Epilepsy Advanced Sequencing and CNV Evaluation—
Generalized, Absence, Focal, and Myoclonic Epilepsies

<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—Generalized, Absence, Focal, and Myoclonic Epilepsies. This letter documents the medical necessity for this test in light of the patient’s clinical and family history. Results from the test will be used to help establish the genetic basis for epilepsy and to guide appropriate medical care.

**Patient Medical History and/or Diagnosis**

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

<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>

[Add relevant family history]

Taken together, the patient’s clinical and family history are nonspecific but are consistent with a form of <generalized, absence, focal, or myoclonic epilepsy>.

**Rationale for Testing**

Epilepsy is a phenotypically and etiologically heterogeneous condition. Once physical causes 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 which results might provide useful information for clinical care.1

Testing for underlying genetic abnormalities complicated by the large number of genes with putative links to epilepsy, many of which have a relatively low prevalence and limited impact individually.2 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, NG with CNV S targeted at disease-associated genes is appropriate for detecting mutations in disorders with a highly heterogeneous genetic background, such as epilepsy.3

The Epilepsy Advanced Sequencing and CNV Evaluation from Athena Diagnostics uses NGS to identify the genetic causes of epilepsy in patients with clinical features that are consistent with a form of generalized, absence, focal, or myoclonic epilepsy. Specifically, it identifies mutations in 86 genes3 that have been associated with genetic forms of generalized seizures: *ALDH7A1, CACNA1A, CASR, CHRNA2, CHRNA4, CHRNB2, CSTB, DEPDC5, EFHC1, EPM2A, GABRA1, GABRB3, GABRD, GABRG2, GRIN2A, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, LGI1, MBD5, NHLRC1, PCDH19, PRICKLE1, PRICKLE2, PRRT2, SCARB2, SCN1A, SCN1B, SCN2A, SCN9A, SLC2A1, SLC4A10, TBC1D24, ABAT, ADSL, ALG13, ALG9, AMT, ASAH1, ASPM, ATP1A3 , BCKDK, BRAT1, CACNA1H, CACNB4, CHD2, CHRNA7 , CPA6, CRH, CYP27A1, DYNC1H1, FOLR1, GABRB2 , GAMT, GATM, GLDC, GOSR2, GRIN2B, HCN1, HCN4, KCNC1, KCNH2, L2HGDH, LIAS, LMNB2, NDUFA1, PHGDH, PIGO , PNPO, PRIMA1, SCN3A, SCN5A, SLC19A3, SLC25A19, SLC35A2, SLC6A1, SLC6A8, ST3GAL5, STX1B, SUCLA2, SYNJ1, and ALPL.*

The test may provide several important benefits:

1. 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.
2. Depending on the specific mutations identified, test results could help guide antiepileptic pharmacotherapy.4,5 For example, administration of sodium channel blockers would be avoided in patients with Dravet syndrome harboring an *SCN1A* mutation,6 while detection of an *ALDH7A1* mutation might suggest responsiveness to pyridoxine (depending on other clinical features).7
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 and CNV Evaluation - Generalized, Absence, Focal, and Myoclonic Epilepsies test (test code 6008 offered by Athena Diagnostics; CPT codes 81403 (x1), 81404 (x4), 81405 (x6), 81406 (x4), 81407 (x4), and 81479 (x1). Results from this test could minimize additional testing and inform treatment selection. I hope that you will support my decision to pursue NGS testing for my patient. 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. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies--report of the ILAE Genetics Commission. *Epilepsia.* 2010;51:655-670.

 2. Kousi M, Anttila V, Schulz A, et al. Novel mutations consolidate *KCTD7* as a progressive myoclonus epilepsy gene. *J Med Genet.* 2012;49:391-399.

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

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

 5. 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.

 6. Brodie M, Covanis T, Gil-Nagel A, et al. Antiepileptic drug therapy: does mechanism of action matter? *Epilepsy Behav.* 2011;21:490.

 7. Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (*ALDH7A1* deficiency). *Brain.* 2010;133:2148-2159.