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 may be considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders in children 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 despite previous genetic testing that failed to yield a diagnosis;
5. The WES results may directly impact clinical decision-making e.g., guide diagnosis, prognosis and treatment options, including response to therapies;
6. No other causative circumstances (e.g. environmental exposures, injury, infection) have been identified; AND
7. 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.

<u>WES may be considered medically necessary for prenatal testing of fetuses for congenital disorders during the second and third trimester when ALL of the following criteria are met:</u>

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 individual 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 clinical scenario of the patient despite previous genetic testing that failed to yield a diagnosis e.g. fetal aneuploidy testing;
5. The WES results may directly impact clinical decision-making e.g., guide diagnosis and prognosis;
6. No other causative circumstances (e.g. teratogenic exposures) have been identified; AND
7. WES results may preclude the need for multiple and/or invasive procedures that would be recommended in the absence of WES testing.

Not Medically Necessary

- Repeat testing for WES for the above indications is typically considered not medically necessary.
- WES is considered investigational for the diagnosis of genetic disorders for all other indications, except as described above, and therefore not medically necessary.
- WES is considered investigational for screening asymptomatic individuals for genetic disorders and therefore not medically necessary.
- Prenatal diagnosis or preimplantation testing of an embryo using WES is considered investigational and therefore not medically necessary.
- Whole genome sequencing (WGS) for any indication is considered investigational and therefore not medically necessary.

<u>Repeat analysis of **existing** exome data may be considered medically necessary when the individual has a new diagnosis.</u>

During initial analysis missense mutations unrelated to the original diagnosis may not have been recognized as pathogenic and incidental heterozygous pathogenic mutations underlying a recessive condition may not have been reported.

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 Outpatient Prior Authorization Request form; and
2. Documentation supporting the medical necessity of the requested test which **must** include:
    a. Evaluation and signed order for testing;
    b. Office notes;
    c. Test reports including all prior genetic testing results;
    d. How the testing will directly impact clinical decision making and clinical outcome;
    e. How the results will preclude further need for multiple and/or invasive testing;
    f. Genetic counseling notes;
    g. Three generation pedigree; 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
81408	Molecular pathology procedure level 9
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)

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:

- Dixon-Salazar TJ, Shilhavy JL, upda N, et al. Exome Sequencing can improve diagnosis and alter patient management. Sci Transl Med. Jun 13 2012;4(138)ra178.
- Ayuso C, Millan JM, Mancheno M, et al. Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. Eur J Hum Genet. Oct 2013;21(10):1054-1059
- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. Genet Med. Apr 2012;14(4):393-398
- De Ligt J, Boone PM, Pfundt R, et al. Detection of clinically relevant copy number variants with whole exome sequencing. Hum Mutat. Oct 2013;34(10):1439-1448
- Dewey FE, Grove ME, Pan C, et al. Clinical interpretation and implications of whole genome sequencing. JAMA Mar 12 2014;311(10):1035-1045
- Green RC, Berg JS, Grody WW, et al. ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing, Genet Med Jul 2013;15(7):565-574
- American College of Medical Genetics and Genomics (ACMG) Policy Statement: Points to Consider in the Clinical Application of Genomic Sequencing. May 15, 2012
- Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet Nove 2011;12(11):745-755
- Jiang YH, Yen RK, Jin X, et al. Detection of clinical relevant genetic variants in autism spectrum disorder by whole genome sequencing. AM J Hum Genet. August 8, 2013;93(2):249-263
- Yang Y, Muzny DM, Reid JG, et al. Clinical whole exome sequencing for the diagnosis of mendelian disorders N Engl J Med. Oct 17 2013;369(16):1502-1511
- Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. Sci Transl Med. Jun 13 2012;4(138):138ra178.
- McLaughlin HM, Ceyhan-Birsoy O, Christensen KD, et al. A systematic approach to the reporting of medically relevant findings from whole genome sequencing. BMC Med Genet. 2014;15:134.
- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. Genet Med. Apr 2012;14(4):393-398.
- Rehm HL, Bale SJ, Bayrak-Toydemir P, et al. ACMG clinical laboratory standards for next-generation sequencing. Genet Med. Sep 2013;15(9):733-747.
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. May 2015;17(5):405-424.
- Greenway SC, McLeod R, Hume S, et al. Exome sequencing identifies a novel variant in ACTC1 associated with familial atrial septal defect. Can J Cardiol. Feb 2014;30(2):181-187.

- Jiang YH, Yuen RK, Jin X, et al. Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing. Am J Hum Genet. Aug 8 2013;93(2):249-263.
- Kim HJ, Won HH, Park KJ, et al. SNP linkage analysis and whole exome sequencing identify a novel POU4F3 mutation in autosomal dominant late-onset nonsyndromic hearing loss (DFNA15). PLoS One. 2013;8(11):e79063.
- Weeke P, Mosley JD, Hanna D, et al. Exome sequencing implicates an increased burden of rare potassium channel variants in the risk of drug-induced long QT interval syndrome. J Am Coll Cardiol. Apr 15 2014;63(14):1430-1437.
- Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. Mar 6 2014;370(10):911-920.
- Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. Nov 12 2014;312(18):1880-1887.
- Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. Nov 12 2014;312(18):1870-1879.
- Tammimies K, Marshall CR, Walker S, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. JAMA. Sep 1 2015;314(9):895-903.
- Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. Jul 2015;47(7):717-726.
- Golbus JR, Puckelwartz MJ, Dellefave-Castillo L, et al. Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy. Circ Cardiovasc Genet. Dec 2014;7(6):751-759.
- Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med. Dec 3 2014;6(265):265ra168.
- Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol. Oct 2014;76(4):473-483.
- Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. Genet Med. Dec 2014;16(12):922-931.
- Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. Jul 2013;15(7):565-574.
- Taylor J, Martin H, Lise S, et.al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. 2015 July; 47(7): 717-726
- Yang Y, Muzny D, Reid J, et.al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders, N Engl J Med 2013 October 17;369(16): 1502-1511
- Richards S, Aziz N, Bale Sherri, et.al. Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendations of the American College of Medical Genetics and Genomics and Association of Molecular Pathology, Genet Med. 2015 May 17(5): 405-424
- Dewey F, Grove M, Cuiping P, et. al. Clinical Interpretation and Implications of Whole Genome Sequencing. JAMA 2014 March 12; 311(10): 1035-1045
- Rehm H, Bale Sherri, Bayrak-Toydemir P, et.al. ACMG Clinical Laboratory Standards for Next Generation Sequencing. Genet Med 2013 September; 15(9): 733-747

- Allen NM, Conroy J, Shahwan A, et. al. Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion. Epilepsia Jan 2016;57(1):e12-17.
- Farwell KD, Shahmirzadi L, El-Khechan D, et. al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 families with undiagnosed genetic conditions. Genet Med Jul 2015;17(7):578-586.
- Nolan D, Carlson M. Whole exome sequencing in pediatric neurology patients: clinical implications and estimated cost analysis. J Child Neurol. Jun 2016;31(7):887-894.
- Stark Z, Tan TY, Chong B, et. al. A prospective evaluation of whole exome sequencing as a first tier molecular test in infants with suspected monogenic disorders. Genet Med. Nov 2016;18(11):1090-1096.
- Ghaoui R, Cooper ST, Lek M, et. al. Use of whole exome sequencing for diagnosis of limb-girdle muscular dystrophy: outcomes and lessions learned . JAMA Neurol. Dec 2015. Dec 2015;72(12):1424-1432.
- Ellinford JM, Barton S, Bhaskar S, et. al. Whole genome sequencing increases molecular diagnostic yield compared with current diagnostic testing for inherited retinal disease. Ophthalmology May 2016;123(5):1143-1150.
- Posey JE, Rosenfeld JA, James RA, et. al. Molecular diagnostic experience of whole exome sequencing in adult patients. Genet Med July 2016;18(7):678-685.
- Valencia CA, Husami A, Holle J, et. al. Clinical impact and cost effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience, Front Pediatr 2015;3:67.
- Wortmann SB, Koolen DA, Smeitink JA, et. al. Whole exome sequencing of suspcted mitochondrial patients in clinical practice. J Inherit Metab Dis. May 2015;38(3):437-443.
- Narayanaswami P, Weiss M, Selcen D, et. al. Evidence based guideline summary: diagnosis and treatment of limb girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology Oct 14 2014;83(16):1453-1463.
- American College of Medical Genetics and Genomics (ACMG) Clinical Utility of Genetic and Genomic Services: A Position Statement of the American College of Medical Genetics and Genomics. Genetics in Medicine Volume 17, Number 6 June 2015.
- Moeschler J, Shevell M. Comprehensive Evaluation of the Child with Intellectual Disability or Global Developmental Delays. American Academy of Pediatrics. Pediatrics Volume 134 Number 3 September 2014.
- Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenge of next generation genome sequencing for clinical care. JAMA Inter Med Volume 174, Number 2 February 2014
- Ream M, Patel A. Obtaining genetic testing in pediatric elilepsy. Epilepsia 56(10):1505-1514 2015
- UpToDate. Principles and Clinical Applications of Next-Generation DNA Sequencing. Peter J. Hulick M.D., MMSc, FACMG. Topic last upated July 18, 2016.
- UpToDate. Intellectual Disability in Children: Evaluation for a Cause. Penelope Pivalizza M.D., Seema R. Lalani M.D. Topic last updated May 26, 2016.

- UpToDate. Birth Defects: Approach to Evaluation. Carlos A. Bacino M.D., FACMG. Topic last updated December 19, 2016.
- UpToDate. Prenatal Genetic Evaluation of the Anomalous Fetus. Neeta Vora M.D., Sarah Harris MS, CGC. Topic last updated June 15, 2017.
- UpToDate. Clinical and Laboratory Diagnosis of Seizures in Infants and Children. Angus Wilfong M.D., Topic last updated August 22, 2016.
- UpToDate. Preimplantation Genetic Diagnosis. Glenn L Schattman M.D. Topic last updated November 18, 2016.
- Wapner RJ, Levy B. The impact of new genomic technologies in reproductive medicine. Discov Med. Jun 2014;17996):313-318.
- Treff NR, Fedick A, Tao X, et. al. Evaluation of targeted next generation sequencing based preimplantation genetic diagnosis of monogenic disease. Fetil Steril. Apr 2013;99(5):3177-1384 e1376.
- Martin J, Cervero A, Mir P, et. al. The impact of next generation sequencing technology on preimplantation genetic diagnosis and screening. Fertil Steril. Mar 15 2013;99(4):1054-1061 e1053.
- American Society of Reproductive Medicine. Preimplantation Genetic Testing: A Practice Committee Opinion. Fertil Steril 2008 Nov:90(5 Suppl):S136-43.
- American College of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 430. Preimplantation Genetic Screening for Aneuploidy. Obstet Gynecol. Mar 2009, reaffirmed 2014;113(3):766-767.
- American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 162 New Prenatal Testing Guidelines for Genetic Disorders. April 2016
- American College of Obstetricians and Gynecologists (ACOG) Committee Opinion Number 690 March 2017

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.

Please note that authorization is based on medical necessity at the time the authorization is issued and is not a guarantee of payment. Payment is based on the individual having active coverage, benefits and policies in effect at the time of service.

To determine if a service or procedure requires prior authorization, CMAP Providers may refer to the *Benefit and Authorization Grids* summaries on www.ct.gov/husky by clicking on “For Providers” followed by “Benefit Grids”. For a definitive list of benefits and service limitations, CMAP Providers may access the CMAP provider fee schedules and regulations at www.ctdssmap.com.