

**LETTER OF MEDICAL NECESSITY**

**HSP, Complete Recessive Evaluation**

**Instructions for Healthcare Provider:**

1. This letter template is being provided as a tool for clinicians to assist communication with payers.
2. Include specific patient information in the letter for this tool to be effective. The areas that must be edited/deleted are indicated in grey on the template.
3. Print the template on the physician’s letterhead, **NOT** Athena letterhead. There should be no Athena branding on the letter.

[LMN: HSP, Complete Recessive Evaluation (7/6/22)]

<Date>

ATTN: <Medical Director/ Physician Name>, MD

 <Institution/Insurance Company>

  <Street Address>

 <City>**,** <State> <Zip>

RE: <Patient Name>

DOB: <MM/DD/YYYY>

Member ID: <Insurance ID Number>

Group #: <Enter Group #>

Dear Doctor <Medical Director/ Physician Name>:

I am writing this letter on behalf of my patient <Patient Name> to request coverage for the HSP (hereditary spastic paraplegia), Complete Recessive Evaluation, or HSP Recessive, to determine the underlying genetic cause of my patient’s HSP. This expanded gene panel uses next-generation sequencing (NGS) to detect DNA sequence variants in 12 genes associated with HSP. This letter documents the medical necessity for HSP Recessive in light of the patient’s medical history. Results from the test will be used to guide appropriate medical care for the patient.

I have determined that this test is medically necessary because of the following aspects of this patient’s history:

<Patient name> is a <age>-year old <gender> with a suspected diagnosis of <disease name>. Symptoms and clinical findings are consistent with this diagnosis:

1. <Symptom #1 with ICD-10 code>

2. <Symptom #2 with ICD-10 code>

<Symptoms should support diagnosis or risk of genetic disease.>

<Add details such as age-of-onset and any relevant family or other personal history, such as 1st/2nd-degree relatives with features associated with a genetic basis of HSP.>

<Consider adding details from physical and neurological exams such as gait disturbance due to slowly progressing spastic paraparesis, ataxia, and cognitive impairment as well as relevant results from neuroimaging and neurophysical studies.>

**Rationale for Testing**

HSP is a syndromic designation for a group of neurodegenerative or neurodevelopmental disorders that are characterized by progressive weakness and spasticity in the lower limbs.1-3 The mode of inheritance can be Mendelian (autosomal dominant [AD-HSP], autosomal recessive [AR-HSP], X-linked) or non-Mendelian (mitochondrial maternal).1 Approximately 25% to 30% of individuals with HSP have AR-HSP, and it is more prevalent in populations with a higher degree of consanguinity.4 The global prevalence of AR-HSP is approximately 1.8 per 100,000 persons.5

The diagnosis of AR-HSP is difficult owing to the phenotypic, etiologic, and genetic overlap with numerous other conditions, including the hereditary cerebellar ataxias, other inherited neuropathies (eg, Charcot-Marie-Tooth disease), leukodystrophies, hereditary amyotrophic lateral sclerosis, monogenic Parkinson disease, and other metabolic disorders (eg, arginase and biotinidase deficiencies, phenylketonuria).2,3,6 Accordingly, diagnostic evaluation is extensive and includes clinical examination, family history, metabolic analysis, radiological assessment (mainly magnetic resonance imaging [MRI] of the brain and spinal cord), and electrophysiological tests (eg, electromyogram).6,7 Diagnostic clues for AR-HSP include the presence of consanguinity, few affected family members, and the presence of complicated forms of HSP (ie, the spastic paraplegia phenotype is associated with other neurological or non-neurological signs).1

Genetic testing is appropriate to provide a molecularly confirmed diagnosis in cases of unremarkable baseline clinical investigations and/or when family history and clinical features suggest a diagnosis of AR-HSP.8 The clinical presentation and inheritance pattern can help focus genetic investigations and increase the likelihood of making a definitive molecular diagnosis.8 However, identifying which gene(s) to test is complex because of genetic heterogeneity, genetic overlap of HSP genes with other conditions, the possibility of variants within an HSP gene to have different inheritance patterns (eg, AD and AR), and the possibility of concurrent HSP-related gene variants within a single patient.3 Furthermore, many cases of apparently sporadic spastic paraplegias likely have a genetic cause even with negative family history due to asymptomatic affected relatives and *de novo* mutations.1 Obtaining a molecular diagnosis provides diagnostic certainty, can prevent further unnecessary tests, informs prognosis, assists genetic counseling, and allows for preimplantation or prenatal diagnosis.3,9 However, 71% to 82% of families with AR-HSP undergoing systematic testing for HSP do not receive a genetic diagnosis.5

The European Federation of Neurological Societies recommends sequential testing for SPG11 and SPG15 in patients with AR-HSP and thin corpus callosum, and testing for SPG7 may be performed especially in patients with cerebellar features.10 However, these guidelines were published in 2010, and multiplexed genetic testing using NGS is now favored rather than testing on a gene-by-gene basis.7,9 NGS provides a lower-cost and high-throughput platform compared with traditional genetic analysis using Sanger sequencing.11 Multigene panels are more capable than serial single-gene testing at identifying the genetic cause of AR-HSP while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.4 For example, a study showed that out of 15 patients with AR or sporadic inheritance who were tested with a 9-gene AR-HSP NGS panel, 6 (40%) had a genetic cause of HSP identified (SPG5 or SPG7). None were identified with SPG11 or SPG15, highlighting the limitations of guideline-recommended serial testing.12

In summary, testing with HSP Recessive confirms the diagnosis of HSP, which is valuable because of the genetic and phenotypic complexity of the condition. The test also demonstrates clinical utility by providing valuable information that can inform clinical management and family planning decisions. Therefore, I am requesting that <Patient Name> be approved for the HSP, Complete Recessive Evaluation (Test Code 6620, CPT code 81448(1)) offered by Athena Diagnostics.

I hope you will support this letter of medical necessity for <Patient Name>. Please feel free to contact me at <Physician Phone> if you have additional questions.

Sincerely,

<Physician Name>, MD

NPI #: <Physician NPI#>

Contact information:

< Address>

<City>**,** <State> <Zip>

Contact Phone: <phone number>

The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

**References**

**1.** de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, et al. Hereditary spastic paraplegia: clinical and genetic hallmarks. *Cerebellum*. 2017;16(2):525-551. doi:10.1007/s12311-016-0803-z

**2.** Murala S, Nagarajan E, Bollu PC. Hereditary spastic paraplegia. *Neurol Sci*. 2021;42(3):883-894. doi:10.1007/s10072-020-04981-7

**3.** Saputra L, Kumar KR. Challenges and controversies in the genetic diagnosis of hereditary spastic paraplegia. *Curr Neurol Neurosci Rep*. 2021;21(4):15. doi:10.1007/s11910-021-01099-x

**4.** Hedera P. Hereditary spastic paraplegia overview. August 15, 2000 [Updated February 11, 2021]. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2022.

**5.** Ruano L, Melo C, Silva MC, et al. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology*. 2014;42(3):174-183. doi:10.1159/000358801

**6.** Shribman S, Reid E, Crosby AH, et al. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*. 2019;18(12):1136-1146. doi:10.1016/s1474-4422(19)30235-2

**7.** Elsayed LEO, Eltazi IZ, Ahmed AE, et al. Insights into clinical, genetic, and pathological aspects of hereditary spastic paraplegias: a comprehensive overview. *Front Mol Biosci*. 2021;8:690899. doi:10.3389/fmolb.2021.690899

**8.** Hensiek A, Kirker S, Reid E. Diagnosis, investigation and management of hereditary spastic paraplegias in the era of next-generation sequencing. *J Neurol*. 2015;262(7):1601-1612. doi:10.1007/s00415-014-7598-y

**9.** Kumar KR, Blair NF, Sue CM. An update on the hereditary spastic paraplegias: new genes and new disease models. *Mov Disord Clin Pract*. 2015;2(3):213-223. doi:10.1002/mdc3.12184

**10.** Gasser T, Finsterer J, Baets J, et al. EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias. *Eur J Neurol*. 2010;17(2):179-188. doi:10.1111/j.1468-1331.2009.02873.x

**11.** Sun H, Shen XR, Fang ZB, et al. Next-generation sequencing technologies and neurogenetic Diseases. *Life (Basel)*. 2021;11(4):361. doi:10.3390/life11040361

**12.** Kumar KR, Blair NF, Vandebona H, et al. Targeted next generation sequencing in SPAST-negative hereditary spastic paraplegia. *J Neurol*. 2013;260(10):2516-2522. doi:10.1007/s00415-013-7008-x