**Letter of Medical Necessity for Exome Sequencing with Mitochondrial Genome Testing**

**Patient Information**

**Date:**

**Patient Name:**

**Patient DOB:**

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

**Policy Number:**

**Group Number:**

**ICD10 Codes:**

**Test Information**

**Test Name:** XomeDxPlus (Duo) Exome Sequencing with Mitochondrial Genome Sequencing and Deletion Analysis

**CPT Codes:** 81415, 81416x1, 81460

**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 in regards to my patient, [FIRST NAME LAST NAME], to request full coverage for the XomeDxPlus test, which includes Exome Sequencing with Mitochondrial Genome Sequencing and Deletion Testing, 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.

**Patient Clinical and Family History**

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

* Add Phenotype
* Add Phenotype
* Add 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

**Clinical Evidence and Guidelines for Testing**

The American College of Medical Genetics and Genomics (ACMG) recommends exome sequencing for patients with a disorder that has a suspected genetic etiology when the patient’s phenotype is not consistent with a specific disorder that has more targeted genetic testing currently available, the testing currently available for the patient’s phenotype has failed to arrive at a diagnosis, or the suspected genetic condition is associated with a high degree of genetic heterogeneity.1

Overall, the diagnostic yield of exome sequencing has been reported to range from 25-37% for individuals with a broad range of clinical phenotypes, specifically including neurodevelopmental disorders, epilepsy and other neurologic disorders, multiple congenital anomalies, and other suspected monogenic disorders.2-6 The diagnostic yield is highest when parental samples or other relevant family members are included in the analysis.2-6

A recent multidisciplinary consensus statement recommended exome sequencing as a first-tier genetic test for individuals with neurodevelopmental disorders including intellectual disability, global developmental delay, and autism spectrum disorder due to the high diagnostic yield.2 Multiple studies have found that exome sequencing is more cost effective than traditional testing approaches such as sequential single gene testing, multi-gene panels, serial imaging, biopsies, and other diagnostic approaches, and is most cost-effective when done early in the testing process.7-12

In addition to exome sequencing, this test includes Next Generation sequence analysis and deletion testing of the mitochondrial DNA (mtDNA) to evaluate for primary mitochondrial disorders, which are clinically heterogeneous and can present at any age. A consensus statement from the Mitochondrial Medicine Society recommends Next Generation sequence analysis with deletion/duplication testing as the preferred testing methodology for patients with suspected mitochondrial disorders.13 This testing is expected to identify a mitochondrial DNA variant in approximately 40% of adults and 10-20% of pediatric patients with a primary mitochondrial disorder.14,15

**Patient Clinical Utility and Medical Management Implications**

The test results will guide and tailor appropriate medical management and treatment for this patient, which would not be possible without this testing. Exome sequencing can lead to direct changes in medical management, including modifications to medications, surgical interventions, surveillance regimens, or preventative measures that may be life-saving, and can eliminate the need for other expensive and often invasive diagnostic procedures. 8-10,13

Specifically for this patient, the results of exome sequencing will also {ADD ADDITIONAL INFORMATION}

**Summary**

The XomeDxPlus Exome Sequencing with Mitochondrial Genome Sequencing at GeneDx is a highly sensitive and cost-effective genetic test. I am requesting coverage for this medically necessary test in order 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

1. ACMG Board of Directors. ACMG Policy Statement: Points to consider in the clinical application of genomic sequencing. *Genet Med.* 2012 14(8):759-61. (PMID: 22863877)
2. 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 (PMID: 31182824)
3. Retterer K et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med.* 2016 18(7):696-704. (PMID: 26633542)
4. Farwell KD 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):578-86. (PMID: 25356970)
5. Lee H et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014 312(18):1880-7. (PMID: 25326637)
6. Yang Y et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. 2014 312(18):1870-9. (PMID: 25326635)
7. Vrijenhoek T et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur. J. Hum. Genet.* 2019 26 (11):1566-1571 (PMID: 29959382)
8. Tan TY et al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children with Suspected Monogenic Conditions. *JAMA Pediatr* 2017 171 (9):855-862 (PMID: 28759686)
9. Vissers et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet. Med.* 2017 19 (9):1055-1063 (PMID: 28333917)
10. Stark Z et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med*. 2016 Nov 18(11):1090-1096. (PMID: 26938784)
11. Stark Z et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. *Genet. Med.* 2017 19 (8):867-874. (PMID: 28125081)
12. Monroe GR, et al. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. Genet Med. 2016 18(9):949-56. (PMID: 26845106)
13. Parikh S et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet. Med.* 2015 17 (9):689-701 (PMID: 25503498)
14. Chinnery P et al. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev* 2006 (1):CD004426 (PMID: 16437486)
15. Zeviani M et al. Mitochondrial disorders. *Brain* 2004 127 (Pt 10):2153-72 (PMID: 15358637)