**Letter of Medical Necessity for Exome Sequencing (Trio) for Epilepsy**

**Patient Information**

**Date:**

**Patient Name:**

**Patient DOB:**

**Insurance Company Name, Address, City, State:**

**Policy Number:**

**Group Number:**

**ICD10 Codes:**

**Test Information**

**Test Name:** XomeDx - Trio

**CPT Codes:** 81415x1, 81416x2

**Laboratory:**

GeneDx, Inc.

(NPI#1487632998 / TAXID#205446298 / CLIA#21D0969951)

207 Perry Parkway

Gaithersburg, MD 20877

Telephone: (301) 519-2100

Fax: (201) 421-2010

This letter is regarding my patient, [FIRST NAME LAST NAME], to request full coverage for the XomeDx*-*Triotest for exome sequencing (ES) to be performed by GeneDx. It is my professional determination that testing is medically necessary and will have a direct impact on this patient’s treatment and management. I have included relevant information for my patient as well as summaries of the guidelines and published peer-reviewed evidence that support this testing.

**Patient Clinical and Family History and Potential Impact of Test Results**

This testing is requested due to this patient’s personal medical history, which includes the following clinical findings:

* Add Relevant Phenotype
* Add Relevant Phenotype
* Add Relevant Phenotype

The patient’s family history is negative for related conditions / unknown / remarkable for the following related clinical features:

The patient has previously had the following uninformative genetic and other testing:

* Add test
* Add test
* Add test

Due to this history, the differential diagnosis includes (list at least 3 conditions you are considering for this patient).

Specifically for my patient, results of ES will guide prognosis and improve clinical decision-making which can improve clinical outcomes by: (keep all bullets you think are relevant and provide examples/details for each included)

* change in medication: (provide examples of potential new treatments or halting of existing ones that may be recommended based results)
* alteration to diet: (provide examples of potential alteration to diet that may be recommended based results)
* change in planned procedures or surveillance: (provide examples of potential alteration surgery, imaging, and/or diagnostic studies that may be recommended based on results especially state if includes discontinuation of unnecessary procedures)
* Impact on future reproductive planning by informing genetic counseling related to recurrence risk and prenatal diagnosis options: (include and provide additional details if patient’s first degree relative is pregnant or considering pregnancy)

**Clinical Guidelines Support Exome Sequencing**

National Society of Genetic Counselors (NSGC) with endorsement by the American Epilepsy Society (AES)

In 2022 the NSGC published an evidence-based guideline strongly recommending ES as a first-tier test for individuals with unexplained epilepsy regardless of age.1 This guideline was based on a systematic evidence review of peer-reviewed literature which included 40 studies with over 3,000 patients who had ES and demonstrated a genetic diagnosis led to changes in clinical management.2 Additionally, the guideline discussed expanding access to genetic testing may “*lead to a decrease in existing health disparities*;” but acknowledged insurance reimbursement remains a barrier.1 This guideline has been endorsed by the AES.

American College of Medical Genetics and Genomics (ACMG)

Some individuals with epilepsy also have other clinical features. In 2021 ACMG published an evidence-based practice guideline “*strongly recommending*” ES as a first-tier or second-tier test for patients with 1 or more congenital anomalies (CA) prior to 1 year of age or developmental delay (DD)/intellectual disability (ID) with onset prior to 18 years of age. This guideline was based on a systematic evidence review of peer-reviewed literature which “*supports the clinical utility and desirable effects of ES … on active and long-term clinical management of patients with CA/DD/ID*.” The guideline additionally stated that “*compared with standard genetic testing, ES… has a higher diagnostic yield and may be more cost-effective when ordered early in the diagnostic evaluation*,” and that “*the various stakeholders (i.e., health-care providers, patients, families, laboratories) are uniformly in favor of the use of ES... in obtaining a clinical diagnosis*.”3

**Diagnostic Yield of Exome Sequencing in Individuals with Epilepsy**

ES has a diagnostic yield higher than traditional genetic testing in individuals with epilepsy (e.g. chromosomal microarray, single gene or targeted panel testing). In a systematic evidence review and meta-analysis including 154 articles with 39,094 individuals with epilepsy, the diagnostic yield of exome sequencing was 24% compared to 9% for microarray and 19% for multigene panels.2 Additional meta-analyses have also demonstrated a higher diagnostic yield with exome sequencing compared to multigene panels and microarray in individuals with epilepsy.4,5

**Exome sequencing Leads to Changes in Medical Management**

Clinical utility studies have reported exome sequencing results in changes in management in individuals with epilepsy. In a systematic review including 24 studies, 38% of individuals with epilepsy and positive exome sequencing had changes in medical management, including:

1. avoiding, stopping, or initiating specific antiseizure medications
2. starting a ketogenic diet
3. treating with vitamins/supplements
4. halting plan for surgery

The genetic diagnosis enabled the opportunity for better treatment, including up to 90% seizure reduction in some cases. Additionally, the diagnostic odyssey ended (along with additional testing and procedures), enabling families to focus on treatment. Many studies also reported the potential impact of genetic diagnosis on recurrence risk estimation and family planning, which included subsequent use of prenatal diagnosis.2

**Exome Sequencing Demonstrates Clinical Benefit and Economic Savings**

For individuals with epilepsy, diagnostic assessment may include neurological and clinical genetics review, screening for metabolic disorders, neuroimaging, neurophysiology, chromosomal microarray, and targeted genetic testing, typically performed in a tiered or staged fashion. This approach is a time-consuming and expensive process.6-8 However, studies have demonstrated that including exome sequencing in the diagnostic pathway for individuals with epilepsy results in a higher diagnostic yield at a lower cost, and exome sequencing is “more cost effective than the standard diagnostic pathway,” according to a NSGC Practice Guideline.1 Thus, utilization of exome sequencing early in the diagnostic journey can accelerate the introduction of gene-specific interventions, eliminate unnecessary testing, and prevent or bring an immediate end to a long, frustrating, and costly diagnostic odyssey.

**Comparator Analysis**

ES typically includes the use of familial DNA samples (typically the biological parents) for genetic comparison. The use of one or two comparator samples is known as duo or trio testing, respectively. The familial DNA for comparison helps in the interpretation of variants identified by ES by allowing the laboratory scientists to better contextualize identified variants. With this added context, this comprehensive analysis enables prioritization of disease-causing variants leading to a higher diagnostic yield and decreased chance of finding a variant of unknown significance (VUS) compared to proband-only analysis. Publications have reported an additional yield of about 7% to 15% for trio analysis compared to proband-only9-12 and a reduction in VUSs of about 9%.13 Guidelines prefer the use of trio analysis, for example, ACMG states *“best practice includes familial comparators (“trio”) if available to help contextualize rare variants.”*3

**Summary**

XomeDx is a highly sensitive and cost-effective genetic test. I am requesting coverage for this medically necessary test to establish appropriate medical management for this patient. Without testing, treatment would be suboptimal, subjecting this patient to increased morbidity and potentially early mortality.

Thank you for your review and consideration. If you have questions, or if I can be of further assistance, please do not hesitate to call me at (XXX) XXX-XXXX.

Sincerely,

Signature

Ordering Provider’s Name

**References**

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