MEDICAL POLICY

POLICY TITLE	**WHOLE EXOME AND WHOLE GENOME SEQUENCING FOR DIAGNOSIS OF GENETIC DISORDERS**
POLICY NUMBER	**MP 2.324**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**2/1/2025**

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I. POLICY

Standard whole exome (WES) or standard whole genome sequencing (WGS), with trio testing, when possible (see policy guidelines), may be considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorder in pediatrics under 21 years of age when ALL of the following criteria are met:

- The individual has been evaluated by a clinician with expertise in clinical genetics and counseling was provided about the potential risks of genetic testing; **and**
- There is potential for a change in management and clinical outcome for the individual being tested; **and**
- One of the following criteria is met:
  - Previous genetic testing is non-diagnostic and there remains a strong clinical suspicion of genetic etiology **OR**
  - Previous genetic testing is non-diagnostic, and the individual would otherwise be faced with invasive testing or procedures **OR**
  - Clinical presentation does not fit a well-described syndrome for which preferred testing is available (e.g., single gene testing, comparative genomic hybridization [CHG]/chromosomal microarray analysis [CMA])

Standard WES or WGS may be considered necessary for biological parents or biological siblings of children meeting the criteria above when completed as part of trio testing.

Rapid WES or rapid WGS, with trio testing, when possible (see Policy Guidelines), may be considered **medically necessary** for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when **BOTH** of the following criteria are met:

- **At least one** of the following criteria is met:

  - Multiple congenital anomalies (see Policy Guidelines);
  - An abnormal laboratory test or clinical features suggests a genetic disease or complex metabolic phenotype (see Policy Guidelines);
  - An abnormal response to standard therapy for a major underlying condition; AND
- **None** of the following criteria apply regarding the reason for admission to intensive care:
  - An infection with normal response to therapy;
  - Isolated prematurity;
  - Isolated unconjugated hyperbilirubinemia;
  - Hypoxic ischemic encephalopathy;
  - Confirmed genetic diagnosis explains illness;
  - Isolated transient neonatal tachypnea

Rapid WES or rapid WGS may be considered necessary for biological parents or biological siblings of children meeting the criteria above when completed as part of trio testing.

WES and WGS (standard or rapid) are considered **investigational** for the diagnosis of genetic disorders in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with the testing.

WES and WGS are considered **investigational** for screening for genetic disorders as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with the testing.

Optical genome mapping is considered **investigational** for screening or diagnosis of genetic disorders as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with the testing.

Policy Guidelines

The policy statement is intended to address the use of whole exome and whole genome sequencing for diagnosis in individuals with suspected genetic disorders and for population-based screening.

This policy does not address the use of whole exome, whole genome sequencing, or other types of genome mapping for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or testing of cancer cells.

Trio Testing

The recommended option for testing, when possible, is testing of the child and both parents*. Trio testing increases the chance of finding a definitive diagnosis and reduces false-positive findings.

Trio testing is preferred whenever possible but should not delay testing of a critically ill individual when rapid testing is indicated. Testing of one available parent should be done if both are not immediately available and one or both parents can be done later if needed. Duo testing is an alternate option (child and one parent*) if only one parent is available.

*a biological sibling may be considered as a substitute if a parent is unavailable.

Rapid Sequencing
In the NSIGHT1 trial (Petrikin, 2018) rapid Whole Genome Sequencing (rWGS) provided time to provisional diagnosis by 10 days with time to final report of approximately 17 days although the trial required confirmatory testing of WGS results which lengthened the time to rWGS diagnosis by 7–10 days. The WGS was performed in 'rapid run' mode with minimum depth of 90 Gb per genome and average depth of coverage of 40-fold.

For rapid WES or WGS, the individual should be critically ill and, in the NICU or PICU, when the test is ordered but may be discharged before results are delivered.

Copy number variation (CNV) analysis should be performed in parallel with rWGS using chromosomal microarray analysis (CMA) or directly within rWGS if the test is validated for CNV analysis.

Examples of specific malformations highly suggestive of a genetic etiology, include but are not limited to any of the following:

- Choanal atresia
- Coloboma
- Hirschsprung disease
- Meconium ileus

Examples of an abnormal laboratory test suggesting a genetic disease or complex metabolic phenotype include, but are not limited to, any of the following:

- Abnormal newborn screen
- Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
- Hyperammonemia
- Lactic acidosis not due to poor perfusion
- Refractory or severe hypoglycemia

Examples of clinical features suggesting a genetic disease include, but not limited to, any of the following:

- Significant hypotonia
- Persistent seizures

- Infant with high-risk stratification on evaluation for a brief resolved unexplained event (BRUE) (see below) with any of the following features:
  - Recurrent events without respiratory infection
  - Recurrent witnessed seizure like events
  - Required cardiopulmonary resuscitation (CPR)
  - Significantly abnormal chemistry including but not limited to electrolytes, bicarbonate or lactic acid, venous blood gas, glucose, or other tests that suggest an inborn error of metabolism
- Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
- Family history of:
  - Arrhythmia
  - BRUE in sibling
  - Developmental delay
  - Inborn error of metabolism or genetic disease
  - Long QT syndrome (LQTS)
  - Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant

BRUE

Brief Resolved Unexplained Event (BRUE) was previously known as apparent life-threatening event (ALTE). In a practice guideline from the American Academy of Pediatrics (AAP), BRUE is defined as an event occurring in an infant younger than 1 year of age when the observer reports a sudden, brief (usually less than one minute), and now resolved episode of one or more of the following:

- Absent, decreased, or irregular breathing
- Altered level of responsiveness
- Cyanosis or pallor
- Marked change in tone (hyper- or hypotonia)

A BRUE is diagnosed only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination. Note: More information is available at: https://pediatrics.aappublications.org/content/137/5/e20160590.

Genetic Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table

PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology— "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-Reference:

MP 2.242 Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

POLICY TITLE	WHOLE EXOME AND WHOLE GENOME SEQUENCING FOR DIAGNOSIS OF GENETIC DISORDERS
POLICY NUMBER	MP 2.324

MP 2.321 Genetic Testing for Facioscapulohumeral Muscular Dystrophy
MP 2.262 Genetic Testing for Epilepsy
MP 2.332 Genetic Testing for Limb Girdle Muscular Dystrophies

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Whole Exome Sequencing and Whole Genome Sequencing

Whole exome sequencing (WES) is targeted next-generation sequencing (NGS) of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses NGS techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process.

Whole Exome Sequencing and Whole Genome Sequencing Technology

WES or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual (greater than 85%), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing variants. WES has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. WES shares some limitations with

Sanger sequencing. For example, it will not identify the following: intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications; or rearrangements within genes, nucleotide repeats, or epigenetic changes. WGS uses techniques similar to WES but includes noncoding regions. WGS has a greater ability to detect large deletions or duplications in protein-coding regions compared with WES but requires greater data analytics.

Technical aspects of WES and WGS are evolving, including the development of databases such as the National Institutes of Health's ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) to catalog variants, uneven sequencing coverage, gaps in exon capture before sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate mutations. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to standardize terminology for describing sequence variants. In 2015, guidelines developed by this workgroup describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

In 2021, the American College of Medical Genetics and Genomics released their practice guideline for exome and genome sequencing for pediatric patients with congenital anomalies (CA) or intellectual disability (ID). In this guideline they strongly recommend exome sequencing and genome sequencing as a first-tier or second-tier test for patients with one or more CA prior to one year of age or for patients with developmental delay/ID with onset prior to 18 years of age. They noted that isolated autism without ID or congenital malformation is formally out of scope for their recommendation, but that evaluation of exome/genome studies are ongoing.

Optical Genome Mapping

Optical Genome Mapping (OGM) is an imaging technology which evaluates the fluorescent labeling pattern of individual DNA molecules to perform an unbiased assessment of genome-wide structural variants down to 500 base pairs (bp) in size, a resolution that exceeds conventional cytogenetic approaches. OGM relies on a specifically designed extraction protocol facilitating the isolation of ultra-high molecular weight DNA. In essence, this imaging technology converts DNA into a "barcode" whose labeling profile and characteristics can resolve copy number and structural variation without the need to sequence level data. In germline-settings, where copy number variants (CNVs) detection is primarily performed by chromosomal microarray analysis, recent studies have shown that OGM has the capacity to detect all clinically relevant variants observed by standard of care studies. OGM may have the ability to yield the information obtained from a combination of karyotyping, FISH and microarrays in one diagnostic work up.

Despite successes, there are inherent limitations of this technology which begins with the need for ultra-high weight molecular DNA. This precludes the capacity to evaluate specimens which have undergone fixation or to profile DNA that was isolated using conventional extractions. Moreover, not all specimens may yield effective isolation, which may be influenced by pre-analytical variables (specimen quality) or related to the technical performance of the isolation. OGM is also not presently a high-throughput technology. OGM also does not provide sequence level data and thus may require orthogonal, sequenced-based approaches to confirm certain classes of structural variants (i.e., small insertional events). Finally, with its increased detection of cryptic structural variants, OGM may detect increased genomic variation of unknown significance and challenges current interpretative capabilities.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). WES or WGS tests as a clinical service are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who are children that are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup who receive WES with trio testing, when possible, the evidence includes large case series and within-subject comparisons. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup who receive WES with trio testing, when possible, the evidence includes small case series and prospective research studies. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. There is an increasing

number of reports evaluating the use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage with uncertainty about changes in patient management. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup or WES who receive WGS with trio testing, when possible, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. In studies of children with congenital anomalies and developmental delays of unknown etiology following standard clinical workup, the yield of WGS has ranged between 20% and 40%. A majority of studies described methods for interpretation of WGS indicating that only pathogenic or likely pathogenic variants were included in the diagnostic yield and that variants of uncertain significance (VUS) were frequently not reported. In a systematic review, the pooled (9 studies, N=648) diagnostic yield of WGS was 40% (95% CI 32% to 49%). Although the diagnostic yield of WGS is at least as high as WES in patients without a diagnosis following standard clinical workup, WGS results in the identification of more VUS than WES, and the clinical implications of this are uncertain. Evidence on the diagnostic yield of WGS in patients who have no diagnosis following WES is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup who receive who receive WGS with trio testing, when possible, the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. WGS has also been studied in other genetic conditions with yield ranging from 9% to 55%. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WGS as well as information regarding meaningful changes in management for these disorders is at an early stage. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following standard workup who receive rapid WGS (rWGS) or rapid WES (rWES) with trio testing, when possible, the evidence includes randomized controlled trials (RCTs) and case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. One RCT comparing rapid trio WGS (rWGS) with standard genetic tests to diagnose suspected genetic disorders in critically ill infants was terminated early due to loss of equipoise. The rate of genetic diagnosis within 28 days of

enrollment was higher for rWGS versus standard tests (31% vs. 3%; p=0.003). Changes in management due to test results were reported in 41% vs. 21% (p=0.11) of rWGS vs control patients; however, 73% of control subjects received broad genetic tests (e.g., next-generation sequencing panel testing, WES, or WGS) as part of standard testing. A second RCT compared rWGS to rWES in seriously ill infants with diseases of unknown etiology from the neonatal intensive care unit, pediatric intensive care unit, and cardiovascular intensive care unit. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). The NICUSeq RCT compared rWGS (test results returned in 15 days) to a delayed reporting group (WGS with test results returned in 60 days) in 354 infants admitted to an ICU with a suspected genetic disease. Diagnostic yield was higher in the rWGS group (31.0%; 95% CI 25.5% to 38.7% vs. 15.0%; 95% CI 10.2% to 21.3%). Additionally, significantly more infants in the rWGS group had a change in management compared with the delayed arm (21.1% vs. 10.3%; p=.009; odds ratio 2.3; 95% CI 1.22 to 4.32). Several retrospective and prospective studies including more than 800 critically ill infants and children in total have reported on diagnostic yield for rWGS or rWES. These studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60% for pathogenic or likely pathogenic variants. Studies have also reported associated changes in patient management for patients receiving a diagnosis from rWGS or rWES, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS or rWES. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are

solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
0260U	0264U	0267U	0454U					

Covered when medically necessary:

Procedure Codes							
0094U	0212U	0213U	0214U	0215U	0265U	0425U	0426U
81415	81416	81417	81425	81426	81427		

ICD-10-CM Diagnosis Code	Description
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F78.A1	SYNGAP1-related intellectual disability
F78.A9	Other genetic related intellectual disability
F79	Unspecified intellectual disabilities
F80.0	Phonological disorder
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder

ICD-10-CM Diagnosis Code	Description
F80.82	Social pragmatic communication disorder
F80.89	Other developmental disorders of speech and language
F90.9	Developmental disorder of speech and language, unspecified
Q00-Q07	Congenital malformations of the nervous system
Q10-Q18	Congenital malformations of eye, ear, face, and neck
Q20-Q28	Congenital malformations of the circulatory system
Q30-Q34	Congenital malformations of the respiratory system
Q35-Q37	Cleft lip and cleft palate
Q38-Q45	Other Congenital malformations of the digestive system
Q50-Q56	Congenital malformations of genital organs
Q60-Q64	Congenital malformations of the urinary system
Q65-Q79.59	Congenital malformations and deformations of the musculoskeletal system
Q79.60-Q79.69	Ehlers-Danlos syndromes
Q79.8	Other congenital malformations of musculoskeletal system
Q79.9	Congenital malformation of musculoskeletal system, unspecified
Q80-Q89.9	Other congenital malformations
Q90-Q99.9	Chromosomal abnormalities, not elsewhere classified

IX. REFERENCES

TOP

1. *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. PMID 22700954*
2. *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. PMID 25741868*
3. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. TEC Assessments.2013;Volume 28:Tab 3.*
4. *Smith HS, Swint JM, Lalani SR, et al. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. Genet. Med., 2018 May 16;21(1). PMID 29760485*
5. *Vissers L, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. Genet Med. Sep 2017;19(9):1055-1063. PMID 28333917*

6. *Cordoba M, Rodriguez-Quiroga SA, Vega PA, et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. PLoS ONE, 2018 Feb 2;13(2). PMID 29389947*
7. *Ewans LJ, Schofield D, Shrestha R, et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. Genet. Med., 2018 Mar 30;20(12). PMID 29595814*
8. *Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. Genet. Med., 2018 Mar 23;20(11). PMID 29565416*
9. *Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. Genet Med. Jan 11, 2018. PMID 29323667*
10. *Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. Apr 4 2015;385(9975):1305-1314. PMID 25529582*
11. *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. Jun 2018;20(6):645-654. PMID 29095811*
12. *Tsuchida N, Nakashima M, Kato M, et al. Detection of copy number variations in epilepsy using exome data. Clin Genet. Mar 2018;93(3):577-587. PMID 28940419*
13. *Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. Mol Genet Metab. Aug 2017;121(4):297-307. PMID 28688840*
14. *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. PMID 26863999*
15. *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. PMID 26648591*
16. *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. PMID 26938784*
17. *Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome sequencing and the management of neurometabolic disorders. N Engl J Med. Jun 9, 2016;374(23):2246-2255. PMID 27276562*
18. *Farwell KD, Shahmirzadi L, El-Khechen D, 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. Jul 2015;17(7):578-586. PMID 25356970*
19. *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. PMID 25326635*
20. *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. PMID 25326637*

21. *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. PMID 24901346*
22. *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. PMID 25473036*
23. *Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol. Oct 2014;76(4):473-483. PMID 25131622*
24. *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. PMID 24088041*
25. *Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med. Jun 2018;20(6):630-638. PMID 29758562*
26. *Rossi M, El-Khechen D, Black MH, et al. Outcomes of diagnostic exome sequencing in patients with diagnosed or suspected autism spectrum disorders. Pediatr Neurol. May 2017;70:34-43.e32. PMID 28330790*
27. *Walsh M, Bell KM, Chong B, et al. Diagnostic and cost utility of whole exome sequencing in peripheral neuropathy. Ann Clin Transl Neurol. May 2017;4(5):318-325. PMID 28491899*
28. *Miller KA, Twigg SR, McGowan SJ, et al. Diagnostic value of exome and whole genome sequencing in craniosynostosis. J Med Genet. Apr 2017;54(4):260-268. PMID 27884935*
29. *Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. Genet Med. Jul 2016;18(7):678-685. PMID 26633545*
30. *Ghaoui R, Cooper ST, Lek M, et al. Use of whole-exome sequencing for diagnosis of limb-girdle muscular dystrophy: outcomes and lessons learned. JAMA Neurol. Dec 2015;72(12):1424-1432. PMID 26436962*
31. *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. Aug 2015;3:67. PMID 26284228*
32. *Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. J Inherit Metab Dis. May 2015;38(3):437-443. PMID 25735936*
33. *Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of Sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. Dec 2013;34(12):1721-1726. PMID 24123792*
34. *Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. Genet Med. Apr 2018;20(4):435-443. PMID 28771251*
35. *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. May 2018;26(5):740-744. PMID 29453418*

36. *Stavropoulos DJ, Merico D, Jobling R, et al. Whole Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Pediatric Medicine. NPJ Genom Med. Jan 13, 2016;1. PMID 28567303*
37. *Hiatt SM, Amaral MD, Bowling KM, et al. Systematic reanalysis of genomic data improves quality of variant interpretation. Clin. Genet. 2018 Jul;94(1). PMID 29652076*
38. *Bowling KM, Thompson ML, Amaral MD, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. Genome Med. May 30, 2017;9(1):43. PMID 28554332*
39. *Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. Nature. Jul 17 2014;511(7509):344-347. PMID 24896178*
40. *Thiffault I, Farrow E, Zellmer L, et al. Clinical genome sequencing in an unbiased pediatric cohort. Genet. Med., 2018 Jul 17;21(2). PMID 30008475*
41. *Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. Genet Med. Nov 2018;20(11):1328-1333. PMID 29565419*
42. *Carss KJ, Arno G, Erwood M, et al. Comprehensive rare variant analysis via whole-genome sequencing to determine the molecular pathology of inherited retinal disease. Am J Hum Genet. Jan 05 2017;100(1):75-90. PMID 28041643*
43. *Ellingford 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. PMID 26872967*
44. *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. PMID 25985138*
45. *Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med. Feb 2015;21(2):185-191. PMID 25621899*
46. *Wu ET, Hwu WL, Chien YH, et al. Critical Trio Exome Benefits In-Time Decision-Making for Pediatric Patients With Severe Illnesses. Pediatr Crit Care Med. 2019 Nov;20(11). PMID 31261230*
47. *Elliott AM, du Souich C, Lehman A, et al. RAPIDOMICS: rapid genome-wide sequencing in a neonatal intensive care unit-successes and challenges. Eur. J. Pediatr. 2019 Aug;178(8). PMID 31172278*
48. *Gubbels CS, VanNoy GE, Madden JA, et al. Prospective, phenotype-driven selection of critically ill neonates for rapid exome sequencing is associated with high diagnostic yield. Genet Med. Apr 2020; 22(4): 736-744. PMID 31780822*
49. *Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. Genet Med. Mar 15, 2018. PMID 29543227*
50. *Meng L, Pammi M, Saronwala A, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. JAMA Pediatr. Dec 4 2017;171(12):e173438. PMID 28973083*
51. *French CE, Delon I, Dolling H, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. Intensive Care Med, 2019 Mar 9;45(5). PMID 30847515*

52. *Sanford EF, Clark MM, Farnaes L, et al. Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. Pediatr Crit Care Med, 2019 Jun 28. PMID 31246743*
53. *Hauser NS, Solomon BD, Vilboux T, et al. Experience with genomic sequencing in pediatric patients with congenital cardiac defects in a large community hospital. Mol Genet Genomic Med. Mar 2018;6(2):200-212. PMID 29368431*
54. *Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med.2018;3:10. PMID 29644095*
55. *Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. J Med Genet. Nov 2018;55(11):721-728. PMID 30049826*
56. *van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. Pediatrics. Oct 2017;140(4). PMID 28939701*
57. *Willig LK, Petrikin JE, Smith LD, 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. May 2015;3(5):377-387. PMID 25937001*
58. *Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am. J. Hum. Genet. 2019 Oct;105(4). PMID 31564432*
59. *Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. NPJ Genom Med.2018;3:6. PMID 29449963*
60. *ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. Aug 2012;14(8):759-761. PMID 22863877*
61. *Alford RL, Arnos KS, Fox M, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. Apr 2014;16(4):347-355. PMID 24651602*
62. *Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Feb 2017;19(2):249-255. PMID 27854360*
63. *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. PMID 25313375*
64. *Kwong AK, Tsang MH, Fung JL, et al. Exome sequencing in paediatric patients with movement disorders. Orphanet J Rare Dis. Jan 15 2021; 16(1): 32. PMID 33446253*
65. *Gileles-Hillel A, Mor-Shaked H, Shoseyov D, et al. Whole-exome sequencing accuracy in the diagnosis of primary ciliary dyskinesia. ERJ Open Res. Oct 2020; 6(4). PMID 33447612*
66. *Kim SY, Jang SS, Kim H, et al. Genetic diagnosis of infantile-onset epilepsy in the clinic: Application of whole-exome sequencing following epilepsy gene panel testing. Clin Genet. Mar 2021; 99(3): 418-424. PMID 33349918*

67. *Vandersluis S, Li CM, Cheng L, et al. Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment. Ont Health Technol Assess Ser. 2020; 20(11): 1-178. PMID 32194879*
68. *Costain G, Walker S, Marano M, et al. Genome Sequencing as a Diagnostic Test in Children With Unexplained Medical Complexity. JAMA Netw Open. Sep 01 2020; 3(9): e2018109. PMID 32960281*
69. *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 Medical Genetics and Genomics (ACMG). Genet Med. Nov 2021; 23(11): 2029-2037. PMID 34211152*
70. *Krantz ID, Medne L, Weatherly JM, et al. Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease: A Randomized Clinical Trial. JAMA Pediatr. Dec 01 2021; 175(12): 1218-1226. PMID 34570182*
71. *Hardin AP, Hackell JM; COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE. Age Limit of Pediatrics. Pediatrics. 2017;140(3):e20172151. doi:10.1542/peds.2017-2151*
72. *Dimmock DP, Clark MM, Gaughran M, et al. An RCT of Rapid Genomic Sequencing among Seriously Ill Infants Results in High Clinical Utility, Changes in Management, and Low Perceived Harm. Am J Hum Genet. Nov 05 2020; 107(5): 942-952. PMID 33157007*
73. *Lindstrand A, Ek M, Kvarnung M, et al. Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability. Genet Med. Nov 2022; 24(11): 2296-2307. PMID 36066546*
74. *Dai P, Honda A, Ewans L, et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: A systematic review and meta-analysis. Genet Med. Aug 2022; 24(8): 1618-1629. PMID 35550369*
75. *Ewans LJ, Minoche AE, Schofield D, et al. Whole exome and genome sequencing in mendelian disorders: a diagnostic and health economic analysis. Eur J Hum Genet. Oct 2022; 30(10): 1121-1131. PMID 35970915*
76. *Halfmeyer I, Bartolomaeus T, Popp B, et al. Approach to Cohort-Wide Re-Analysis of Exome Data in 1000 Individuals with Neurodevelopmental Disorders. Genes (Basel). Dec 22 2022; 14(1). PMID 36672771*
77. *Sun Y, Peng J, Liang D, et al. Genome sequencing demonstrates high diagnostic yield in children with undiagnosed global developmental delay/intellectual disability: A prospective study. Hum Mutat. May 2022; 43(5): 568-581. PMID 35143101*
78. *Brody S, Dubuc AM, and Kim AS. Optical Genome Mapping: A 'Tool' with Significant Potential from Discovery to Diagnostics. College of Amreican Pathologists. May 10, 2023.*
79. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.102, Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders. April 2023*

POLICY TITLE	WHOLE EXOME AND WHOLE GENOME SEQUENCING FOR DIAGNOSIS OF GENETIC DISORDERS
POLICY NUMBER	MP 2.324

X. POLICY HISTORY

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MP 2.324	**02/20/2020 Consensus Review.** No change to policy statements. References updated. Coding reviewed.
	10/01/2020 Administrative Update. New codes 0212U and 0213U added. Effective 10/1/20.
	09/01/2021 Administrative Update. New codes 0260U, 0264U, 0265U, and 0267U added; effective 10/1/21
	03/16/2021 Major Review. Added the following as medically necessary with criteria: rapid WES; rapid WGS; recommendation of "trio testing when possible". Updated policy guidelines, summary of evidence, and references. Revised coding: CPT code 0094U moved from investigational to covered when medically necessary codes; 0214U and 0215U added as covered when medically necessary; dx codes updated; added 81425, 81426, 8142 for rapid testing (not standard) only.
	09/01/2021 Administrative Update. Added new codes 0260U, 0264U, 0265U, and 0267U, F78.A1 and F78.A9. Effective 10/1/21
	05/17/2022 Consensus Review. No change to policy statement. FEP language updated. Rationale and References revised.
	09/14/2022 Administrative Update. Added new code 0336U. Effective 10/1/22
	06/28/2023 Minor Review. Standard whole genome sequencing is now MN. Age expanded from 5 to 21 years old. Added criteria point to allow WES and WGS as 1st line testing. Added INV statement for optical genome mapping. Updated cross references, background and references. Updated coding table.
	12/12/2023 Administrative Update. Added 0425U and 0426U.
	06/07/2024 Administrative Update. Added 0454U. Eff 7/1/24.
	07/25/2024 Consensus Review. Updated cross-references and references. No changes to coding.

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