Incidental)	Pathogenic or likely pathogenic variants identified in non-ALS linked genes	May have health implications for the patient and their relatives. For example, a cancer associated BRCA1 variant could be identified. While this may not benefit the person living with ALS directly, it may allow relatives to access screening or other interventions.

reassurance that their children are not at apparent increased risk. Others want to obtain information for their children e.g. to support their decision making around predictive and reproductive testing - especially in families where there is a family history. However, it is important to counsel patients that having no variant identified does not exclude such increased risk, since a significant proportion of familial ALS cases do not yet have a known cause.

Individuals with ALS may feel they have enough to deal with individually and as a family, particularly in the early stages of a clinical diagnosis. They may feel apprehensive about the possibility of facing additional uncertainty about positive or uncertain results. They may also worry about the attitudes and reaction of other family members including adult children, and there may be anticipation of guilt in parents. Some people may feel it would offer no benefit or value to their lives e.g. due to limited available treatments, or their family situation (maybe no children or children have completed their families). Some people opt to store their DNA and/or contribute to research rather than know about their genetic makeup, others do decline DNA storage or testing (21).

It is also helpful to gauge how families are coping with the diagnosis of ALS and determine the optimum time to discuss the complexities and uncertainties of genomic testing. As clinicians we can be guided on the timing of discussions around WGS by the patient and their family and their readiness to discuss new information. It may be appropriate to offer involvement of other family members in these discussions, for example adult children, especially given the potential for some ALS patients to develop cognitive impairment or FTD; in our clinics, we sometimes defer WGS to the second clinic visit. Whilst this paper presumes the patient has capacity to make the test decision, this will not always be the case. In this scenario, clinicians would be guided in the usual way by the Mental Capacity Act and a best interest meting may be required.

How to discuss diagnostic genomic testing in clinic

The clinical diagnosis may already be suspected by the patient and their relatives if other relatives are affected with ALS. However, neurologists still need to ensure there is no alternative cause to the patient's presentation.

Where there have been additional cases of ALS in the family, conversations can be complex since the person may have previously witnessed or cared for a relative living with ALS or frontotemporal dementia, another neurodegenerative condition. Feelings of fear and helplessness can be overwhelming. It is therefore key to focus on the physical and psychosocial needs of the patient and gauging the optimum time to discuss WGS and its implications.

When discussing diagnostic testing, one ought to rehearse different possible test outcomes and how the individual may discuss this with their relatives. It is also important to explain that no variant identified does not exclude a genetic cause to their disease. Exploring potential treatments and research studies should be included early in the discussion to reflect a more realistic picture of

Table 3. Key points to remember when counseling patients about WGS and possible ways to discuss these (informed by Crook A et al., 2022).

Core discussion points	Consultation examples
The genetics of ALS	• For most people with ALS, we do not have an explanation for why their disease developed. • A proportion of people with ALS will have an underlying genetic/inherited cause that made them more susceptible to developing disease. • This means that other family members may also be susceptible to developing ALS or other neurological conditions.
Genetic testing for ALS: possible results and implications	• Genetic testing is available to you to clarify whether a genetic explanation can be identified. • Most of the time, your genetic test results do not change your management. In a small proportion of people with ALS, your genetic test results can change the way your ALS is managed. • There is a possibility of an uncertain result, meaning that we don't know whether the result is significant for you and other relatives. We will be guided by experts in this area regarding the need for any more tests.
The voluntary nature of genetic testing, the option of opting out and alternative options (e.g. DNA storage, deferring testing).	• There is no obligation to have genetic testing now or at all • If you prefer, you can be referred to a genetics service for a more detailed discussion or we can chat at another time. • We can also look to store your DNA sample, and testing can be arranged by you or by your family if appropriate at a later date.
Implications for relatives and family communication	• Your genetic test results can help to understand whether your relatives have an increased susceptibility to ALS and could access predictive genetic testing. • Sometimes, families may wish to discuss the option of genetic testing together before they proceed with a test. Is this something you would like to consider? If so, we could store a DNA sample in the lab and request the genetic test once you have had a chance to speak with your relatives.
Practical steps in genetic testing	• Genetic testing involves a blood test. The results take ## weeks. • If you would like to go ahead with testing, we will need to complete some paperwork, and you can have your blood test after this. • We will discuss your test results by phone, face to face or by letter once they are available. • Who would you like to be given the results if you become too unwell.
Consent for Whole Genome Sequencing, including the use, privacy, and storage of results now and in the future. In the UK the record of discussion is used: https://www.england.nhs.uk/wp-content/uploads/2021/09/nhs-genomic-medicine-service-record-of-discussion-form.pdf	• Results from genetic testing provide us with information about you and potentially information that could change your care and the care of your relatives now or in the future.
Information resources to support the discussion. • The option of additional genetic counseling to support decision-making, facilitate adjustment, family communication and help integrate results into daily life. • A means to contact the clinical team.	• Sometimes people may benefit from meeting a health professional who specializes in this area. Our local genetic counseling service is … • If you have any questions between now and when results are available, please contact us. • The following resources maybe useful to help you better understand genetic testing discussion • https://www.mndassociation.org/about-mnd/mnd-explained/inherited-mnd • https://healthtalk.org/experiences/motor-neurone-disease-mnd/possible-causes-mnd-including-inherited-forms-mnd/ • https://healthtalk.org/introduction/inherited-motor-neurone-disease-mnd/ • https://hexi.ox.ac.uk/Familial-MND/overview • https://lesturnerals.org/als-and-genetics/ • https://lesturnerals.org/genetic/about-this-decision-tool/
Optional discussion points	
The uncertainties regarding disease presentation, age of onset, disease progression and penetrance. All may vary between different family members.	• There is still a lot we don't know about genetic ALS. • For most genetic forms of ALS, there is a large amount of variability between family members. This means we can't accurately predict if, when or how disease could develop. • Some forms are also associated with susceptibilities to other progressive neurological conditions like frontotemporal dementia, often shortened to FTD. FTD can affect behavior, language and personality.
The likelihood of pathogenic variant detection based on the personal and family history.	• In looking at your personal history and age at diagnosis, along with your family history, there is a high likelihood/ relatively low likelihood that we may detect a genetic explanation.
The implications of genetic testing for the person with ALS (e.g. eligibility for clinical trials or research studies).	• If a genetic explanation is identified in you, we may be able to offer you additional treatment options and/or involvement in a clinical trial or research study. It also is possible that your management or research options will not change. • If a genetic explanation is identified in you, your children/siblings/parents would (generally) have a 50% risk of carrying the same ALS gene. More distant relatives, such as cousins, could also be at risk.

(*Continued*)

Table 3. (*Continued*).

Core discussion points	Consultation examples
The implications of genetic testing for the relatives (e.g. risk for relatives and the availability of predictive and/or reproductive testing, eligibility for clinical trials or research studies).	• If a genetic explanation is identified in you, your relatives may be able to consider predictive testing. This looks to see if they have inherited the gene change and have an increased risk of developing ALS in the future. • Most people need time to adjust to being at risk of a genetic condition before choosing to have a predictive test or not. • There are many reasons why people choose to pursue predictive testing or choose not to know. Some relatives may wish to proceed with testing to seek important information, support their future planning and assist their decision-making e.g. around taking part in research or reproductive options. • Others may choose not to proceed with testing as they do not feel this information would be useful to them and their future planning, or because they are concerned about their response to finding out their result. • Reproductive genetic testing may be another option available once a genetic explanation has been identified, for those who wish to prevent the gene change being inherited. Individuals can screen for the genetic change either before pregnancy (pre-implantation genetic testing or PGT-M) or during pregnancy (prenatal testing), with a view to terminate the pregnancy if the genetic change is confirmed. • Genetic counseling is a requirement of both predictive and reproductive genetic testing.
The emotional implications for the person or the relatives	• People with ALS, their relatives and carers can experience a range of emotions and can respond differently when they receive genetic testing results. There may be neutral feelings, relief, hope, worry, sadness, numbness, guilt, anger, and an increase in anxiety or depression symptoms.
The possible benefits of communicating to family members that a pathogenic variant (mutation) has been identified.	• If a genetic explanation is identified in you, this can mean that other family members may also have the same genetic change to developing ALS (or other conditions). • Knowledge about the genetic risk can be important for other family members to know about to help them to be prepared, or to help with their future planning (e.g. if wanting to use this information in family planning). • A genetic counseling team could support you in having these discussions.

*Depending on the needs of the person with ALS and their family or support people, there may be brief discussions before testing, and a more detailed discussion after testing, as informed by the genetic testing results.

what the person may be able to access should there be a pathogenic variant.

If there are no known affected relatives, the priority is to confirm the diagnosis of ALS and to ensure that patients and their relatives are given sufficient time to adjust to the serious and possibly unexpected diagnosis. Often following a clinical diagnosis people living with ALS and their families will need to focus on more practical aspects of their lives including finances, work and home adaptions. Supporting children is often a key concern for families living with ALS. In this situation, some defer discussions around WGS to the next visit to allow families time to adjust and learn how to live with ALS. It is worth noting that some patients may struggle to disclose the diagnosis of ALS to their children and relatives. This may be the first time that the individual and family have considered the possibility that ALS can be a genetic condition and that other relatives may be at risk. Providing these families with sufficient support (that may include a toolkit) to have an open and honest conversation about living with ALS is key. Only then, conversations about WGS can be meaningful. Table 3 offers the reader some examples of how to discuss complex genetics in a busy neurology clinic.

This article intended to open up conversations about how genetic testing can be offered in neurology clinics as there are currently minimal standards of care addressing this important and complex topic. As more trials and treatments

Checklist before ALS genomic testing (adapted from Craufurd et al. (23))

- Has the person living with ALS been appropriately counseled about the implications of WGS for the individual and wider family and possible test outcomes, including incidental findings and variants of uncertain significance?
- Has the patient's family or caregiver been included in discussions about the ALS genomic test and possible hereditary implications of ALS?
  - Where the family are not in agreement about the decision to test or would like further discussions, consider offer of referral for genetic counseling.
- Has appropriate informed consent for diagnostic WGS been obtained by the patient/legal representative?
- Has the timescale for expecting a result been made clear to the patient/family?
- Has an appointment with the person requesting the genomic test been arranged to give the result?

Checklist following an abnormal genomic test result for ALS (adapted from Craufurd et al. (23))

- Has a plan for follow-up been discussed with the patient and his/her family?
- Have options to participate in research been discussed?
- Do the patient and their relatives wish/need to be referred for genetic counseling to explore options around predictive testing and reproductive testing?

become available, it is likely that conversations will evolve, reflecting the dynamic and evolving nature of this field.

Author contributions

The original draft was written by Dr AC and Dr RM. All coauthors were involved in the critical review and editing of the manuscript.

Declaration of interest

No potential conflict of interest was reported by the author(s).

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