**LETTER OF MEDICAL NECESSITY FOR PRENATAL EXOME SEQUENCING**

**(ExomeNext-Proband, Duo and Trio)**

Date: Date of service/claim

To: Utilization Review Department

Insurance Company Name, Address, City, State

Re: Patient Name, DOB, ID #

This letter is regarding my patient and your subscriber, referenced above, requesting full coverage of medically indicated prenatal genetic testing for exome sequencing to be performed by Ambry Genetics Corporation.

Exome sequencing analyzes the set of protein-coding regions of the human genome. Approximately 85% of genetic changes that cause known diseases occur within exomes.1 Although not required, testing of additional family members (usually parents and/or siblings) along with the patient/proband, referred to as duo or trio testing, can add additional comparative information that is helpful in reaching a genetic diagnosis. Whole exome sequencing has been shown to be highly effective for diagnosing individuals with previously unidentified genetic conditions.2,3,4

The American College of Medical Genetics and Genomics (ACMG) 2012 Policy Statement on genomic sequencing5 recommended exome sequencing for the following clinical scenarios**:**

* The patient’s clinical presentation (phenotype) and family history strongly implicate a genetic etiology, but phenotype does not correspond with a specific disorder for which a clinical targeted genetic test is available; or
* **Clinical presentation (including fetal, with limitations) suggests a likely genetic disorder, but specific genetic tests (including targeted sequencing tests) for phenotype have failed to provide a diagnosis**; or
* A defined genetic disorder with a high degree of genetic heterogeneity is suspected, making whole exome or genome sequencing of multiple genes simultaneously a more practical approach

In 2020, the ACMG published a “points to consider” document regarding the use of fetal exome sequencing in prenatal diagnosis6, which states that **“exome sequencing may be considered when a diagnosis cannot be obtained using routine prenatal methods in a fetus with one or more significant anomalies**.” Prenatal exome sequencing provides a diagnosis in approximately 31% of cases when chromosome microarray or karyotype is non-diagnostic9

More recently, the ACMG 2021 clinical guideline on genomic sequencing7 **strongly recommends exome sequencing as a first- or second-tier test for patients with one or more congenital anomalies diagnosed prior to one year of age.**

**Significant aspects of my patient’s medical and/or family history that raise suspicion of an underlying genetic diagnosis are as follows: [check all that apply]**

* Two or more anomalies affecting more than one unrelated organ system
* An anomaly affecting a single organ system
* Anatomic findings characteristic of a genetic abnormality
* Fetal hydrops of unknown etiology
* Family history strongly suggestive of a genetic etiology
* Previous prenatal testing has failed to identify a diagnosis in my patient

**Clinical exome sequencing has a significant likelihood of providing my patient and family with an accurate diagnosis** 8,9**.** This, in turn, can lead to:

* Specific treatment or management strategies that can dramatically change the clinical outcome.2,3,4
* Identification of necessary postnatal medical referrals, screening for associated complications, and recurrence risk counseling.2,3,4
* Decreased medical costs due to ending the diagnostic odyssey.2,3

**As such, I am ordering this medically necessary test and affirm that my patient has provided informed consent for genetic testing.** I recommend that you support this request for coverage of exome sequencing in my patient.

Thank you for your time and please don’t hesitate to contact me with any questions.

Sincerely,

Ordering Clinician Name (Signature Provided on Test Requisition Form)

(MD/DO, Clinical Nurse Specialist, Nurse-Midwives, Nurse Practitioner, Physician Assistant, Genetic Counselor\*)

\*Authorized clinician requirements vary by state

**Test Details**

CPT codes: 81415, 81416x2, 81460

Laboratory: Ambry Genetics Corporation (TIN 33-0892453 / NPI 1861568784), a CAP-accredited and CLIA-certified laboratory located at 7 Argonaut, Aliso Viejo, CA 92656

**References**

1. Pussegoda KA. Exome sequencing: locating causative genes in rare disorders. Clin Genet. 2010 Jul;78(1):32-3.
2. Biesecker LG and Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014;370:2418-25.
3. Iglesias A, *et al*. The usefulness of whole-exome sequencing in routine clinical practice. Genet Med. 2014;16:922-931.
4. Malinowski J, *et al.* Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med. 2020;22(6):986-1004.
5. ACMG Board of Directors. ACMG Policy Statement: Points to consider in the clinical application of genomic sequencing. Genet Med. 2012;14(8):759-76.
6. Monaghan KG, *et al.* The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22:675-680.
7. Manickam K. 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 2021:23:2029-2037.
8. 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.](http://www.ncbi.nlm.nih.gov/pubmed/25356970) 2015;17:578-586.
9. Mellis R, *et al.* Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta-analysis. Prenat Diagnos. 2022;662-685.