Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Amyotrophic Lateral Sclerosis

Description/Background

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by gradual onset of muscle weakness, atrophy, and, ultimately, paralysis of limbs and respiratory muscles. ALS causes these motor neurons to degenerate over time until they eventually die. When the motor neurons die, the brain can no longer initiate and control muscle movement. When voluntary muscle action is progressively affected, people may lose the ability to speak, eat, move and breathe. ALS involves both the upper motor neurons (UMNs) and the lower motor neurons (LMNs). UMN signs include hyper-reflexia, extensor plantar response, increased muscle tone and weakness in a topographical representation. LMN signs include weakness, muscle wasting, hypo-reflexia, muscle cramps and fasciculations. Affected individuals typically present with asymmetric focal weakness of the extremities, stumbling, poor handgrip or bulbar findings. The disease will progress to paralysis, hoarseness, slow speech pattern, difficulty swallowing, difficulty breathing, head drop and respiratory collapse.

According to the ALS Association, symptoms generally show between the ages of 40 and 70, with an average age of 55 at the time of diagnosis. ALS appears to be sporadic in the majority of cases. Only 5-10% of cases are familial. These familial forms may be autosomal dominant, autosomal recessive or x-linked dominant. According to the National Institutes of Health Genetics Home Reference, “Mutations in several genes, including the *C9orf72*, *SOD1*, *TARDBP*, *FUS*, *ANG*, *ALS2*, *SETX*, and *VAPB* genes, cause familial ALS and contribute to the development of sporadic ALS. Mutations in the *C9orf72* gene are responsible for 30 to 40 percent of familial ALS in the United States and Europe. Worldwide, *SOD1* gene mutations cause about 20 percent of familial ALS, *TARDBP* gene mutations account for about 5 percent, *FUS* gene mutations cause about 5 percent, and *ANG* gene mutations account for around 1 percent. The other genes that have been associated with familial ALS each account for a small proportion of cases. It is estimated that 60 percent of individuals with familial ALS have an

identified genetic mutation. The cause of the condition in the remaining individuals remains unknown." The mean survival time from onset with ALS is 2 to 5 years, with a range of 5 to 10 years or even longer. There is currently no cure for ALS.

A diagnosis of ALS is based primarily on:
- Clinical features
- History and physical
- Neurological exam
- Electrodiagnostic testing
- Exclusion of other health conditions with related symptoms

Although GT for ALS does not change the final disease outcome it can provide guidance for drug therapy. Additionally, preconception genetic testing and counseling may be helpful when the test result may play a role in the individuals decision for family planning.

Regulatory Status

N/A

Medical Policy Statement

Preconception genetic counseling and testing of any genes associated with amyotrophic lateral sclerosis (ALS) are considered established when the test results will impact decisions regarding family planning.

Genetic testing in individuals with ALS is considered established when the test result will guide drug treatment.

Inclusionary and Exclusionary Guidelines

Inclusions:
Preconception genetic testing for ALS in individuals of reproductive years is indicated when any of the following criteria are met:
- A known mutation of any ALS-associated gene exists in a parent or sibling
- There are 1 or more first degree relatives with ALS of unknown genetic cause

Genetic testing in individuals with ALS who are being considered for treatment with an FDA approved gene targeted drug. Reference Pharmacy Policy for coverage details.

Exclusions:
- Genetic testing for ALS in individuals not meeting the above criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

S3800 81403 81404 81405 81406 81479

Other codes (investigational, not medically necessary, etc.):

N/A

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

There is no known cure or treatment that halts or reverses ALS. Currently, providers engage in a national standard of best-practice multidisciplinary care. Objectives include symptom management, enhancing quality of life and maintaining as much independence as possible for people who are affected by ALS. Researchers do not fully understand what triggers motor neurons to degenerate in people with ALS.

Sporadic ALS is the most common form, accounting for approximately 90-95% of cases in the United States. The remaining 5-10% are considered familial ALS. Mutations in the gene encoding superoxide dismutase 1 (*SOD1*) account for an estimated 12-23% of familial cases. Mutations in other genes, including *C9orf72, TARDBP, FUS, ANG, ALS2, SETX*, and *VAPB* are believed to cause familial ALS and are believed to contribute to the development of sporadic ALS; however, other genetic loci have variable penetrance's. At this time, clinical testing is performed primarily on *SOD1*.

According to the ALS Association, "Since the vast majority of individuals do not have the hereditary type of ALS, a diagnosis of ALS is not determined by a genetic test. Instead, a neurologist makes the diagnosis after a review of a person's symptoms, a neurological exam, and results on nerve and muscle function tests." Preconception genetic testing and counseling may play a role in the individual's decision for family planning.

Roggenbuck et al (2021) conducted a multicenter, prospective cohort of 573 people with a family history of ALS, dementia, or both ALS and dementia with the objective to report the frequency of ALS genetic variants in a nationwide cohort. Individuals who had a diagnosis of definite or probable ALS per El-Escorial criteria were offered ALS genetic testing using a testing algorithm based on family history over an 18-month period (January 2019 to June 2020). A pathogenic or likely pathogenic variant was identified in 171/573 (30%) of program participants. Several barriers to testing access were identified and included cost, identifying appropriate candidates for testing, appropriate test selection, and access to genetic counseling. Testing practices were found to vary widely. The authors concluded that genetic testing is not standard of care.

Roggenbuck (2023) received a grant from the ALS Association to support the development of genetic testing guidelines for all individuals with ALS. The director of research at the ALS Association (2025) indicated it is important for people with ALS to know their genetic status in order to access treatments as early as possible and to potentially be eligible to participate in genetically based clinical trials. The guidelines recommend that all people with ALS, regardless of their family history, be offered genetic counseling in addition to testing for mutations in the most common genes linked to the disease – *C9orf72, SOD1, FUS* and *TARDBP* (at a minimum) – because genetic mutations can occur in both the familial and sporadic forms of the disease.

The American Neurological Association (2025) indicates in a question and answer format that it is important for patients and families with ALS to define what type of ALS they have through genetic testing. New therapies are being developed and tested for specific genetic forms of ALS. Knowing what type of variant is present may allow the individual to participate in clinical trials and to receive these therapies.

The American Neurological Association and the American Academy of Neurology have not published guidelines regarding genetic testing for ALS.

Government Regulations

National:

There is no CMS National Coverage Determination (NCD) for genetic testing for ALS.

Local:

There is no CMS Local Coverage Determination (LCD) for genetic testing for ALS.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling
Genetic Testing – Carrier Screening for Genetic Diseases

References

1. ALS Association, “Genetic Testing for ALS,” 2024; https://www.als.org/understanding-als/who-gets-als/genetic-testing. Accessed February 7, 2025.
2. ALS Association, “ALS Symptoms and Diagnosis.” 2024. https://www.als.org/understanding-als/symptoms-diagnosis#:~:text=There%20is%20no%20one%20test,a%20diagnosis%20can%20be%20.%20Accessed%20March%2020,%202024. Accessed February 7, 2025.
3. ALS Association, “New National Guidelines are Step Toward ‘More Consistent and Comprehensive Approach’ to ALS genetic Counseling and Testing.” 2025.

https://www.als.org/stories-news/new-national-guidelines-are-step-toward-more-consistent-and-comprehensive-approach-als. Accessed February 7, 2025.
4. ALS Association, "Understanding ALS?" 2024; https://www.als.org/understanding-als. Accessed February 15, 2024.
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6. Dunckley, Travis, PhD, et al., "Whole-Genome Analysis of Sporadic Amyotrophic Lateral Sclerosis," *The New England Journal of Medicine,* Vol. 357, No. 8, August 23, 2007, pp.775-787.
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8. *HAYES GTE Report, "*Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig Disease)," Lansdale, PA: Hayes, INC., January 29, 2009.
9. *HAYES Update Search*, "Amyotrophic Lateral Sclerosis (ALS; Lou Gehrig Disease)," Lansdale, PA: Hayes, INC., January 14, 2013.
10. Hosler, Betsy, PhD, et al., "Linkage of Familial Amyotrophic Lateral Sclerosis with Frontotemporal Dementia to Chromosome 9q21-q22," *The Journal of the American Medical Association*, Vol. 284, No. 13, October 4, 2000, pp. 1664-1669.
11. Kinsley, Lisa and Siddique, Teepu, "Amyotrophic Lateral Sclerosis Overview," *GeneReviews*, Initial Posting March 2001, Last Update February 2015
12. National Institutes of Health, Genetics Home Reference, "Amyotrophic lateral sclerosis," reviewed March 2016; http://ghr.nlm.nih.gov/condition/amyotrophic-lateral-sclerosis. Accessed February 7, 2025.
13. Roggenbuck J, Eubank BHF, Wright J, et al. "ALS Genetic Testing and Counseling Guidelines Expert Panel. Evidence-based consensus guidelines for ALS genetic testing and counseling." Ann Clin Transl Neurol. 2023 Nov;10(11):2074-2091. doi: 10.1002/acn3.51895. Epub 2023 Sep 10. PMID: 37691292.
14. Roggenbuck, J., Rich, KA., et al. "Amyotrophic Lateral Sclerosis Genetic Access Program Paving the Way for Genetic Characterization of ALS in the Clinic." Neurol Genet Oct 2021, 7 (5) e615; DOI: 10.1212/NXG.0000000000000615.
15. Rowland, Lewis P. and Neil A. Shneider, MD, PhD, "Amyotrophic Lateral Sclerosis," *The New England Journal of Medicine*," Vol. 344, No. 22, May 31 2001, pp. 1688-1700.
16. Schymick, Jennifer C., et al., "Genome-Wide Genotyping in Amyotrophic Lateral Sclerosis and Neurologically Normal Controls: First Stage Analysis and Public Release of Data," *Lancet Neurology*, Vol. 6, 2007, pp. 322-328.
17. Wisconsin Physicians Service (WPS), "Molecular Diagnostic Tests," *Local Coverage* Determination, L36807, Original Effective Date 2/16/17, Revision Effective Date 12/30/21.
18. Wisconsin Physicians Service (WPS), Local Coverage Article, A55247, MolDX: Excluded Test List, Retired Eff. 1/1/18.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 2/7/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/07	3/20/07	3/20/07	Joint policy established
9/1/07	7/1/07	8/29/07	Code update
9/1/08	7/3/08	7/3/08	Routine maintenance
11/1/09	8/18/09	8/18/09	Routine maintenance
11/1/11	8/16/11	8/16/11	Routine maintenance
1/1/13	10/16/12	10/16/12	Routine maintenance
5/1/14	2/28/14	3/3/14	Routine maintenance; codes 81403-81406 and 81479 added to policy; MPS and Inclusion sections were revised to include all genes associated with ALS
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
7/1/18	4/17/18	4/17/18	Routine maintenance Updated Medicare information
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (slp) Vendor Managed: N/A
7/1/24	4/16/24		• Routine maintenance (slp) • Vendor managed: N/A • Inclusion added for medication which are associated with GT with reference to pharmacy's policy • Exclusion clarified for anything not outlined in inclusions • MPS statement added to include FDA approved GT for medication guidance in ALS individuals

7/1/25	4/15/25		• Routine maintenance (slp) • Vendor Managed: N/A

Next Review Date: 2nd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR AMYOTROPHIC LATERAL SCLEROSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply
BCNA (Medicare Advantage)	Refer to Medicare information under Government Regulations
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.