Epilepsy Advanced Sequencing and CNV Evaluation—Epileptic Encephalopathy

<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 Medical Director:

I am writing this letter on behalf of my patient <Patient Name> to request coverage for the following test: Epilepsy Advanced Sequencing and CNV Evaluation—Epileptic Encephalopathy. This letter documents the medical necessity for this test in light of the patient’s medical and family. Results from the test will be used to help establish the genetic basis for epilepsy in my patient and to guide appropriate medical care.

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

**Patient Medical History and/or Diagnosis:**

<Patient Name> is a <age> -year-old <gender > with a suspected diagnosis of <type of epilepsy suspected> due to the following symptoms and clinical findings:

1. <Symptom #1 with ICD code>

2. <Symptom #2 with ICD code>

3. <Symptom #3 with ICD code>

<Add additional details, such as results of EEG or neuroimaging tests>

**Family History**

<Add relevant family history>

Taken together, the patient’s clinical history is consistent with an epileptic encephalopathy of undetermined etiology.

**Rationale for Testing**

Epilepsy is a phenotypically and etiologically heterogeneous disorder. The term “epileptic encephalopathies” refers to a heterogeneous group of disorders in which epileptic activity is thought to contribute to progressive cognitive and behavioral impairments.1 Patients with an epileptic encephalopathy have severe epilepsy and developmental delay, usually beginning at an early age. Characteristic findings include marked slowing of the EEG background with multifocal spikes, along with generalized or focal seizures.2 As a group, epileptic encephalopathies do not respond well to pharmacotherapy.1 However, in some cases early intervention may improve seizure control and developmental outcomes.1 Clinically well-characterized forms of epileptic encephalopathies include Dravet, West, Landau-Kleffner, and Lennox-Gastaut syndromes,2 but not all patients who exhibit an encephalopathic course have a clearly defined syndrome.1

Once physical causes of epilepsy such as trauma, tumors, and infection have been ruled out in cases of sporadic epilepsy, a genetic cause or predisposition can reasonably be suspected. Genetic testing has been reported to be “very useful” for diagnosis of several phenotypic subgroups of epilepsy, in that results might provide information helpful for clinical care.3 These types include some genetic forms of epileptic encephalopathies, such as Dravet and related syndromes, as well as Ohtahara syndrome.3,4

Testing for underlying genetic abnormalities is complicated by the large number of genes with putative links to epilepsy, many of which have a relatively low prevalence and limited individual impact.5 Traditional Sanger sequencing-based detection of individual mutations can be time-consuming and costly. Next-generation sequencing (NGS), on the other hand, allows sequencing of numerous genes simultaneously and can be leveraged to detect copy number variants (CNV). CNVs, when detected, can then be confirmed through customer Microarrays. Thus, NGS with CNV targeted at disease-associated genes is appropriate for detecting mutations in disorders with a highly heterogeneous genetic background, such as epilepsy.5

The Epilepsy Advanced Sequencing and CNV Evaluation—Epileptic Encephalopathy test uses NGS to identify the genetic causes of epilepsy in patients with clinical features that are consistent with an epileptic encephalopathy. Specifically, it identifies mutations in 68 genes5 that have been associated with a genetic form of epileptic encephalopathy: *ARHGEF9, ARX, CDKL5, CNTNAP2, FOXG1, GABRG2, GRIN2A, KCNT1, MECP2, NRXN1, PCDH19, PNKP, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SLC25A22, SLC2A1, SLC9A6, SPTAN1, STXBP1, SYNGAP1, TCF4, TREX1, UBE3A, ZEB2, ADSL, ALG13, ALG9, AMT, BRAT1, CACNA2D1, CACNA2D2, CHD2, DNM1, DOCK7, EEF1A2, GLDC, GNAO1, GRIN1, GRIN2B, HCN1, HNRNPU, KCNA2, KCNB1 , KCNJ11, LIAS, PIGA, PIGN, PLCB1, PNPO, PURA, QARS, SIK1, SLC13A5, SLC19A3, SLC25A19, SLC35A2, ST3GAL5, SZT2, WDR45, and WWOX.*

This test may provide several important benefits for patients exhibiting clinical features consistent with an epileptic encephalopathy:

1. Depending on the specific mutations identified, test results could help guide antiepileptic pharmacotherapy.6,7 For example, administration of sodium ion channel blockers could be avoided in patients with Dravet syndrome harboring an *SCN1A* mutation.
2. Because the NGS assay covers multiple relevant genes using a single blood draw, it can potentially help avoid a long series of laborious, costly, and stressful diagnostic procedures.
3. Results may help in counseling the patient concerning the risk of recurrence.

In summary, I am requesting that <Patient Name> be approved for the Epilepsy Advanced Sequencing Evaluation—Epileptic Encephalopathy test offered by Athena Diagnostics: test code 6010; CPT codes 81302 (x1), 81304 (x1), 81403 (x2), 81404 (x4), 81405 (x6), 81406 (x6), 81407 (x1), 81479 (x1). Results from this test could minimize additional testing and inform treatment selection. I hope you that will approve coverage for this test 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>

**References**

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia.* 2010;51:676-685.

2. Lado FA, Rubboli G, Capovilla P, et al. Pathophysiology of epileptic encephalopathies. *Epilepsia.* 2013;54 Suppl 8:6-13.

3. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies--report of the ILAE Genetics Commission. *Epilepsia.* 2010;51:655-670.

4. Garofalo S, Cornacchione M, Di CA. From genetics to genomics of epilepsy. *Neurol Res Int.* 2012;2012:876234.

5. Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. *Epilepsia.* 2012;53:1387-1398.

6. Hirose S, Scheffer IE, Marini C, et al. *SCN1A* testing for epilepsy: application in clinical practice. *Epilepsia.* 2013;54:946-952.

7. Stenhouse SA, Ellis R, Zuberi S. *SCN1A* genetic test for Dravet syndrome (severe myoclonic epilepsy of infancy and its clinical subtypes) for use in the diagnosis, prognosis, treatment and management of Dravet syndrome. *PLoS Curr.* 2013;5.