**Letter of Medical Necessity for Exome Sequencing (Duo)**

**Patient Information**

**Date:**

**Patient Name:**

**Patient DOB:**

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

**Policy Number:**

**Group Number:**

**ICD10 Codes:**

**Test Information**

**Test Name:** XomeDx - Duo

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

**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*-*Duotest 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**

American College of Medical Genetics and Genomics (ACMG)

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*.”1

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.2 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.3 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.2 This guideline has been endorsed by the AES.

**Diagnostic Yield of Exome Sequencing**

ES has a diagnostic yield two to three times higher than traditional genetic testing (e.g. chromosomal microarray, single gene or targeted panel testing).4, 5 A systematic review and meta-analysis of 37 studies, which included >20,000 patients with suspected rare disease, reported a diagnostic yield of 36% for ES.4 A technology assessment that included 34 studies and >9000 patients with unexplained development disability and/or multiple congenital anomalies reported a 37% (95% confidence interval, 34% to 40%) diagnostic yield for ES.6

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

Clinical utility studies have reported a 26% to 64% change in medical management for individuals with a positive ES result.7,8 In a systematic evidence review of ES for patients with congenital anomalies (CAs), developmental delay (DD), and/or intellectual disability (ID) initiated by ACMG, 95% of the 167 included studies reported a change to clinical management.9 These modifications included change in medication (new treatment or halting an existing one), alteration to diet, change in planned procedures or surveillance (surgery, imaging, and/or diagnostic studies), referral to specialist, testing of family members, and/or impact on future reproductive planning.9 Some of these changes included discontinuation of unnecessary procedures (e.g. diagnostic tissue biopsy), avoidance of certain drugs, or withdrawal of care/start of palliative care.9 In 2 additional systematic reviews, similar changes in management were reported following ES for patients in select populations. These systematic reviews reported 38% of patients with epilepsy and positive ES having a change in medical management3 as well as neurodevelopmental disorders including intellectual disability, developmental delay, and autism in which 30% with a diagnosis by ES had a change in clinical management and 80% in reproductive planning.10

**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 comparator analysis compared to proband-only11-14 and a reduction in VUSs of about 9%.15 Guidelines prefer the use of comparator analysis, for example, ACMG states *“best practice includes familial comparators … if available to help contextualize rare variants.”*1

**Summary**

XomeDx-Duo 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**

1. Manickam, K., et al., *Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG).* Genet Med, 2021. **23**(11): p. 2029-2037.

2. Smith, L., et al., *Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors.* J Genet Couns, 2022.

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4. Clark, M.M., et al., *Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases.* NPJ Genom Med, 2018. **3**: p. 16.

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7. Incerti, D., et al., *Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases.* Genet Med, 2022. **24**(1): p. 109-118.

8. Niguidula, N., et al., *Clinical whole-exome sequencing results impact medical management.* Mol Genet Genomic Med, 2018. **6**(6): p. 1068-1078.

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10. Srivastava, S., et al., *Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders.* Genet Med, 2019. **21**(11): p. 2413-2421.

11. Farwell, K.D., et al., *Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions.* Genet Med, 2015. **17**(7): p. 578-86.

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13. Retterer, K., et al., *Clinical application of whole-exome sequencing across clinical indications.* Genet Med, 2016. **18**(7): p. 696-704.

14. Sawyer, S.L., et al., *Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care.* Clin Genet, 2016. **89**(3): p. 275-84.

15. Rehm, H.L., et al., *The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change.* Genet Med, 2023: p. 100947.