WHOLE EXOME AND WHOLE GENOME SEQUENCING

The purpose of this document is to assist providers enrolled in the Connecticut Medical Assistance Program (CMAP) with the information needed to support a medical necessity determination for whole exome sequencing (WES) and whole genome sequencing (WGS). By clarifying the information needed for prior authorization of services, HUSKY Health hopes to facilitate timely review of requests so that individuals obtain the medically necessary care they need as quickly as possible.

WES

The evolution of next generation sequencing has led to the development of tests that sequence multiple genes simultaneously. Whole exome sequencing (WES) sequences the portion of the genome that contains protein-coding DNA. WES has been proposed in patients with certain disorders or anomalies that have not been explained by a standard clinical evaluation who may be left without a clinical diagnosis despite a lengthy diagnostic workup. For a portion of these patients, WES may find a likely pathogenic variant. Determining a genetic cause of disease and establishing a molecular diagnosis in clinical practice can: confirm a suspected diagnosis; inform prognosis; and assist in selecting treatment, surveillance or preventative options.

WGS

Whole genome sequencing (WGS) consists of analysis of most of the DNA content in an individual's genome. WGS has been used as a tool to establish a diagnosis in individuals with exceptionally complex and severe phenotypes and has also been used in the oncology setting to characterize tumor genomes. High-quality clinical trial data are lacking in the published peer reviewed medical literature to inform on the use and effectiveness of whole genome sequencing in routine clinical practice. At this time the clinical utility of this testing to impact clinical management and improve health outcomes has not been established.

CLINICAL GUIDELINE

Coverage guidelines for WES and WGS are made in accordance with the DSS definition of Medical Necessity. The following criteria are guidelines *only*. Coverage determinations are based on an individual assessment of the member and their unique clinical needs. If the guidelines conflict with the definition of Medical Necessity, the definition of Medical Necessity shall prevail. The guidelines are as follows:

WES (CPT Code 81415)

WES may be considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders, multiple genetic anomalies, moderate to severe intellectual disability or epilepsy/seizure disorder in children ≤ 21 years of age when ALL of the following criteria are met:

1. The test is ordered by a board certified medical geneticist or other board certified physician with specialty specific expertise in clinical genetics who is not employed by or contracted with a commercial genetic testing laboratory;

2. The child has been evaluated by a board-certified medical geneticist or other board-certified physician specialist with expertise in the conditions and genes for which testing is being considered;
3. Genetic counseling has been completed by a board certified medical geneticist or other board certified physician with expertise in clinical genetics;
4. A genetic etiology is considered the most likely explanation for the phenotype;
5. The previous genetic testing (e.g., CGA, CMA, FISH analysis, single-gene or targeted panel testing) has failed to yield a diagnosis (a differential diagnosis and comprehensive testing algorithm must be submitted with all prior authorization requests);
6. Clinical picture does not fit a well-described syndrome;
7. A diagnosis cannot be made by standard clinical work-up; excluding invasive procedures such as muscle biopsy;
8. No other causative circumstances (e.g. environmental exposures, injury, infection) have been identified;
9. There is a predicted impact on health outcomes including:
    a. Reducing diagnostic uncertainty (e.g., eliminating lower yield testing and additional screening tests that may later be proved unnecessary once a diagnosis is achieved);
    b. Guiding prognosis and improving clinical decision making;
    c. Application of specific treatments;
    d. Withholding of contraindicated treatments; and
    e. Surveillance for later-onset comorbidities; or initiation of palliative care; or modification of care; and
10. WES results may preclude the need for multiple and/or invasive procedures (e.g., muscle biopsy) that would be recommended in the absence of WES testing.

WES Comparator Testing (CPT Code 81416)
Family trio testing (WES of the biological parents or siblings of the affected individual) is considered medically necessary when the criteria for WES for the affected individual have been met and testing is being performed concurrently or has been previously performed on the affected individual.

WES Reanalysis (CPT Code 81417)
Reanalysis of previously obtained standard WES for one of the above medically necessary indications, may be considered medically necessary when the above criteria for WES have been met and any one of the following criteria for WES reanalysis is met:

1. New scientific knowledge has demonstrated a previously unknown link between the individual's findings and specific genes/pathogenic variants; or
2. There has been an onset of new symptoms that broadens the phenotype assessed during the original exome evaluation; or
3. There has been the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture.

Reanalysis or repeat testing for standard whole exome sequencing (WES) not meeting one the above indications is typically considered not medically necessary.

Not Medically Necessary
- WES is considered investigational for the diagnosis of genetic disorders for all other indications,

except as described above
- WES is considered investigational for screening asymptomatic individuals for genetic disorders
- Prenatal diagnosis or preimplantation testing of an embryo using WES is considered investigational

Note:
Prenatal testing of fetuses for congenital disorders is generally considered investigational and therefore not medically necessary. Requests for WES for fetuses with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis will be reviewed on a case-by-case basis.

Whole Genome Sequencing (CPT Codes 81425-81427)
Whole genome sequencing (WGS) for any indication is considered investigational and therefore not medically necessary.

Whole Mitochondrial Genome Sequencing (81460 and 81465)
Whole mitochondrial genome sequencing (WGS) for any indication is considered investigational and therefore not medically necessary.

NOTE: EPSDT Special Provision
Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) is a federal Medicaid requirement that requires the Connecticut Medical Assistance Program (CMAP) to cover services, products, or procedures for Medicaid enrollees under 21 years of age where the service or good is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition identified through a screening examination. The applicable definition of medical necessity is set forth in Conn. Gen. Stat. Section 17b-259b (2011) [ref. CMAP Provider Bulletin PB 2011-36].

PROCEDURE
Prior authorization of genetic testing is required. Requests for coverage of WES and WGS will be reviewed in accordance with procedures in place for reviewing requests for genetic testing. Coverage determinations will be based upon a review of requested and/or submitted case-specific information.

The following information is needed to review requests for WES and WGS:
1. Fully completed State of Connecticut Department of Social Services WES/WGS Prior Authorization Request Form;
2. All clinical information as outlined on the WES/WGS Prior Authorization Request Form; and
3. Other information as requested by CHNCT.

EFFECTIVE DATE
This Policy is effective for prior authorization requests for WES and WGS for individuals covered under the HUSKY Health Program on or after February 1, 2017.

LIMITATIONS
Not Applicable

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); sequence analysis, each comparator genome (e.g., parents, siblings)
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)
81460	Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection if performed

DEFINITIONS

1. **Current Procedural Terminology (CPT):** The most recent edition of a listing, published by the American Medical Association, of descriptive terms and identifying codes for reporting medical services performed by providers.
2. **HUSKY A**: Connecticut children and their parents or a relative caregiver; and pregnant women may qualify for HUSKY A (also known as Medicaid). Income limits apply.
3. **HUSKY B**: Uninsured children under the age of 19 in higher income households may be eligible for HUSKY B (also known as the Children's Health Insurance Program) depending on their family income level. Family cost-sharing may apply.
4. **HUSKY C**: Connecticut residents who are age 65 or older or residents who are ages 18-64 and who are blind, or have another disability, may qualify for Medicaid coverage under HUSKY C (this includes Medicaid for Employees with Disabilities (MED-Connect), if working). Income and asset limits apply.
5. **HUSKY D**: Connecticut residents who are ages 19-64 without dependent children and who: (1) do not qualify for HUSKY A; (2) do not receive Medicare; and (3) are not pregnant, may qualify for HUSKY D (also known as Medicaid for the Lowest-Income populations).
6. **HUSKY Health Program**: The HUSKY A, HUSKY B, HUSKY C, HUSKY D and HUSKY Limited Benefit programs, collectively.
7. **HUSKY Limited Benefit Program or HUSKY, LBP**: Connecticut's implementation of limited health insurance coverage under Medicaid for individuals with tuberculosis or for family planning purposes and such coverage is substantially less than the full Medicaid coverage.
8. **HUSKY Plus Physical Program (or HUSKY Plus Program):** A supplemental physical health program pursuant to Conn. Gen. Stat. § 17b-294, for medically eligible members of HUSKY B in

Income Bands 1 and 2, whose intensive physical health needs cannot be accommodated within the HUSKY Plan, Part B.

9. **Medically Necessary or Medical Necessity**: (as defined in Connecticut General Statutes § 17b-259b) Those health services required to prevent, identify, diagnose, treat, rehabilitate or ameliorate an individual's medical condition, including mental illness, or its effects, in order to attain or maintain the individual's achievable health and independent functioning provided such services are: (1) Consistent with generally-accepted standards of medical practice that are defined as standards that are based on (A) credible scientific evidence published in peer-reviewed medical literature that is generally recognized by the relevant medical community, (B) recommendations of a physician-specialty society, (C) the views of physicians practicing in relevant clinical areas, and (D) any other relevant factors; (2) clinically appropriate in terms of type, frequency, timing, site, extent and duration and considered effective for the individual's illness, injury or disease; (3) not primarily for the convenience of the individual, the individual's health care provider or other health care providers; (4) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the individual's illness, injury or disease; and (5) based on an assessment of the individual and his or her medical condition.
10. **Prior authorization**: A process for approving covered services prior to the delivery of the service or initiation of the plan of care based on a determination by CHNCT as to whether the requested service is medically necessary.

ADDITIONAL RESOURCES AND REFERENCES:

- ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2015;17(6):505-507. doi:10.1038/gim.2015.41
- ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. 2012;14(8):759-761. doi:10.1038/gim.2012.74
- ACOG Committee Opinion No. 430: preimplantation genetic screening for aneuploidy. *Obstet Gynecol*. 2009;113(3):766-767. doi:10.1097/AOG.0b013e31819e9f05
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal–Fetal Medicine. Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders. *Obstet Gynecol*. 2016;127(5):e108-e122. doi:10.1097/AOG.0000000000001405
- Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstet Gynecol*. 2016;128(6):e262-e268. doi:10.1097/AOG.0000000000001817
- Committee Opinion No. 690 Summary: Carrier Screening in the Age of Genomic Medicine. *Obstet Gynecol*. 2017;129(3):595-596. doi:10.1097/AOG.0000000000001947
- International Society for Prenatal Diagnosis; Society for Maternal and Fetal Medicine; Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. *Prenat Diagn*. 2018;38(1):6-9. doi:10.1002/pd.5195
- Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice

Committee opinion. *Fertil Steril*. 2008;90(5 Suppl):S136-S143. doi:10.1016/j.fertnstert.2008.08.062
- UpToDate. Next-Generation DNA Sequencing (NGS): Principles and Clinical Applications. Peter J. Hulick M.D., MMSc, FACMG. Topic last upated November 16, 2021.
- UpToDate. Intellectual Disability in Children: Evaluation for a Cause. Penelope Pivalizza M.D., Seema R. Lalani M.D. Topic last updated July 13, 2018.
- UpToDate. Birth Defects: Approach to Evaluation. Carlos A. Bacino M.D., FACMG. Topic last updated July 16, 2021.
- UpToDate. Prenatal Genetic Evaluation of the Fetus with Anomalies or Soft Markers. Neeta Vora M.D., Sarah Harris MS, CGC. Topic last updated June 15, 2022.
- UpToDate. Seizures and Epilepsy in Children; Classification, Etiology, and Clinical Features. Angus Wilfong M.D., Topic last updated June 1, 2022.
- UpToDate. Preimplantation Genetic Diagnosis. Glenn L Schattman M.D., Kangpu Xu, PhD. Topic last updated April 4, 2022.

PUBLICATION HISTORY

Status	Date	Action Taken
Original publication	December 2017	Policy approved at the September 27, 2017 Medical Policy Review Committee meeting. Policy approved at the December 18, 2017 Clinical Quality Subcommittee meeting. Policy approved by DSS on December 21, 2017.
Updated	September 2018	Added "who is not employed by or contracted with a commercial genetic testing laboratory" to requirement for ordering physicians in Clinical Guideline section. Change reviewed at the September 12, 2018 Medical Policy Review Committee meeting with recommendation to send to Genetic Advisory Council. Recommended change approved by council members. Change approved at the September 17, 2018 Clinical Quality Subcommittee meeting. Change approved by DSS on January 28, 2019.
Reviewed	October 2019	Reviewed and approved without changes at the October 23, 2019 Medical Reviewer meeting. Approved by the CHNCT Clinical Quality Subcommittee on December 16, 2019. Approved by DSS on December 30, 2019.
Updated	September 2020	Update to policy section. Added indications for WES to include intellectual disability, seizure disorder, and multiple genetic anomalies. Clarified age of children as those individuals under 21. Provided examples for previous genetic testing. Provided examples for impact on health outcomes. Update to reflect that WES performed

		prenatally on fetuses is typically considered investigational. Added criteria for trio testing and WES reanalysis. Updated information needed for review as PA form for WES expanded. Changes approved at the September 9, 2020 MD Reviewer meeting. Changes approved by the CHNCT Clinical Quality Subcommittee on September 21, 2020. Approved by DSS on October 7, 2020.
Updated	September 2021	Added need for a differential diagnosis and comprehensive testing algorithm to be submitted with all prior authorization requests to criteria #5. Removed "from which single gene or targeted panel testing is available" from criteria #6. Changes approved at the September 8, 2021 CHNCT Medical Reviewer meeting. Changes approved by the CHNCT Clinical Quality Subcommittee on September 20, 2021. Changes approved by DSS on September 30, 2021.
Updated	September 2022	Update to wording in reanalysis criteria. Added criteria for whole mitochondrial genome sequencing. Changes approved at the August 10, 2022 CHNCT Medical Reviewer meeting. Changes approved by the CHNCT Clinical Quality Subcommittee on September 19, 2022. Approved by DSS on September 28, 2022.