Medical Necessity Guidelines:

Genetic Testing: Whole Exome Sequencing and Whole Genome Sequencing

Effective: January 1, 2025

Prior Authorization Required If REQUIRED, submit supporting clinical documentation pertinent to service request to the FAX numbers below	Yes ☒ No ☐
Notification Required IF REQUIRED, concurrent review may apply	Yes ☐ No ☒

Applies to:

Commercial Products

☐ Harvard Pilgrim Health Care Commercial products; 800-232-0816

☒ Tufts Health Plan Commercial products; 617-972-9409

CareLink℠ – Refer to CareLink Procedures, Services and Items Requiring Prior Authorization

Public Plans Products

☐ Tufts Health Direct – A Massachusetts Qualified Health Plan (QHP) (a commercial product); 888-415-9055

☐ Tufts Health Together – MassHealth MCO Plan and Accountable Care Partnership Plans; 888-415-9055

☐ Tufts Health RITogether – A Rhode Island Medicaid Plan; 857-304-6404

☐ Tufts Health OneCare – A dual-eligible product; 857-304-6304

Senior Products

☐ Harvard Pilgrim Health Care Stride Medicare Advantage; 866-874-0857

☐ Tufts Health Plan Senior Care Options (SCO), (a dual-eligible product); 617-673-0965

☐ Tufts Medicare Preferred HMO, (a Medicare Advantage product); 617-673-0965

☐ Tufts Medicare Preferred PPO, (a Medicare Advantage product); 617-673-0965

Note: While you may not be the provider responsible for obtaining prior authorization or notifying Point32Health, as a condition of payment you will need to ensure that any necessary prior authorization has been obtained and/or Point32Health has received proper notification. If notification is required, providers may additionally be required to provide updated clinical information to qualify for continued service.

Overview

The human genome refers to an individual's complete set of DNA. The exome is a small section (1 to 2 percent) of the genome. It contains DNA sequences (exons) which provide instruction (coding) for making proteins, the building blocks of cells.

Whole exome sequencing (WES) sequences only the coding region (1 to 2 percent) of an individual's genome. Whole exome sequencing can be used to identify variations in the protein-coding region of any gene rather than in only a select few genes. Because most known pathogenic variant(s) that cause disease occur in exons, WES is thought to be an efficient method to identify possible disease-causing pathogenic variant(s).

Whole genome sequencing (WGS) sequences an individual's entire genome. It determines the order of all the nucleotides (the DNA building blocks) in an individual's DNA and can determine variations in any part of the genome. WES may potentially miss a pathogenic variant(s) in a non-coding region of the genome, therefore WGS may be used in selected cases if initial exome sequencing is not diagnostic. While WGS can accurately achieve copy number variation (CNV) detection, the use of chromosomal microarray analysis (CMA) continues to be the gold standard.

Whole exome sequencing (WES) or whole genome sequencing (WGS) may be appropriate when there is no known cause of a patient's symptoms (e.g., prematurity, trauma, environmental, infectious, maternal immune disorder), clinical

presentation does not suggest a known genetic disorder, targeted single gene or targeted multi-gene pane sequencing is unlikely to provide a diagnosis, conventional genetic testing (e.g., chromosomal microarray analysis, single gene sequencing, targeted multi-gene sequencing) of suspected known genetic disorders had proven negative, or the genetic diagnosis being considered and/or the clinical presentation would require testing of multiple genes. WGS may be more efficient than sequential testing of suspected single genes or multiple genes and may obviate extensive and exhaustive diagnostic testing and procedures to arrive at a diagnostic conclusion.

The Plan requires the following form to be submitted and faxed to the appropriate fax number listed above: Genetic and Molecular Diagnostics Testing Authorization Request Form. Include all relevant clinical information as applicable. Documentation should include a letter of medical necessity supporting the request for WES/WGS which includes the member's family history (include three-generation pedigree) and member's history, physical examination and, if performed, any conventional diagnostic testing that did not result in a definitive diagnosis of suspected disorder.

Note: Conventional diagnostic testing is not required prior to WGS.

Documentation must include how the results of the testing will directly alter the medical management of the member.

Note: Medical necessity letters or genetic testing request forms submitted by the performing lab and signed by the requesting provider will not be accepted as sole documentation.

Refer to the following Medical Necessity Guidelines for genetic/molecular diagnostic testing not included within this guideline:

- Genetic Testing: BRCA1 and BRCA2; Hereditary Breast, Ovarian and Pancreatic Cancer
- Comprehensive Genomic Profiling with FoundationOne® CDx or FoundationOne® Liquid CDx to Guide Cancer Treatment in Patients with Advanced Cancer
- Guardant 360 CDx
- Breast Cancer Index
- Genetic Testing: Gene Expression for Cancer of Unknown Primary
- Genetic Testing: Prenatal Diagnosis, Carrier Screening
- Cell-Free DNA Screening for Fetal Trisomy
- Preimplantation Genetic Testing (PGT)
- Human Leukocyte Antigen Genotyping
- Medical Necessity Guidelines: Genetic and Molecular Diagnostic Testing for Tufts Health Direct, Tufts Health Together, Tufts Health RITogether, Tufts Health OneCare
- Human Leukocyte Antigen Genotyping for Tufts Health Direct, Tufts Health Together, Tufts Health RITogether, Tufts Health OneCare

Refer to Medical Necessity Guidelines: Noncovered Investigational Services for genetic tests which are considered investigational and therefore not covered.

Clinical Guideline Coverage Criteria

The Plan may consider Whole Exome Sequencing OR Whole Genome Sequencing as reasonable and medically necessary for members under 18 years of age in an outpatient setting when **ALL** of the following are met:

1. WES/WGS is ordered by a board-certified medical geneticist or a board-certified physician with specialty in the condition being tested; **and**
2. Member's clinical presentation of symptoms is not consistent with an established or known condition and a genetic etiology is suspected based on one of the following:
    a. Significant developmental delay or intellectual disability diagnosed prior to age 18; **or**
    b. Multiple congenital anomalies which involve more than one organ system prior to one year of age; **or**
    c. Fetal testing when standard diagnostic genetic testing (e.g., chromosomal microarray analysis and/or karyotyping) is inconclusive as the initial testing and **ONE** of the following is present:
        i. Multiple fetal structural anomalies impacting unrelated organ systems; **or**
        ii. Fetal hydrops of unknown etiology; **or**
    d. Congenital or early onset epilepsy (before age 3 years) without suspected environmental etiology.
3. There is a reasonable expectation that the testing will result in confirmation or establishment of a clinical diagnosis; **and**
4. Genetic test counseling by a medical geneticist, a board-certified physician with specialty in the condition being tested, a board-certified genetic counselor, or a credentialed genetic nurse will occur pre and posttest including education of genetic testing, discussion of potential benefits/harms, interpretation of results, and disease management.

Note: Testing must be performed by a contracting lab when available.

Limitations

The Plan will not cover Whole Exome and Whole Genome Sequencing for members who do not meet the criteria above. Whole Genome Sequencing is not covered for members who have previously undergone Whole Exome Sequencing.

In addition, the Plan considers WES/WGS as not medically necessary for the following:

1. Screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
2. Testing for the purposes of confirming a suspected diagnosis of a disorder that can be diagnosed based on clinical evaluation alone.
3. Testing for the following:
    a. Oncology indications
    b. Carrier screening
    c. Preimplantation genetic testing
4. Fetal testing other than the Coverage Criteria listed above.

Codes

The following code(s) require prior authorization:

Table 1: CPT/HCPCS Codes

Code	Description
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequency analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome; re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome

References:

1. RARE disease facts [Internet]. Global Genes. 2023 [cited 2023 July 5]. Available from: https://globalgenes.org/learn/rare-disease-facts/
2. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020 Feb;28(2):165-173. PMID: 31527858.
3. Shashi V, McConkie-Rosell A, Rosell B, et al The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2014 Feb; 16: 176–182. PMID: 23928913
4. Smith HS, Swint JM, Lalani SR, Yamal JM, de Oliveira Otto MC, Castellanos S, Taylor A, Lee BH, Russell HV. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. Genet Med. 2019 Jan;21(1):3-16. PMID: 29760485
5. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. Eur J Hum Genet. 2018 May;26(5):740-744. PMID: 29453418
6. Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC; ACMG Professional Practice and Guidelines Committee. 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(4):675-680. doi:10.1038/s41436-019-0731-7
7. Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: Substantial interest of prospective annual reanalysis. Genet Med. 2018 Jun;20(6):645-654. PMID: 29095811
8. Manickam K, McClain MR, Demmer LA, 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

Approval And Revision History

March 20, 2024: Reviewed by the Medical Policy Approval Committee (MPAC) to establish coverage for Whole Exome Sequencing and Whole Genome Sequencing, effective May 1, 2024

Subsequent endorsement date(s) and changes made:

- August 30, 2024: Reviewed by MPAC. Added indication of epilepsy to criteria. Effective date. October 1, 2024.
- November 21, 2024: Reviewed by MPAC. Minor language clarification to overview section, effective January 1, 2025.

Background, Product and Disclaimer Information

Medical Necessity Guidelines are developed to determine coverage for benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. We make coverage decisions using these guidelines, along with the Member's benefit document, and in coordination with the Member's physician(s) on a case-by-case basis considering the individual Member's health care needs.

Medical Necessity Guidelines are developed for selected therapeutic or diagnostic services found to be safe and proven effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in our service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. We revise and update Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Medical Necessity Guideline and a self-insured Member's benefit document, the provisions of the benefit document will govern. For Tufts Health Together (Medicaid), coverage may be available beyond these guidelines for pediatric members under age 21 under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefits of the plan in accordance with 130 CMR 450.140 and 130 CMR 447.000, and with prior authorization.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this guideline is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to eligibility and benefits on the date of service, coordination of benefits, referral/authorization, utilization management guidelines when applicable, and adherence to plan policies, plan procedures, and claims editing logic.