Epilepsy Advanced Sequencing and CNV Evaluation—Developmental Brain Malformations

<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 requesting coverage for the Epilepsy Advanced Sequencing and CNV Evaluation—Developmental Brain Malformations test on behalf of my patient <patient name>. This letter documents the medical necessity for the test in light of my patient’s medical and family history. The results will be used to help establish the genetic basis for Developmental Brain Malformations.

**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 a neuronal migration disorder 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 history and neuroimaging results are consistent with developmental brain malformations.

**Rationale for Testing**

Developmental brain malformations, including neuronal migration/ positioning defects and developmental disruptions, result in conditions such as holoprosencephaly, lissencephaly, pachygyria, microcephaly/micrencephaly, or subcortical band heteropia, and others. They have been linked to mutations in genes that affect molecular pathways regulating neuronal development and axon outgrowth.1 The resulting brain abnormalities are sometimes very subtle on magnetic resonance imaging (MRI) and cannot be fully characterized. Clinical features are variable, and often include seizures, poor muscle tone and motor function, developmental delay and intellectual disability, difficulties with feeding, failure to thrive, and micorencephaly.2,3

Genetic testing is complicated by the large number of genes that have been linked to NMDs. 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 developmental brain malformations.

The Epilepsy Advanced Sequencing and CNV Evaluation—Developmental Brain Malformations test uses NGS to identify the genetic causes of epilepsy in patients with clinical features that are consistent with developmental brain malformations. Specifically, it identifies mutations in 40 genes that have been associated with a genetic form of NMD: *ARFGEF2, ARX, COL4A1, CPT2, DCX, EMX2, FGFR3, FKRP, FKTN, FLNA, GPR56, LAMA2, LARGE1, PAFAH1B1, PAX6, PEX7, POMGNT1, POMT1, POMT2, PQBP1, RAB3GAP1, RELN, SRPX2, TUBA1A, TUBA8, TUBB2B, WDR62, ASPM, CENPJ, DEAF1, DPYD, FOLR1, MCPH1, NDE1, QARS, SHH, SIX3, SLC25A19, STIL,* and *TSEN54.*4,5 This test may provide several important benefits for my patient:

1. It can provide molecular confirmation of diagnosis.
2. It may allow genetic counseling for relatives of affected individuals.
3. 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.

In summary, I am requesting that <patient name> be approved for the Epilepsy Advanced Sequencing and Evaluation— Developmental Brain Malformations test (test code 6018 offered by Athena Diagnostics; CPT codes 81403 (x1), 81404 (x4), 81405 (x4), 81406 (x4), 81407 (x2), 81408 (x2), 81479 (x1). Results from this test could minimize additional testing. Please support my decision to pursue genetic testing by NGS 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. Liu JS. Molecular genetics of neuronal migration disorders. *Curr Neurol Neurosci Rep.* 2011;11:171-178.

2. Verrotti A, Spalice A, Ursitti F, et al. New trends in neuronal migration disorders. *Eur J Paediatr Neurol.* 2010;14:1-12.

3. Pang T, Atefy R, Sheen V. Malformations of cortical development. *Neurologist.* 2008;14:181-191.

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

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