Epilepsy Advanced Sequencing and CNV Evaluation—Infantile Spasms

<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—Infantile Spasms. This letter documents the medical necessity for the test in light of my patient’s clinical <and family> history. Results from the test will be used to help confirm the diagnosis and identify the specific type of infantile spasm (IS).

**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 infantile spasm> 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 biochemical or genetic tests>

<Add relevant family history>

Taken together, the patient’s clinical <and family> history are consistent with <type of infantile spasm suspected> of unknown etiology.

**Rationale for Testing**

Infantile spasms are uncommon epilepsy syndromes that are generally characterized by brief episodes of clustered, involuntary flexion movements of the trunk, neck, arms, and legs. The episodes are associated with abnormal brain wave activity, including ictal electrodecrement and, in many cases, hypsarrhythmia.1 These characteristic clinical manifestations result from abnormalities in key brain development pathways. Onset is usually before the age of 1year.1

Infantile spasm syndromes are genetically heterogeneous. At least 16 genes have been associated with these conditions (i.e., those included in this test),1,2 although incomplete penetrance and expressivity mean that mutations in these genes do not always lead to a clearly defined phenotype. Individually, mutations in each associated gene may account for a small proportion of infantile spasm cases1; cumulatively, however, they are not rare causes.

Genetic testing is complicated by the large number of mutations linked to IS syndromes. Traditional Sanger sequencing-based detection of individual mutations can be time-consuming and costly. Next-generation sequencing (NGS) 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.3

The Epilepsy Advanced Sequencing and CNV Evaluation—Infantile Spasms test uses NGS to identify the genetic cause of IS. Specifically, it identifies mutations in 16 genes1,2 that have been associated with a syndrome characterized by flexor spasms and hypsarrythmia or an electrodecremental response on electroencepahologram (EEG): *ARX* (West syndrome), *CDKL5* (X-linked infantile spasm syndrome), *FOXG1* (congenital variant of Rett syndrome), *GABRB3* (susceptibility to childhood absence epilepsy; infantile spasms), *GRIN2A* (early-onset epileptic spasms associated with epilepsy with neurodevelopmental defects), *MEF2C* (infantile spasms associated with mental retardation, stereotypic movements, and/or cerebral malformations), *SCN2A* (benign familial neonatal-infantile seizures-3 [BFIS3]), *SLC25A22* (early infantile epileptic encephalopathy-3), *SPTAN1* (early infantile epileptic encephalopathy-5), *STXBP1* (early infantile epileptic encephalopathy-4), *ADSL* (adenylosuccinase deficiency with psychomotor retardation, seizures and developmental delay), *CACNA2D1* (intellectual disability and epilepsy), *NR2F1*(Bosch-Boonstra-Schaaf optic atrophy syndrome), *SLC35A2* (early infantile epileptic encephalopathy and congenital disorder of glycosylation, type IIm), *ST3GAL3* (early infantile epileptic encephalopathy-15 and mental retardation), and *TBL1XR1* (Peirpont syndrome and mental retardation).

This test is appropriate for patients exhibiting clinical features consistent with an IS and may provide several important benefits for my patient:

1. Results may provide molecular basis to confirm the diagnosis and identify the specific IS.
2. Because the NGS assay covers multiple relevant genes using a single blood draw, it can potentially help avoid additional diagnostic procedures.
3. Results may allow genetic counseling for relatives of affected individuals.

In summary, I am requesting that <Patient Name> be approved for the Epilepsy Advanced Sequencing and CNV Evaluation—Infantile Spasms test offered by Athena Diagnostics: test code 6038; CPT codes 81403 (x1), 81404 (x2), 81405 (x1), 81406 (x2), 81479 (x1). Results from this test could minimize additional testing and inform treatment selection. Please 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. Paciorkowski AR, Thio LL, Dobyns WB. Genetic and biologic classification of infantile spasms. *Pediatr Neurol.* 2011;45:355-367.

2. Allen AS, Berkovic SF, Cossette P, et al. De novo mutations in epileptic encephalopathies. *Nature.* 2013;501:217-221.

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.