Epilepsy Advanced Sequencing and CNV Evaluation—Intellectual Disability

<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—Intellectual Disability. This letter documents the medical necessity for this test in light of the patient’s medical and family history. Results will be used to help establish the genetic basis for epilepsy with intellectual disability in my patient.

**Patient Medical History and/or Diagnosis**

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

<Patient Name> is a <Age> -year-old <Gender > with a suspected diagnosis of epilepsy with intellectual disability due to the flowing 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; neuroimaging tests; and fragile X and chromosomal microarray testing>

<Add relevant family history suggestive of epilepsy with intellectual disability>

Taken together, the patient’s clinical and family history are consistent with epilepsy with intellectual disability that is not explained by an *FMR1* expansion or chromosomal abnormalities.

**Rationale for Testing**

About 10% of individuals with intellectual disability have an XLID, a phenotypically and genetically heterogeneous group of disorders arising from aberrations of the X-chromosome. Seizures accompany intellectual disability in almost half of the XLIDs.1 They may be the only clinical abnormality aside from intellectual disability or may be one of many neurologic manifestations.1 The seizures themselves are also highly variable, ranging from isolated, fever-induced seizures to medication-resistant recurrent seizures. Unlike epileptic encephalopathies, in which epileptic activity contributes to progressive cognitive and behavioral impairments, seizure activity in XLID is likely a consequence rather than a cause of neuronal network disturbance.1 The clinical variability of XLID-associated epilepsy may stem in part from the variety of potential underlying genetic causes, which can include mutations in a number of genes, aberrant DNA methylation, X chromosome random or skewed inactivation, and genetic mosaicism.2

Genetic testing plays an important role in the diagnosis of specific XLIDs. For example, the results may reveal the true phenotypic spectrum of an XLID epilepsy disorder in patients with an uncommon or unspecific presentation. Once fragile X syndrome and chromosomal abnormalities have been ruled out,3 testing for additional underlying genetic aberrations may be complicated by the large number of genes with links to XLID. 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,4 such as epilepsy with intellectual disability. Because this NGS panel focuses on mutations that are associated with both seizures and intellectual disability, it covers fewer genes than general epilepsy or intellectual disability mutation panels.

This panel uses NGS to identify mutations that are associated with both seizures and intellectual disability (eg, Christianson syndrome, epilepsy and intellectual disability restricted to females, Rett syndrome, Rolandic seizures, West syndrome, X-linked infantile spasms, Pelizaeus-Merzbacher disease, and early infantile epileptic encephalopathy 1, 2, 8, or 9). Specifically, it identifies mutations in 56 genes that have been associated with one or more of these causes of epilepsy4: *ARHGEF9, ARX, ATP6AP2, ATRX, CASK, CDKL5, CUL4B, DCX, FGD1, GPC3, GRIA3, HSD17B10, KDM5C, MECP2, OFD1, OPHN1, PAK3, PCDH19, PHF6, PLP1, PQBP1, RAB39B, SLC9A6, SMC1A, SMS, SRPX2, SYP, ABAT, ADSL, ALG13, ALG9, BCKDK, CACNA2D1, CHRNA7 , DEAF1, DPYD, DYRK1A, EEF1A2, FOLR1, GABRB2 , GAMT, GATM, GFAP, GRIN2B, HNRNPU, IQSEC2, KIAA2022, PURA, RBFOX1, SETD2, SLC35A2, SLC6A8, SNAP25, SPATA5, SYN1, and WDR45.* It does not detect aberrations associated with fragile X syndrome, which should be ruled out along with chromosomal abnormalities before ordering this test.

Results could provide several important benefits for my patient:

1. Results could help identify the genetic background of my patient’s X-linked epilepsy phenotype (eg, a de novo *ARX*, *CDKL5*, or *PCHD19* mutation).
2. Detection of a specific mutation could allow the prediction of future disease development or help guide antiepileptic pharmacotherapy.
3. Establishing the genetic cause of the XLID can help avoid a long series of potentially laborious, costly, and stressful diagnostic procedures. The NGS assay covers multiple relevant genes using a single blood draw, minimizing the number of blood collection procedures required.
4. The 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—Intellectual Disability test (test code 6019 offered by Athena Diagnostics; CPT codes 81302 (x1), 81304 (x1), 81404 (x3), 81405 (x6), 81406 (x2), 81407 (x1), 81479 (x1). Results from this test could minimize additional diagnostic procedures. 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. Stevenson RE, Holden KR, Rogers RC, et al. Seizures and X-linked intellectual disability. *Eur J Med Genet.* 2012;55:307-312.

2. Deng H, Zheng W, Song Z. Genetics, Molecular Biology, and Phenotypes of X-Linked Epilepsy. *Mol Neurobiol.* 2013.

3. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86:749-764.

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.