**Letter of Medical Necessity for Rapid Genome 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:** Genome*Xpress* -Duo

**CPT Codes:** 81425x1, 81426x1

**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 Genome*Xpress-Duo* for rapid genome sequencing (rGS) 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 published peer-reviewed evidence and clinical guidelines 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 rGS 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 Evidence and Guidelines for Testing**

More than 20 studies have reported diagnostic rates of rGS in critically ill infants and children.1 Most studies report a diagnostic yield in the range of ~40% to 50% for rGS.2-8 Multiple studies have reported rGS has a diagnostic yield at least two times greater than traditional testing (e.g. chromosomal microarray and multigene panel testing) in both randomized controlled trials (RCTs)9,10 and non-randomized studies.3,8 Not only does rGS have a higher diagnostic yield, it can also decrease the time to diagnosis which is important for diagnosis of critically ill infants. A RCT reported the median age of diagnosis was significantly lower (25 days vs. 130 days) and time to diagnosis was significantly less (13 days vs. 107 days) in infants with rGS compared to standard of care testing.10

Prominent professional societies including the American College of Genetics and Genomics (ACMG) have published evidence-based guidelines strongly recommending genome sequencing (GS) as a first-tier test.11

**Rapid Genome Sequencing Leads to Changes in Medical Management**

Clinical utility studies have reported approximately a 40% to 60% change in medical management for individuals with a positive rGS result. 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), and/or impact on future reproductive planning. Some of these changes included preventing the need for expensive and/or invasive testing or surgical procedures, discontinuing ineffective medications, or withdrawal of care/start of palliative care.2,3,6-10,12-14 In a United States based study, management changes based on rGS results prevented morbidity in over 50% of the diagnosed infants compared to no infants who had traditional testing.3 In a RCT in the United States, after two months twice as many infants with rGS had a change in management compared to those with traditional testing.9

**Comparator Analysis**

GS 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 GS 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 10% to 15% for comparator analysis compared to proband-only15, 16 and a reduction in VUSs of about 9%.17 Guidelines prefer the use of comparator analysis, for example, ACMG states *“best practice includes familial comparators … if available to help contextualize rare variants.”*11

**Summary**

Genome*Xpress*-Duois 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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4. Lunke, S., et al., Integrated multi-omics for rapid rare disease diagnosis on a national scale. Nat Med, 2023. 29(7): p. 1681-1691.

5. Mestek-Boukhibar, L., et al., Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. J Med Genet, 2018. 55(11): p. 721-728.

6. Sanford, E.F., et al., Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. Pediatr Crit Care Med, 2019. 20(11): p. 1007-1020.

7. Wang, H., et al., Optimized trio genome sequencing (OTGS) as a first-tier genetic test in critically ill infants: practice in China. Hum Genet, 2020. 139(4): p. 473-482.

8. Willig, L.K., et al., Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. Lancet Respir Med, 2015. 3(5): p. 377-87.

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11. 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.

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13. French, C.E., et al., Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. Intensive Care Med, 2019. 45(5): p. 627-636.

14. Lunke, S., et al., Integrated multi-omics for rapid rare disease diagnosis on a national scale. Nat Med, 2023.

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