NAVIGATING ALS GENETICS

A CLINICIAN'S GUIDE TO GENETIC TESTING IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)



ALS SLA CANADA

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WHO should be offered genetic testing

Because **at least 15% of people with ALS have a genetic component to their disease,**[1,2] information on family history is an insufficient screening tool on its own.

Offering genetic testing to all individuals with ALS is the recommended best practice and **can help ensure accurate diagnosis, guide treatment decisions, and inform family risk.**

This is supported by evidence-based recommendations for genetic counselling and testing in ALS, as well as global best practice recommendations.[3,4]

WHAT ABOUT FAMILY MEMBERS?

When a genetic form of ALS is identified in a family, biological relatives who do not have symptoms may choose to undergo **predictive genetic testing.** This can predict an individual's increased risk of developing ALS, but it **cannot determine if, when, or how symptoms will appear.**

Predictive testing should always be paired with predictive genetic counselling. Family members who are interested can be referred to the Medical Genetics Department.

- **Pathogenic variant** → **Predictive testing may be offered**
- **Variant of uncertain significance/VUS** → **Generally not eligible for predictive testing**
- **Individual under 18 years age** → **Generally not eligible for predictive testing**

All persons with ALS should be offered genetic testing, regardless of reported family history.

Familial ALS
2+ biological relatives with ALS* in one family
→ **~70% likelihood of identifying a genetic cause**[5]

Sporadic ALS
No reported family history of ALS*
→ **~15% likelihood of identifying a genetic cause**[6]

**or related MND spectrum disorder*

WHY genetic testing should be offered[3,4]

- **Potential for prognostication**
- **Diagnostic confirmation**
- **Therapeutic actionability**
- **Clinical trials/ participation in research**
- **Better understanding of genetic risk for biological relatives**
- **Personal utility**

In March 2025, Health Canada approved the first genetically-targeted therapy for ALS, for the genetic subtype *SOD1*-ALS. **als.ca/tofersen**

Due to scientific advances, other genetic subtypes of ALS may also have targeted treatments in the future.

"I want to help the field better understand ALS."

"Why did I get ALS?"

WHEN genetic testing should be offered

Genetic testing should be offered to people diagnosed with ALS **as early as possible**, *ideally at the time of diagnosis, or when strongly suspected.*

SUSPECT ALS/ DIAGNOSIS → **OFFER GENETIC TESTING**

Early testing helps support the earliest initiation of treatment for individuals with genetic ALS.

For example, in the Phase 3 clinical trial, earlier initiation of Qalsody (tofersen) was associated with better clinical outcomes.[7]

Ordering Genetic Testing

1 PRE-TEST COUNSELLING

Genetic counselling, by a board-certified genetic counsellor or other health care professional, should precede the offer of genetic testing.

This discussion should support people with ALS and their families in making informed choices about genetic testing.

KEY POINTS TO INCLUDE IN THE DISCUSSION:

- Genetic testing is available and voluntary.
- Why genetic testing is being offered and possible results (positive, negative, VUS).
- Likelihood of a genetic cause: Higher when there is a family history of ALS, frontotemporal dementia (FTD), or other dementias. Emphasize that a genetic etiology remains possible, even without a known family history.
- Potential implications for the individual's care: Accessing targeted treatments (e.g., Qalsody) or eligibility for clinical trials.
- Potential implications for biological relatives: Information about their own genetic risk.

** Refer to these **evidence-based consensus guidelines** for a comprehensive list of topics to cover during pre-test counselling.[3]*

2 ORDER TEST

Guidelines and recommendations support **broad genetic testing** with a gene panel.[3] This includes:

- Any gene for which there are implications for therapeutic decisions.
- Genes listed as "strong" or "definitively" associated with ALS by the **ClinGen ALS Gene Curation Expert Panel**.

If testing options are limited, or there are significant delays in genetic testing, testing should include, as the absolute minimum: *C9orf72, SOD1, FUS, and TARDBP.*[3,4]

Why broad genetic testing?[6,8]

- In addition to an approved treatment, there are clinical trials for many other genes (including ultra-rare genes).
- Oligogenic risk, where multiple variants contribute to disease causation or risk, is known in ALS.
- The inclusion of FTD overlap genes, given the spectrum between ALS and FTD.

3 POST-TEST COUNSELLING

Post-test counselling helps with interpreting results, navigating potential emotional impacts associated with the result, and understanding what genetic findings may mean for the patient's care and their relatives' health risks.

ALS National Genetic Counsellor (NGC)

The NGC, with ALS Canada, accepts referrals for pre- and post- test counselling for ALS patients across the country. Download the referral form here: **als.ca/geneticreferral**. Services are available in English and French.

WHEN TO REFER FOR GENETIC COUNSELLING

Pre-test Counselling	Negative Result	Indeterminate or Uncertain Result	Positive Result
As needed	If family history of MND/related MND spectrum disorders	**ALWAYS**	**ALWAYS**

Are you an Allied Health Professional?
You can work with your clinic's physician to complete a referral.

1. Shepheard SR, Parker MD, Cooper-Knock J, et al. *Value of systematic genetic screening of patients with amyotrophic lateral sclerosis.* J Neurol Neurosurg Psychiatry. 2021;92:510-8.
2. Grassano M, Calvo A, Moglia C, et al. *Systematic evaluation of genetic mutations in ALS: a population-based study.* J Neurol Neurosurg Psychiatry. 2022;93:1190-3.
3. Roggenbuck, J., Eubank, B. H. F., et al. ALS Genetic Testing and Counseling Guidelines Expert Panel. (2023). *Evidence-based consensus guidelines for ALS genetic testing and counseling.* Annals of Clinical and Translational Neurology, 10(11), 2074-2091.
4. Salmon K, de Majo M, Basak N, et al. *Global best practice recommendations for genetic counselling and testing in amyotrophic lateral sclerosis.* (2026). Brain.
5. Al-Chalabi, A., Andrews, J., & Farhan, S. (2024). *Recent advances in the genetics of familial and sporadic ALS.* International Review of Neurobiology, 176, 49-74.
6. Salmon, K., Kiernan, M. C., Kim, et al. (2022). *The importance of offering early genetic testing in everyone with amyotrophic lateral sclerosis.* Brain, 145(4), 1207-1210.
7. Miller, T. M., Cudkowicz, M. E., et al. VALOR and OLE Working Group. (2025). Long-term Tofersen in SOD1 amyotrophic lateral sclerosis. JAMA Neurology. Advance online publication.
8. Lacoangeli, A., Dilliott, A. A., et al. (2025). *Oligogenic structure of amyotrophic lateral sclerosis has genetic testing, counselling and therapeutic implications.* Journal of Neurology, Neurosurgery & Psychiatry, 96(10), 928-936.