A picture containing drawing

Description automatically generated

**LETTER OF MEDICAL NECESSITY**

**HSP, Comprehensive 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, Comprehensive Evaluation (revised 4/27/22)]

<Date>

ATTN: <Medical Director/ Physician Name>, M.D.

<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, Comprehensive Evaluation (HSP Comprehensive) to determine the underlying genetic cause of my patient’s hereditary spastic paraplegia (HSP). This expanded gene panel uses next-generation sequencing (NGS) to detect DNA sequence variants in 24 genes associated with HSP. This letter documents the medical necessity for HSP Comprehensive 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 HSP. 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 The global prevalences of AD-HSP and AR-HSP are both approximately 1.8 per 100,000 persons.4

The diagnosis of 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).2,3,5 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).5,6

Although acquired causes of symptoms should be excluded through clinical investigation, genetic testing is still necessary to obtain a molecularly confirmed diagnosis of HSP.1,2,5 The clinical utility of genetic testing is highlighted by a study of children misdiagnosed with cerebral palsy (CP). Children can be misdiagnosed with CP since spastic diplegia presenting in infancy can be common to both CP and HSP.7 In a study of 20 patients under the age of 3 years who were initially diagnosed with CP, but had clinical suspicion of HSP, 14 (70%) were diagnosed with HSP after testing with whole-exome sequencing.7

Molecular diagnosis is challenging since there are currently 81 genetic forms of HSP identified, and new HSP-related genes are being identified regularly.3 A guideline by the European Federation of Neurological Societies for the molecular diagnosis of HSP recommends initial testing of the most common gene variants (eg, *SPAST* in AD-HSP and *SPG11* in AR-HSP) based on clinical evaluation and mode of inheritance.8,9 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.6,9 Studies have shown that the diagnostic yield of targeted gene panels ranges from approximately 20% to 50% after exclusion of common HSP genes at initial testing.10-13 In studies using NGS-based targeted gene panels (16-206 genes) with no prior testing, molecular confirmation of HSP diagnosis was reported in 21% to 62% of patients with clinically diagnosed or suspected HSP.14-22

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 A molecular diagnosis may also facilitate participation in clinical trials. There is ongoing research to develop therapies based on metabolic pathways that are affected by HSP gene variants. For example, clinical trials are planned for patients with confirmed SPG11 to examine treatments that affect glycosphingolipid production.23,24 In addition, recent and ongoing clinical trials are examining whether patients with confirmed SPG5 may be effectively treated with cholesterol-lowering drugs.2,5,25,26 Although these studies of SPG5 only examined biochemical outcomes, they may set up future studies that examine whether these treatments impact neurological outcomes. Thus, a confirmed molecular diagnosis may facilitate patient enrollment into clinical trials to develop therapies for HSP.

In summary, testing with HSP Comprehensive 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 decisions. Therefore, I am requesting that <Patient Name> be approved for the HSP, Comprehensive Evaluation (Test Code 6630, 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.** 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

**5.** 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

**6.** 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

**7.** Suchowersky O, Ashtiani S, Au PB, et al. Hereditary spastic paraplegia initially diagnosed as cerebral palsy. *Clin Park Relat Disord*. 2021;5:100114. doi:10.1016/j.prdoa.2021.100114

**8.** 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

**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.** 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

**11.** Morais S, Raymond L, Mairey M, et al. Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias. *Eur J Hum Genet*. 2017;25(11):1217-1228. doi:10.1038/ejhg.2017.124

**12.** Elert-Dobkowska E, Stepniak I, Krysa W, et al. Next-generation sequencing study reveals the broader variant spectrum of hereditary spastic paraplegia and related phenotypes. *Neurogenetics*. 2019;20(1):27-38. doi:10.1007/s10048-019-00565-6

**13.** Riso V, Rossi S, Nicoletti TF, et al. Application of a clinical workflow may lead to increased diagnostic precision in hereditary spastic paraplegias and cerebellar ataxias: a single center experience. *Brain Sci*. 2021;11(2):246. doi:10.3390/brainsci11020246

**14.** Balicza P, Grosz Z, Gonzalez MA, et al. Genetic background of the hereditary spastic paraplegia phenotypes in Hungary - an analysis of 58 probands. *J Neurol Sci*. 2016;364:116-121. doi:10.1016/j.jns.2016.03.018

**15.** Lynch DS, Koutsis G, Tucci A, et al. Hereditary spastic paraplegia in Greece: characterisation of a previously unexplored population using next-generation sequencing. *Eur J Hum Genet*. 2016;24(6):857-863. doi:10.1038/ejhg.2015.200

**16.** D'Amore A, Tessa A, Casali C, et al. Next generation molecular diagnosis of hereditary spastic paraplegias: an Italian cross-sectional study. *Front Neurol*. 2018;9:981. doi:10.3389/fneur.2018.00981

**17.** Lu C, Li LX, Dong HL, et al. Targeted next-generation sequencing improves diagnosis of hereditary spastic paraplegia in Chinese patients. *J Mol Med (Berl)*. 2018;96(7):701-712. doi:10.1007/s00109-018-1655-4

**18.** Travaglini L, Aiello C, Stregapede F, et al. The impact of next-generation sequencing on the diagnosis of pediatric-onset hereditary spastic paraplegias: new genotype-phenotype correlations for rare HSP-related genes. *Neurogenetics*. 2018;19(2):111-121. doi:10.1007/s10048-018-0545-9

**19.** Cui F, Sun L, Qiao J, et al. Genetic mutation analysis of hereditary spastic paraplegia: a retrospective study. *Medicine (Baltimore)*. 2020;99(23):e20193. doi:10.1097/md.0000000000020193

**20.** Jiao B, Zhou Z, Hu Z, et al. Homozygosity mapping and next generation sequencing for the genetic diagnosis of hereditary ataxia and spastic paraplegia in consanguineous families. *Parkinsonism Relat Disord*. 2020;80:65-72. doi:10.1016/j.parkreldis.2020.09.013

**21.** Carrasco Salas P, Martínez Fernández E, Méndez Del Barrio C, et al. Clinical and molecular characterization of hereditary spastic paraplegia in a spanish Southern region. *Int J Neurosci*. 2022:1-11. doi:10.1080/00207454.2020.1838514

**22.** Méreaux JL, Banneau G, Papin M, et al. Clinical and genetic spectra of 1550 index patients with hereditary spastic paraplegia. *Brain*. 2022;doi:10.1093/brain/awab386

**23.** ClinicalTrials.gov. Testing miglustat administration in subjects with spastic paraplegia 11 (TreatSPG11). NCT04768166. Accessed March 24, 2022. <https://clinicaltrials.gov/ct2/show/NCT04768166>

**24.** ClinicalTrials.gov. Trehalose administration in subjects with spastic paraplegia 11 (3AL-SPG11) (3AL-SPG11). NCT04912609. Accessed March 24, 2022. <https://clinicaltrials.gov/ct2/show/NCT04912609>

**25.** Marelli C, Lamari F, Rainteau D, et al. Plasma oxysterols: biomarkers for diagnosis and treatment in spastic paraplegia type 5. *Brain*. 2018;141(1):72-84. doi:10.1093/brain/awx297

**26.** ClinicalTrials.gov. PCSK9 inhibitor treatment for patients with SPG5. NCT04101643. Accessed March 24, 2022. <https://clinicaltrials.gov/ct2/show/NCT04101643>