A picture containing drawing

Description automatically generated

**LETTER OF MEDICAL NECESSITY**

**Epilepsy Advanced Sequencing and CNV 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: Epilepsy Advanced Sequencing and CNV Evaluation (updated 3/30/22)]

<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 Epilepsy Advanced Sequencing and CNV Evaluation (Epilepsy Advanced) to determine the underlying genetic cause of my patient’s epilepsy. This expanded gene panel uses next-generation sequencing (NGS) to detect DNA sequence variants and copy number variations (CNVs) in 234 genes associated with epileptic disorders. This letter documents the medical necessity for Epilepsy Advanced in light of my patient’s medical history. Results from the test will be used to guide appropriate medical care for this 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 epilepsy that has a genetic basis. 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 epilepsy.>

<Consider adding details from physical and neurological exams such as dysmorphic facial features, developmental delay, impaired motor functions, and recurrent neurological events, as well as relevant results from neuroimaging or metabolic testing.>

**Rationale for Testing**

Epilepsy is a phenotypically and etiologically heterogeneous disorder that is associated with an increasing number of genetic variants.1 An estimated 70% to 80% of epilepsy cases are thought to have a genetic cause, and there are more than 700 genes implicated in monogenic epilepsies.2,3 Genes may be associated with primary epilepsy or with neurological disorders that have epilepsy as one of the symptoms.2 Obtaining a specific genetic diagnosis for epilepsy is challenging because of its heterogeneity. Initial testing to obtain a genetic diagnosis may include biochemical screening for metabolic disorders and chromosomal analysis, such as comparative genomic hybridization, but additional genetic testing can be performed if the diagnosis remains unknown.2,4

Expanded gene panels demonstrate utility in providing a genetic diagnosis for epilepsy. For example, in a 2015 study by Zhang et al (n = 253), testing with a 300-gene expanded panel provided a genetic diagnosis for 18% of patients who had unexplained epilepsy after initial first-tier clinical examinations.5 In another study of 64 adult patients clinically diagnosed with epilepsy and intellectual disability, expanded NGS epilepsy panels of up to 185 genes provided a genetic diagnosis in 14 (22%) patients, of whom 8 (57%) had a diagnostic change from the presumptive clinical diagnosis.6 Finally, a 2019 meta-analysis of 9 studies across various epilepsy populations estimated the diagnostic yield of expanded gene panels to be 23%.7 The diagnostic yields ranged from 13% to 48%, likely due to differences in the design of gene panels and in the clinical history of patient populations.7

Single-gene analysis is an alternative approach for genetic testing of epilepsy.4 However, studies demonstrate that single-gene testing is an inefficient method for identifying causative variants because of the phenotypic and etiologic heterogeneity of epilepsy and the resulting difficulty for clinicians to predict the causative gene for testing.8-10 For example, in a study that aimed to establish the genetic cause of epilepsy and developmental delay, an expanded gene panel provided a genetic diagnosis in 10 of 41 patients who had remained undiagnosed after at least 1 single-gene analysis.10 In 2 additional studies, clinicians were asked to predict the causative gene for cases of epilepsy based on each patient’s clinical presentation.8,9 Upon diagnosis using expanded gene panels, both studies reported that clinicians’ predictions were correct in only about 15% of cases, suggesting that single-gene testing based on clinical prediction would have failed to provide an accurate diagnosis in a large majority of these patients.8,9 Therefore, genetic testing using expanded gene panels, such as Epilepsy Advanced, can be a more efficient approach to establish a diagnosis of epilepsy compared with single-gene analyses.

Expanded epilepsy gene panels demonstrate clinical utility by informing clinical management decisions.4,11,12 The genetic complexity of epilepsy has created the need for customized treatment (“precision medicine”) since variants in certain genes are associated with particularly effective or ineffective treatments.1,3,4,12,13 For instance, sodium channel blockers are contraindicated in patients with loss-of-function variants in *SCN1A*, which encodes a voltage-gated sodium channel.1,4,12,13 Conversely, sodium channel blockers are indicated in patients with gain-of-function variants in *SCN2A*, also a voltage-gated sodium channel.1,3,12,13 Another example of a specific treatment indicated by certain genetic diagnoses is a ketogenic diet in patients with glucose transporter (GLUT1)-deficiency syndrome caused by alteration of *SLC2A1*.1,4

Various studies have reported changes in management in 17% to 63% of patients with epilepsy who obtain a genetic diagnosis following gene panel testing.9,14-17 In one of these studies, Hoelz et al reported changes in clinical management in 10 of 16 (63%) patients with a pathogenic or likely pathogenic result.16 Of these 10 patients, 7 had a change of medication initiated upon genetic diagnosis, such as starting treatment with alternative drugs or omitting sodium channel blockers.16 Additionally, 8 (50%) of the patients could avoid further diagnostic procedures, such as brain MRI follow-up under anesthesia or long-term video-EEG monitoring.16

Expanded epilepsy gene panel testing also offers utility beyond changes in clinical management. A genetic diagnosis can help identify patients eligible for clinical trials. Two studies reported that, in addition to clinical management changes in patients due to genetic diagnosis, another 25% of patients were eligible for a clinical trial or registry.9,14 Additionally, gene panel testing led to the diagnosis of an affected relative in 31% of families after receiving genetic counselling.9 Thus, establishing a genetic diagnosis with an expanded epilepsy gene panel is beneficial for the patient by providing an end to the diagnostic odyssey, indicating a specific treatment or other changes in clinical management, and informing family planning.4,11,12,18

In summary, testing with an expanded epilepsy gene panel, such as Epilepsy Advanced, effectively provides a genetic diagnosis for a greater number of patients, which in turn provides valuable information for their optimal clinical management. Therefore, I am requesting that <Patient Name> be approved for the Epilepsy Advanced Sequencing and CNV Evaluation (Test Code 6000, CPT code 81419) 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 No.: <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.** Mei D, Parrini E, Marini C, et al. The impact of next-generation sequencing on the diagnosis and treatment of epilepsy in paediatric patients. *Mol Diagn Ther*. 2017;21(4):357-373. doi:10.1007/s40291-017-0257-0

**2.** Dunn P, Albury CL, Maksemous N, et al. Next generation sequencing methods for diagnosis of epilepsy syndromes. *Front Genet*. 2018;9:20. doi:10.3389/fgene.2018.00020

**3.** Møller RS, Hammer TB, Rubboli G, et al. From next-generation sequencing to targeted treatment of non-acquired epilepsies. *Expert Rev Mol Diagn*. 2019;19(3):217-228. doi:10.1080/14737159.2019.1573144

**4.** Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. *Epilepsia*. 2015;56(10):1505-1514. doi:10.1111/epi.13122

**5.** Zhang Y, Kong W, Gao Y, et al. Gene mutation analysis in 253 Chinese children with unexplained epilepsy and intellectual/developmental disabilities. *PLoS One*. 2015;10(11):e0141782. doi:10.1371/journal.pone.0141782

**6.** Borlot F, de Almeida BI, Combe SL, et al. Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability. *Epilepsia*. 2019;60(8):1661-1669. doi:10.1111/epi.16273

**7.** Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, et al. Diagnostic yield of genetic tests in epilepsy: a meta-analysis and cost-effectiveness study. *Neurology*. 2019;92(5):e418-e428. doi:10.1212/wnl.0000000000006850

**8.** Trump N, McTague A, Brittain H, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. *J Med Genet*. 2016;53(5):310-317. doi:10.1136/jmedgenet-2015-103263

**9.** Oates S, Tang S, Rosch R, et al. Incorporating epilepsy genetics into clinical practice: a 360° evaluation. *NPJ Genom Med*. 2018;3:13. doi:10.1038/s41525-018-0052-9

**10.** Ortega-Moreno L, Giraldez BG, Soto-Insuga V, et al. Molecular diagnosis of patients with epilepsy and developmental delay using a customized panel of epilepsy genes. *PLoS One*. 2017;12(11):e0188978. doi:10.1371/journal.pone.0188978

**11.** Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies--report of the ILAE Genetics Commission. *Epilepsia*. 2010;51(4):655-670. doi:10.1111/j.1528-1167.2009.02429.x

**12.** Poduri A. When should genetic testing be performed in epilepsy patients? *Epilepsy Curr*. 2017;17(1):16-22. doi:10.5698/1535-7511-17.1.16

**13.** Scala M, Bianchi A, Bisulli F, et al. Advances in genetic testing and optimization of clinical management in children and adults with epilepsy. *Expert Rev Neurother*. 2020;20(3):251-269. doi:10.1080/14737175.2020.1713101

**14.** Truty R, Patil N, Sankar R, et al. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. *Epilepsia Open*. 2019;4(3):397-408. doi:10.1002/epi4.12348

**15.** Johannesen KM, Nikanorova N, Marjanovic D, et al. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. *Epilepsia*. 2020;61(6):1234-1239. doi:10.1111/epi.16533

**16.** Hoelz H, Herdl C, Gerstl L, et al. Impact on clinical decision making of next-generation sequencing in pediatric epilepsy in a tertiary epilepsy referral center. *Clin EEG Neurosci*. 2020;51(1):61-69. doi:10.1177/1550059419876518

**17.** McKnight D, Bristow SL, Truty RM, et al. Multigene panel testing in a large cohort of adults with epilepsy: diagnostic yield and clinically actionable genetic findings. *Neurol Genet*. 2022;8(1):e650. doi:10.1212/nxg.0000000000000650

**18.** Cornet MC, Sands TT, Cilio MR. Neonatal epilepsies: clinical management. *Semin Fetal Neonatal Med*. 2018;23(3):204-212. doi:10.1016/j.siny.2018.01.004