2.04.102	Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders		
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Section:	2.0 Medicine	**Page:**	Page 1 of 48

Policy Statement

A standard whole exome sequencing (WES), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met:

I. Testing is for the evaluation of unexplained congenital or neurodevelopmental disorder in children when **all** of the following criteria are met:
   A. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, and **all** of the following:
      1. Evaluation includes at least a family history and phenotype description
      2. Patient and family (if applicable) have been counseled about the potential risks of genetic testing
II. Previous genetic testing (e.g., chromosomal microarray analysis [CMA] and/or targeted single-gene testing) has failed to yield a diagnosis
III. Documentation of **one or more** of the following:
   A. A genetic etiology is considered the most likely explanation for the phenotype
   B. The affected individual is faced with invasive procedures or testing (e.g., muscle biopsy) as the next diagnostic step

Rapid whole exome or rapid whole genome sequencing (rWES or rWGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met:

I. For the evaluation of critically ill infants or children less than 18 years of age
II. Hospitalized in neonatal or pediatric intensive care with illness of unknown etiology
III. Documentation that supports **both** of the following:
   A. At least **one** of the following:
      1. Multiple congenital anomalies
      2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following:
         a. Choanal atresia
         b. Coloboma
         c. Hirschsprung disease
         d. Meconium ileus
      3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following:
         a. Abnormal newborn screen
         b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
         c. Hyperammonemia
         d. Lactic acidosis not due to poor perfusion
         e. Refractory or severe hypoglycemia
      4. An abnormal response to standard therapy for a major underlying condition
      5. Significant hypotonia
      6. Persistent seizures
      7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following:
         a. Recurrent events without respiratory infection
         b. Recurrent witnessed seizure like events
         c. Required Cardiopulmonary Resuscitation (CPR)
         d. 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

e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
f. Family history of **one or more** of the following:
   i. Arrhythmia
   ii. BRUE in sibling
   iii. Developmental delay
   iv. Inborn error of metabolism or genetic disease
   v. Long QT syndrome (LQTS)
   vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant

B. **All** of the following have been excluded a reason for admission:
   1. An infection with normal response to therapy
   2. Confirmed genetic diagnosis explains illness
   3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event
   4. Isolated prematurity
   5. Isolated Transient Tachypnea of the Newborn (TTN)
   6. Isolated unconjugated hyperbilirubinemia
   7. Nonviable neonates

Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **all** of the following are met:

I. Performed at the same time as rWES or later
II. The results of the rWES are insufficient to explain the clinical presentation

Rapid whole exome sequencing and rapid whole genome sequencing (rWES and rWGS) is considered **investigational** for the diagnosis of genetic disorders in all other situations.

Standard whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations.

Standard and rapid whole exome sequencing (WES and rWES) and standard and rapid whole genome sequencing (WGS and rWGS)are considered **investigational** when screening for genetic disorders.

Standard whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders.

Separate CMA testing is considered **not medically necessary** with rWGS analysis.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

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

Standard Whole Exome Sequencing or Whole Genome Sequencing
Standard WES or WGS turn-around time is usually 1 to 3 months.

Rapid Whole Exome Sequencing or Whole Genome Sequencing
Rapid means an average turnaround time of less than 14 days, but usually less than 7 days. Rapid results should be called to the clinician immediately if changes in management are likely.

UltraRapid whole genome sequencing has an average turnaround time of 48-72 hours. It has the same indications as for rapid WGS. It is usually reserved for those infants in the first few days of life who are felt by their attending physician to be at immediate risk of death or long term disability, such as intractable seizures.

Note: rWGS analysis has the ability to detect most CNVs.

Organ Transplantation
Rapid WGS and WES may be considered for approval in some cases prior to undergoing organ transplantation when documentation supports the urgent need for testing.

For rapid WES or WGS, the patient should be critically ill and in the Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU) when the test is ordered, but may be discharged before the results are delivered.

Trio Testing
Testing of the child and both parents can increase the chance of finding a definitive diagnosis and better interpretation of results. Trio testing is preferred whenever possible but should not delay testing of a critically ill patient 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.

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

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 to 10 days. The WGS was performed in 'rapid run' mode with minimum depth of 90 gigabases (Gb) per genome and average depth of coverage of 40X.

Genetics 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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

The following CPT codes are specific for this testing:

- **0036U**: Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
- **0094U**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
- **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) (List separately in addition to code for primary procedure)
- **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) (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)

Description

Whole exome sequencing (WES) sequences the portion of the genome that contains protein-coding DNA, while whole genome sequencing (WGS) sequences 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.

Related Policies

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

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 (FDA) has chosen not to require any regulatory review of this test.

Rationale

Background
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.[1,] 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 (»85%), is composed of about 20000 genes and 180000 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.[2,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

This review was informed in part by a TEC Special Report (2013) on exome sequencing for patients with suspected genetic disorders.[3,]

In 2018, Smith et al reported a scoping review of genome and exome sequencing as a diagnostic tool for pediatric patients. [4,] The authors identified 171 publications, although 131 were case reports. They concluded that diagnostic yield was the only consistently reported outcome. The median diagnostic yield in publications including more than single case reports was 33% but varied by broad clinical categories and test type.

The following sections review evidence by test type (WES and WGS), broad type of disorder, and care setting (intensive care vs. not intensive care).

Whole Exome Sequencing for Children with Multiple Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup; Patients who are not Critically Ill

Clinical Context and Test Purpose
The purpose of whole exome sequencing (WES) in children who have multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup is to establish a molecular diagnosis. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests;
- The clinical utility of a diagnosis has been established (e.g., by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes); and
- Establishing the diagnosis by genetic testing will end the clinical workup for other disorders.

The question addressed in this evidence review is: Does the use of WES improve health outcomes when used for the diagnosis of children with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup?
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children presenting with multiple unexplained congenital anomalies or a neurodevelopmental disorder that are suspected to have a genetic basis, but are not explained by a standard clinical workup.

Intervention
The relevant intervention of interest is WES with trio testing when possible.

Comparators
The following practice is currently being used to diagnose multiple unexplained congenital anomalies or a neurodevelopmental disorder: standard clinical workup without WES.
A standard clinical workup for an individual with a suspected genetic condition varies by patient phenotype but generally involves a thorough history, physical exam (including dysmorphology and neurodevelopmental assessment, if applicable), routine laboratory testing, and imaging. If the results suggest a specific genetic syndrome, then established diagnostic methods relevant for that syndrome would be used.

Outcomes
There is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies; therefore, diagnostic yield will be the clinical validity outcome of interest.
The health outcomes of interest are reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

False-positive test results can lead to misdiagnosis and inappropriate clinical management. False-negative test results can lead to a lack of a genetic diagnosis and continuation of the diagnostic odyssey.

Study Selection Criteria
For the evaluation of clinical validity of WES, studies that met the following eligibility criteria were considered:

- Reported on the diagnostic yield or performance characteristics such as sensitivity and specificity of WES;
- Patient/sample clinical characteristics were described; children with congenital abnormalities or neurodevelopmental disorders were included;
- Patient/sample selection criteria were described;
- Included at least 20 patients.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A number of studies have reported on the use of WES in clinical practice (Table 1). Typically, the populations included in these studies have had suspected rare genetic disorders, although the specific populations vary.

Series have been reported with as many as 2000 patients. The most common reason for referral to a tertiary care center was an unexplained neurodevelopmental disorder. Many patients had been through a standard clinical workup and testing without identification of a genetic variant to explain their condition. Diagnostic yield in these studies, defined as the proportion of tested patients with clinically relevant genomic abnormalities, ranged from 25% to 48%. Because there is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies, clinical confirmation may be the only method for determining false-positive and false-negative rates. No reports were identified of incorrect diagnoses, and how often they might occur is unclear.

When used as a first-line test in infants with multiple congenital abnormalities and dysmorphic features, diagnostic yield may be as high as 58%. Testing parent-child trios has been reported to increase diagnostic yield, to identify an inherited variant from an unaffected parent and be considered benign, or to identify a de novo variant not present in an unaffected parent. First-line trio testing for children with complex neurologic disorders was shown to increase the diagnostic yield (29%, plus a possible diagnostic finding in 27%) compared with a standard clinical pathway (7%) performed in parallel in the same patients.[5]

Table 1. Diagnostic Yields of Whole Exome Sequencing for Congenital Anomalies or a Neurodevelopmental Disorder

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Cordoba et al (2018)[6]	Patients suspected of having a neurogenetic condition: typical findings of known neurogenetic diseases and/or hints of monogenic etiology such as familial aggregation or chronic and progressive course Mean age was 23 yrs	40	Prospective consecutive patients selected from a Neurogeneti c Clinic of a tertiary hospital in Argentina (Unclear how many were trio testing)	16 (40)	Results led to altered treatment in 14 patients
Ewans et al (2018)[7]	Patients from families with a distinctive	37 families	54 individuals from 37 families	11 (30)	Reanalysis at 12 mos improved

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
	phenotype likely to have a monogenic etiology with a family structure consistent with Mendelian inheritance. Prior diagnostic testing had all been negative. The majority of disorders were intellectual disability or neurological (62%) but 13% were skeletal and 11% were hematological; two-thirds pediatric		recruited from clinical genetics units in New South Wales from 2013 to 2014. Proband plus family members(s) underwent WES.		diagnostic success from 30 to 41%
Powis et al (2018) [8]	Neonates (birth to 1 mo of age). The majority had multiple congenital anomalies or dysmorphic features.	66	Trio or singleton WES 6 infants received rapid WES	Overall: 25 (38) Rapid WES: 3 (50)	VUS noted in 6 patients
Wright et al (2018)[9], re-analysisWright et al (2015)[10], original analysis	Children with severe undiagnosed NDDs and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral phenotypes	1133	Consecutive family trios from a U.K.-wide patient recruitment network	454 (40), re-analysis 311 (27), original analysis	Wright et al (2018) is a reanalysis of existing data from an earlier Wright et al (2015) publication from a DDD study using improved variant calling methodologies, novel variant detection algorithms, updated variant annotation, evidence-based filtering strategies, and newly discovered disease-associated genes
Nambot et al (2018)[11]	Children with congenital	461	Consecutive cases	31%	Initial yield in y 1: 22%

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
	anomalies and intellectual disability with negative prior diagnostic workup		meeting criteria referred to specialty clinic in France		Reanalysis led to increased yield
Tsuchida et al (2018)[12]	Children with epilepsy (»63% with early-onset epileptic encephalopathies) with no causative SNV in known epilepsy-associated genes	168	Consecutive unsolved cases referred to a single-center	18 (11)	Performed WES with CNV detection tools
Evers et al (2017)[13]	Children with undiagnosed NDDs (63%), neurometabolic disorders, and dystonias	72	Prospective study, referral and selection unclear	• 36% in NDD • 43% in neurometabolic disorders • 25% in dystonias	Results reported to be important for family planning, used for a prenatal diagnostic procedure in 4 cases, management changes reported in 8 cases; surveillance for other disease-associated complications initiated in 6 cases
Vissers et al (2017)[5]	Children with complex neurologic disorders of suspected genetic origin	150	Prospective comparative study at a tertiary center	• 44 (29) conclusive • 41 (27) possible	First-line WES had 29% yield vs. 7% yield for a standard diagnostic workup[b]
Nolan and Carlson (2016)[14]	Children with unexplained NDDs	50	Pediatric neurology clinic	41 (48)	Changed medication, systemic investigation, and family planning
Allen et al (2016)[15]	Patients with unexplained early-onset epileptic encephalopathy	50 (95% <1 y)	Single-center	11 (22)	2 VUS for follow-up, 11 variants identified as de novo
Stark et al (2016)[16]	Infants (≤2 y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features	80 overall; 37 critically ill	Prospective comparative study at a tertiary center	46 (58) overall; 19 (51) in critically ill infants	First-line WES increased yield by 44%, changed clinical management and family planning.

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Tarailo-Graovac et al (2016)[17,]	Intellectual developmental disorders and unexplained metabolic phenotypes (all ages)	41	Consecutively enrolled patients referred to a single-center	28 (68)	WES diagnosis affected the clinical treatment of 18 (44%) probands
Farwell et al (2015)[18,]	Unexplained neurologic disorders (65% pediatric)	500	WES laboratory	152 (30)	Trio (37.5% yield) vs. proband only (20.6% yield); 31 (7.5% de novo)
Yang et al (2014)[19,]	Suspected genetic disorder (88% neurologic or developmental)	2000 (45% <5 y; 42% 5-18 yrs; 12% adults)	Consecutive patients at single-center	504 (25)	Identification of novel variants. End of the diagnostic odyssey and change in management
Lee et al (2014)[20,]	Suspected rare Mendelian disorders (57% of children had developmental delay; 26% of adults had ataxia)	814 (49% <5 y; 15% 5-18 y; 36% adults)	Consecutive patients at single-center	213 (26)	Trio (31% yield) vs. proband only (22% yield)
Iglesias et al (2014)[21,]	Birth defects (24%); developmental delay (25%); seizures (32%)	115 (79% children)	Single-center tertiary clinic	37 (32)	Discontinuation of planned testing, changed medical management, and family planning
Soden et al (2014)[22,]	Children with unexplained NDDs	119 (100 families)	Single-center database[a]	53 (45)	Change in clinical care or impression in 49% of families
Srivastava et al (2014)[23,]	Children with unexplained NDDs	78	Pediatric neurogenetics clinic	32 (41)	Change in medical management, prognostication, and family planning
Yang et al (2013)[24,]	Suspected genetic disorder (80% neurologic)	250 (1% fetus; 50% <5 y; 38% 5-18 yrs; 11% adults)	Consecutive patients at single-center	62 (25)	Identification of atypical phenotypes of known genetic diseases and blended phenotypes

CNV: copy number variant; DDD: Deciphering Developmental Disorders; NDD: neurodevelopmental disorder; SNV: single nucleotide variants; VUS: variant of uncertain significance; WES: whole exome sequencing.

[a] Included both WES and whole genome sequencing.

[b] Standard diagnostic workup included an average of 23.3 physician-patient contacts, imaging studies, muscle biopsies or lumbar punctures, other laboratory tests, and an average of 5.4 sequential gene by gene tests.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs assessing the use of WES to diagnose multiple unexplained congenital anomalies or a neurodevelopmental disorder were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Cohort studies following children from presentation to outcomes have not been reported. There are considerable challenges conducting studies of sufficient size given underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes. Studies addressing clinical utility have reported mainly diagnostic yield and management changes. Thus, it is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to the heterogeneity of disorders, rarity, and outcome importance that may differ according to identified pathogenic variants. Actionable items following testing in the reviewed studies (Table 2) included family planning, change in management, change or avoidance of additional testing, surveillance for associated morbidities, prognosis, and ending the diagnostic odyssey.

The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. When recurrence risk can be estimated for an identified variant (e.g., by including parent testing), future reproductive decisions can be affected. Early use of WES can reduce the time to diagnosis and reduce the financial and psychological burdens associated with prolonged investigation.

Section Summary: Whole Exome Sequencing for Children with Multiple Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup
The evidence on WES in children who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology of unknown etiology following a standard workup includes case series. These series have reported diagnostic yields of WES ranging from 22% to 58%, depending on the individual's age, phenotype, and previous workup. Comparative studies have reported an increase in diagnostic yield compared with standard testing strategies. Thus, for individuals who have a suspected genetic etiology but for whom the specific genetic alteration is unclear or unidentified by a standard clinical workup, WES may return a likely pathogenic variant. A genetic diagnosis for these patients is reported to change management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning.

Whole Exome Sequencing for Children with a Suspected Genetic Disorder other than Multiple Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup; Patients who are not Critically Ill

Clinical Context and Test Purpose
Most of the literature on WES is on neurodevelopmental disorders in children; however, other potential indications for WES have been reported (Table 3). These include limb-girdle muscular dystrophy, inherited retinal disease, and other disorders including mitochondrial, endocrine, and immunologic disorders.

The purpose of WES in patients who have a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup is to establish a molecular diagnosis. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are stated above.

The question addressed in this evidence review is: Does WES improve health outcomes when used for the diagnosis of a suspected genetic condition other than multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup? The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children presenting with a disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder that is suspected to have a genetic basis but is not explained by a standard clinical workup.

Intervention
The relevant intervention of interest is WES.

Comparators
The following practice is currently being used to diagnose a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder: a standard clinical workup without WES. A standard clinical workup for an individual with a suspected genetic condition varies by patient phenotype but generally involves a thorough history, physical exam (including dysmorphology and neurodevelopmental assessment, if applicable), routine laboratory testing, and imaging. If the results suggest a specific genetic syndrome, then established diagnostic methods relevant for that syndrome would be used.

Outcomes
There is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies, therefore diagnostic yield will be the clinical validity outcome of interest. The health outcomes of interest are reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

Study Selection Criteria
For the evaluation of clinical validity of WES, studies that met the following eligibility criteria were considered:

- Reported on the diagnostic yield or performance characteristics such as sensitivity and specificity of WES;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included at least 20 patients.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Studies have assessed WES for a broad spectrum of disorders. The diagnostic yield in patient populations restricted to specific phenotypes ranges from 3% for colorectal cancer to 60% for unexplained limb-girdle muscular dystrophy (Table 2). Some studies used a virtual gene panel that is restricted to genes associated with the phenotype, while others have examined the whole exome, either initially or sequentially. An advantage of WES over individual gene or gene panel testing is that the stored data allows reanalysis as new genes are linked to the patient phenotype. Whole exome sequencing has also been reported to be beneficial in patients with atypical presentations.

Table 2. Diagnostic Yields of Whole Exome Sequencing for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Kwong et al (2021)[25]	Patients with pediatric-onset movement disorders and unrevealing etiologies	31	Cohort of patients who received WES	10 (32)	8 of 10 patients with a genetic diagnosis had alterations in management decisions
Gileles-Hillel et al (2020)[26]	Patients with symptoms highly suggestive of primary ciliary dyskinesia	48	Prospective WES in patients referred to a single-center	36 (75)	WES established an alternative diagnosis in 4 patients
Kim et al (2020)[27]	Patients with infantile-onset epilepsy who tested negative for epilepsy using a gene panel test	59	Cohort of patients who received WES	+9 (+8%)	WES provided an additional 8% diagnostic yield in addition to the original gene panel
Hauer et al (2018)[28]	Short stature in whom common nongenetic causes had been excluded	200 (mostly children)	Randomly selected from a consecutive series of patients referred for workup; trio testing performed	33 (17)	• Standard diagnostic approach yield: 13.6% in the original cohort of 565 • WES results had a possible impact on treatment or additional preventive measurements in 31 (16%) families
Rossi et al (2017)[29]	Patients with autism spectrum disorder diagnosis or autistic features referred for WES	163	Selected from 1200 consecutive retrospective samples from a commercial lab	42 (26)	• 66% of patients already had a clinician-reported autism diagnosis • VUS in 12%
Walsh et al (2017)[30]	Peripheral neuropathy in patients ranging from 2-68 y	• 23 children • 27 adults	Prospective research study at tertiary pediatric and adult centers	19 (38)	Initial targeted analysis with virtual gene panel, followed by WES

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Miller et al (2017)[31]	Craniosynostosis in patients who tested negative on targeted genetic testing	40	Research study of referred patients[a]	15 (38)	Altered management and reproductive decision making
Posey et al (2016)[32]	Adults (overlap of 272 patients reported by Yang et al [2014]),[19] includes neurodevelopmental and other phenotypes	486 (53% 18-30 y; 47% >30 y)	Review of lab findings in a consecutive retrospective series of adults	85 (18)	Yield in patients 18-30 y (24%) vs. those >30 y (10.4%)
Ghaoui et al (2015)[33]	Unexplained limb-girdle muscular dystrophy	60 families	Prospective study of patients identified from a specimen bank	27 (60)	Trio (60% yield) vs. proband only (40% yield)
Valencia et al (2015)[34]	Unexplained disorders: congenital anomalies (30%), neurologic (22%), mitochondrial (25%), endocrine (3%), immunodeficiencies (17%)	40 (<17 y)	Consecutive patients in a single-center	12 (30)	• Altered management including genetic counseling and ending diagnostic odyssey • VUS in 15 (38%) patients
Wortmann et al (2015)[35]	Suspected mitochondrial disorder	109	Patients referred to a single-center	42 (39)	57% yield in patients with a high suspicion of mitochondrial disorder
Neveling et al (2013)[36]	Unexplained disorders: blindness, deafness, movement disorders, mitochondrial disorders, hereditary cancer	186	Outpatient genetic clinic; post hoc comparison with Sanger sequencing	3%-52%	WES increased yield vs. Sanger sequencing Highest yield for blindness and deafness

VUS: variant of uncertain significance; WES: whole exome sequencing.
[a] Included both WES and whole genome sequencing.
Tables 3 and 4 display notable limitations identified in each study.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kwong et al (2021)[25]					
Gileles-Hillel et al (2020)[26]	4. Most patients had high pre-test probability of disease				
Kim et al (2020)[27]					
Hauer et al (2018)[28]					
Rossi et al (2017)[29]	4. Most patients had a clinical diagnosis; only 33% had testing for specific ASD				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	genes before WES				
Walsh et al (2017)[30.]		3. Proband testing only			
Miller et al (2017)[31.]					
Posey et al (2016)[32.]	3. Included highly heterogeneous diseases	3. Proband testing only			
Ghaoui et al (2015)[33.]					
Valencia et al (2015)[34.]	3. Included highly heterogeneous diseases	2. Unclear whether WES performed on parents			
Wortmann et al (2015)[35.]		3. Proband testing only			
Neveling et al (2013)[36.]	3. Included highly heterogeneous diseases	3. Proband testing only			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ASD: autism spectrum disorder; WES: whole exome sequencing.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kwong et al (2021)[25.]						
Gileles-Hillel et al (2020)[26.]						
Kim et al (2020)[27.]						
Hauer et al (2018)[28.]						
Rossi et al (2017)[29.]						
Walsh et al (2017)[30.]						
Miller et al (2017)[31.]	2. Selection not random or consecutive					
Posey et al (2016)[32.]						
Ghaoui et al (2015)[33.]						

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Valencia et al (2015)[34.]						
Wortmann et al (2015)[35.]	1,2. Unclear how patients were selected from those eligible					
Neveling et al (2013)[36.]	1,2. Unclear how patients were selected from those referred					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the use of WES to diagnose a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
A genetic diagnosis for an unexplained disorder can alter management in several ways: such a diagnosis may lead to genetic counseling and ending the diagnostic odyssey, and may affect reproductive decision making.

Because the clinical validity of WES for this indication has not been established, a chain of evidence cannot be constructed.

Section Summary: Whole Exome Sequencing for a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder
There is an increasing number of reports assessing use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies ranged from 3% for colorectal cancer to 60% for trio (parents and child) analysis of limb-girdle muscular dystrophy. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and the authors noted that WES data allow reanalysis as new genes are linked to the patient phenotype. Overall, a

limited number of patients have been studied for any specific disorder, and study of WES in these disorders is at an early stage with uncertainty about changes in patient management.

Whole Genome Sequencing for Children with Multiple Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup; Patients who are not Critically Ill

Clinical Context and Test Purpose
The purpose of whole genome sequencing (WGS) in patients with a suspected genetic disorder of unknown etiology following a standard workup is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are stated above.

The question addressed in this evidence review is: Does WGS improve health outcomes when used for the diagnosis of patients with a suspected genetic disorder of unknown etiology following a standard workup without WES or WGS?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup.

Interventions
The relevant interventions being considered include: WGS with trio testing when possible. Several laboratories offer WGS as a clinical service. Medical centers may also offer rWGS as a clinical service. The median time for standard WGS is several weeks.
Note that this evidence review does not address the use of WGS for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or for testing of cancer cells.

Comparators
The following practice is currently being used to diagnose a suspected genetic disorder: a standard clinical workup without WES or WGS. A standard clinical workup for an individual with a suspected genetic condition varies by patient phenotype but generally involves a thorough history, physical exam (including dysmorphology and neurodevelopmental assessment, if applicable), routine laboratory testing, and imaging. If the results suggest a specific genetic syndrome, then established diagnostic methods relevant for that syndrome would be used.

Outcomes
There is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies; therefore, diagnostic yield will be the clinical validity outcome of interest. The health outcomes of interest are reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

False-positive test results can lead to misdiagnosis and inappropriate clinical management. False-negative test results can lead to a lack of a genetic diagnosis and continuation of the diagnostic odyssey.

Study Selection Criteria
For the evaluation of clinical validity of WGS, studies that met the following eligibility criteria were considered:

- Reported on the diagnostic yield or performance characteristics such as sensitivity and specificity of rapid WGS or WGS;

- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included at least 20 patients.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Studies have shown that WGS can detect more pathogenic variants than WES, due to an improvement in detecting copy number variants, insertions and deletions, intronic single-nucleotide variants, and exonic single-nucleotide variants in regions with poor coverage on WES. 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 not reported. In some studies, the genes examined were those previously associated with the phenotype, while other studies were research-based and conducted more exploratory analysis.[37.] It has been noted that genomes sequenced with WGS are available for future review when new variants associated with clinical diseases are discovered.

The use of WGS has been studied in children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup in several observational studies, both prospective and retrospective. Studies are described in Table 5. The diagnostic yield of WGS has been between 20% and 40%. Additional indirect evidence is available from studies reporting diagnostic yield of WES in a similar population as summarized above, and it is reasonable to expect that WGS is likely to result in similar or better diagnostic yield for pathogenic or likely pathogenic variants as compared with WES.

Table 5. Diagnostic Yields with Whole Genome Sequencing in Children who are not Critically Ill with Multiple Unexplained Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup

Study	Patient Population	N	Design	Yield,n (%)	Additional Information
Lionel et al (2018)[37.]	Well-characterized but genetically heterogeneous cohort of children <18 y that had undergone targeted gene sequencing Referral clinic: 44% metabolic, 23% ophthalmology, 15% Joint laxity/hypermobility	103	ProspectiveTrio WGS testing for patients recruited from pediatric nongenetic subspecialists	42 (41)	Compared with a 24% yield with standard diagnostic testing and a 25% increase in yield from WES Limited information on change in management
Costain et al (2018), re-analysis[38.] Stavropoulos et al (2016)[39.], original analysis	Children (<18 y) with undiagnosed congenital malformations and neurodevelopmental disorders Presentation: abnormalities of the nervous system (77%), skeletal system (68%), growth (44%), eye (34%), cardiovascular (32%), and musculature (27%)	64, re-analysis 100, original analysis	Prospective, consecutive Proband WGS was offered in parallel with clinical CMA testing	7 (11), re-analysis 34 (34), original analysis	Costain (2018) is a re-analysis of undiagnosed patients from Stavropoulos et al (2016) CMA plus targeted gene sequencing yield was 13% WGS yield highest for developmental delay 39%

Study	Patient Population	N	Design	Yield,n (%)	Additional Information
					(22/57) and lowest (15%) for connective tissue disorders Change in management reported for some patients 7 incidental findings
Hiatt et al (2018) [40.] re-analysisBowling et al (2017)[41.] original analysis	Children with developmental and/or intellectual delays of unknown etiology 81% had genetic testing prior to enrollment	Original analysis included 244 Re-analysis included additional 123, for a total cohort of 494	Retrospective, selection method and criteria unclear Trio WGS in a referral center	54 (22)[1], original analysis	Re-analysis: Re-analysis yielded pathogenic or likely pathogenic variants that were not initially reported in 23 patients Downgraded 3 'likely pathogenic' and 6 VUS Original analysis: Compared to 30% yield for WES[1] Changes in management not reported 11% VUS in WGS
Gilissen et al (2014)[42.]	Children with severe intellectual disability who did not have a diagnosis after extensive genetic testing that included whole exome sequencing	50	Trio WGS testing including unaffected parents	201 (42)	Of 21 with a positive diagnosis, 20 had de novo variants Changes in management not reported

CMA: chromosomal microarray analysis; VUS: variant of uncertain significance; WES: whole exome sequencing; WGS: whole genome sequencing.
[1] SNV/indel.
Tables 6 and 7 display notable limitations identified in each study.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lionel et al (2018)[37.]	3. Included highly heterogeneous diseases	3. Proband testing only			
Costain et al (2018), re-analysis[38.]		3. Proband testing only			
Bowling et al (2017)[41.]	4. 19% had no prescreening performed				
Gilissen et al (2014)[42.]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

WGS: whole genome sequencing.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Lionel et al (2018)[37]	1,2. Unclear how patients were selected from those eligible					
Costain et al (2018), re-analysis[38]						
Bowling et al (2017)[41]	1,2. Unclear how patients were selected from those eligible					
Gilissen et al (2014)[42]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. WGS: whole genome sequencing.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the use of WGS to diagnose multiple unexplained congenital anomalies or a neurodevelopmental disorder outside of critical care were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Clinical validity is established based on the meaningful diagnostic yield associated with WGS when a genetic etiology is uncertain after standard workup. Studies on WGS report changes in management that would improve health outcomes. The effect of WGS results on health outcomes are the same as those with WES, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning.
Section Summary: Whole Genome Sequencing for Children with Multiple Congenital Anomalies or a Neurodevelopmental Disorder of Unknown Etiology Following Standard Workup; Patients who are not Critically Ill

Whole genome sequencing has been studied in non-critically ill children with congenital abnormalities and development delays of unknown etiology following a standard workup. The diagnostic yield for WGS has been reported between 20% and 40%. Additional indirect evidence is available from studies reporting diagnostic yield and change in management results of WES in a similar population, and WGS may result in similar or better diagnostic yield for pathogenic or likely pathogenic variants compared with WES although few direct comparisons are available.

Whole Genome Sequencing for a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder; Patients who are not Critically Ill
Clinical Context and Test Purpose
The purpose of WGS in patients with a suspected genetic disorder of unknown etiology following a standard workup is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are stated above.

The question addressed in this evidence review is: Does WGS improve health outcomes when used for the diagnosis of patients with a suspected genetic disorder of unknown etiology following a standard workup without WES or WGS?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup.

Interventions
The relevant interventions being considered include: WGS with trio testing when possible. Several laboratories offer WGS as a clinical service. Medical centers may also offer WGS as a clinical service. The median time for standard WGS is several weeks.

Note that this evidence review does not address the use of WGS for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or for testing of cancer cells.

Comparators
The following practice is currently being used to diagnose a suspected genetic disorder: standard clinical workup without WES or WGS. A standard clinical workup for an individual with a suspected genetic condition varies by patient phenotype but generally involves a thorough history, physical exam (including dysmorphology and neurodevelopmental assessment, if applicable), routine laboratory testing, and imaging. If the results suggest a specific genetic syndrome, then established diagnostic methods relevant for that syndrome would be used.

Outcomes
There is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies; therefore, diagnostic yield will be the clinical validity outcome of interest. The health outcomes of interest are reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

False-positive test results can lead to misdiagnosis and inappropriate clinical management. False-negative test results can lead to a lack of a genetic diagnosis and continuation of the diagnostic odyssey.

Study Selection Criteria
For the evaluation of clinical validity of WGS, studies that met the following eligibility criteria were considered:

- Reported on the diagnostic yield or performance characteristics such as sensitivity and specificity of rapid WGS or WGS;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included at least 20 patients.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The use of WGS has been studied in children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder in several observational studies, both prospective and retrospective. Studies are described in Table 8. The diagnostic yield of WGS has been between 9% and 55%. However, these studies include mixed indications with heterogeneous populations and include little information about associated changes in management following genetic diagnosis.

Table 8. Diagnostic Yields with Whole Genome Sequencing in Children with a Suspected Genetic Disorder other than Multiple Unexplained Congenital Anomalies or a Neurodevelopmental Disorder of Unexplained Etiology Following Standard Workup

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Costain et al (2020)[43]	Children with medical complexity (children with at least one feature from each of the following: technology-dependent or use of high-intensity care, fragility, chronicity, and complexity)	138 (49 probands)	Prospective WGS in patients referred to a single-center	15 (30.6)	Management decisions beyond genetic and reproductive counseling were influenced in at least 11 families
Thiffault et al (2019)[44]	Patients with suspected genetic disorders referred for genetic testing between 2015 and 2017. The majority had previous genetic testing without a diagnosis. The mean age was 7 yrs.	80	Prospective. The majority underwent trio sequencing; WGS was performed for the proband and WES was done for both parents	19 (24)	2 partial gene deletions detected with WGS that would not be detectable with WES
Alfares et al (2018)[45]	Undiagnosed patients (91% pediatric) who had a history of negative WES testing 70% Consanguinity	154 recruited; 108 included in analysis	Retrospective, selection method and criteria unclear	10 (9%)	Reported incremental yield of WGS in patients with negative CGH and WES

Study	Patient Population	N	Design	Yield, n (%)	Additional Information
Carss et al (2017)[46]	Unexplained inherited retinal disease; ages not specified	605	Retrospective NIHR-BioResource Rare Diseases Consortium	331 (55)	Compared with a detection rate of 50% with WES (n=117)
Ellingford et al (2016)[47]	Unexplained inherited retinal disease; ages not specified	46	Prospective WGS in patients referred to a single-center	24 (52)	Estimated 29% increase in yield vs. targeted NGS
Taylor et al (2015)[48]	Broad spectrum of suspected genetic disorders (Mendelian and immunological disorders)	217	Prospective, multicenter series Clinicians and researchers submitted potential candidates for WGS and selections were made by a scientific Steering Committee. Patients were eligible if known candidate genes and large chromosomal copy number changes had been excluded. Trio testing for a subset of 15 families.	46 (21)	34% yield in Mendelian disorders; 57% yield in trios
Yuen et al (2015)[49]	Patients with diagnosed ASD	50	Prospective; unclear how patients were selected; quartet testing of extensively phenotyped families (parents and 2 ASD-affected siblings)	21 (42%)	12/20 had change in management; 1/20 had change in reproductive counseling

ASD: autism spectrum disorder; CGH: comparative genomic hybridization; NGS: next-generation sequencing; NIHR: National Institute for Health Research; WES: whole exome sequencing; WGS: whole genome sequencing.
[1] SNV/indel
Tables 9 and 10 display notable limitations identified in each study.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Costain et al (2020)[43]	3. Included heterogeneous diseases				
Thiffault et al (2019)[44]	3. Included heterogeneous diseases				
Alfares et al (2018)[45]	3: Clinical characteristics not described 4: 70% consanguinity	3. Appears to be proband testing only but not clear			

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Carss et al (2017)[46]	4. 25% had no prescreening performed				
Ellingford et al (2016)[47]		3. Proband testing only			
Taylor et al (2015)[48]	3. Included highly heterogeneous diseases				
Yuen et al (2015)[49]	4: All patients had a clinical diagnosis		3: Results of standard diagnostic methods not discussed		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 10. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Costain et al (2020)[43]						
Thiffault et al (2019)[44]	1,2: Unclear how patients were selected from those eligible					
Alfares et al (2018)[45]	1,2: Unclear how patients were selected from those eligible					
Carss et al (2017)[46]						
Ellingford et al (2016)[47]						
Taylor et al (2015)[48]						
Yuen et al (2015)[49]	1,2. Unclear how patients were selected from those eligible					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the use of WGS to diagnose a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
A genetic diagnosis for an unexplained disorder can alter management in several ways: such a diagnosis may lead to genetic counseling and ending the diagnostic odyssey, and may affect reproductive decision making.

Because the clinical validity of WGS for this indication has not been established, a chain of evidence cannot be constructed.

Section Summary: Whole Genome Sequencing for a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder; Patients who are not Critically Ill

Whole genome sequencing has also been studied in children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup. The diagnostic yield of WGS has been between 9% and 55%. However, these studies include mixed indications with heterogeneous populations and include little information about associated changes in management following genetic diagnosis.

Rapid Whole Exome or Genome Sequencing in Critically Ill Infants or Children
Clinical Context and Test Purpose
The purpose of rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS) in critically ill patients with a suspected genetic disorder of unknown etiology is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are stated above.

The most common cause of death in neonates in the United States is genetic disorders. Currently, critically ill neonates with suspected genetic diseases are frequently discharged or deceased without a diagnosis. There are thousands of rare genetic disorders. The presentation of many of these disorders in neonates may be nonspecific or differ from the presentation in

older patients and the disorder may produce secondary involvement of other systems due to the fragility of the neonate that obscures the primary pathology..

The neonatal intensive care unit (NICU) treatment of suspected genetic diseases is often empirical. Rapid diagnosis is critical for delivery of interventions that reduce morbidity and mortality in genetic diseases for which treatments exist. For many genetic diseases there is no effective treatment and timely diagnosis limits futile intensive care.

The question addressed in this evidence review is: Does rWES or rWGS improve health outcomes when used for the diagnosis of critically ill infants or children with a suspected genetic disorder of unknown etiology without WES or WGS?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is critically ill infants presenting with any of a variety of disorders and anomalies suspected to have a genetic basis but not explained by a standard workup. For example, patients may have a phenotype that does not correspond with a specific disorder for which a genetic test targeting a specific gene is available. Specifically for critically ill infants, the population would also include patients for whom specific diagnostic tests available for that phenotype are not accessible within a reasonable timeframe. Petrikin (2018) identified critically ill infants that are appropriate for rapid testing as meeting the following inclusion criteria: multiple congenital anomalies; an abnormal laboratory test suggests a genetic disease or complex metabolic phenotype; an abnormal response to standard therapy for a major underlying condition; significant hypotonia; or persistent seizures. Exclusion criteria included: an infection with normal response to therapy; isolated prematurity; isolated unconjugated hyperbilirubinemia; Hypoxic Ischemic Encephalopathy; confirmed genetic diagnosis explains illness; Isolated Transient Neonatal Tachypnea; or nonviable neonates.[50,]

Interventions
The relevant interventions being considered include:

- rapid WES with trio testing when possible
- rapid WGS with trio testing when possible

Several laboratories offer WES or WGS as a clinical service. Medical centers may also offer rWES or rWGS or standard WES or WGS as a clinical service. The median time for standard WGS is several weeks. The median time-to-result for rWES or rWGS is approximately 5 days or less.

Note that this evidence review does not address the use of WES or WGS for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or for testing of cancer cells.

Comparators
The following practice is currently being used to diagnose a suspected genetic disorder: a standard clinical workup without WES or WGS. A standard clinical workup for an individual with a suspected genetic condition varies by patient phenotype but generally involves a thorough history, physical exam (including dysmorphology and neurodevelopmental assessment, if applicable), routine laboratory testing, and imaging. If the results suggest a specific genetic syndrome, then established diagnostic methods relevant for that syndrome would be used.

Outcomes
Outcomes of interest are as described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder. For critically ill infants, rapid diagnosis is important therefore, in addition to the outcomes described in the previous section, time to diagnosis and time to discharge are also outcomes of interest.

Of course, mortality is a compelling outcome. However, many of the conditions are untreatable and diagnosis of an untreatable condition may lead to earlier transition to palliative care but may not prolong survival.

Study Selection Criteria
For the evaluation of clinical validity of rWES or rWGS, studies that met the following eligibility criteria were considered:

- Reported on the diagnostic yield or performance characteristics such as sensitivity and specificity of rWES or rWGS;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included at least 20 patients.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The use of rWES and rWGS has been studied in critically ill children in several observational studies, both prospective and retrospective, and 1 RCT. Studies are described in Table 11. The RCT is discussed in more detail in the following 'Clinically useful' section. One study included only infants with cardiac defects and had a diagnostic yield of 6% with WGS. The remaining studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60%.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Wu et al (2019)[51.]			3: Results of standard diagnostic methods not discussed		
Elliott et al (2019) [52.]					
Gubbels et al (2019) [53.]			3: Results of standard diagnostic methods not discussed		
Stark et al (2018)[16.]	3. Included highly heterogeneous diseases	3. Proband testing only	3: Results of standard diagnostic methods not discussed		
Meng et al (2017)[54.]		3: Not all patients received rapid testing	3: Chromosomal microarray analysis was completed for 85% but results not discussed		
French et al (2019)[55.]			3: No comparator		
Sanford et al (2019)[56.]			3: No comparator		
Hauser et al (2018)[57.]			3: No comparator		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Farnaes et al (2018)[58]	3. Included highly heterogeneous diseases				
Mestek-Boukhibar et al (2018)[59]	3. Included highly heterogeneous diseases		3: No comparator		
Van Diemen (2018)[60]	3. Included highly heterogeneous diseases		3: Results of standard diagnostic methods not discussed; were available after rWGS		
Willig et al (2015)[61]	3. Included highly heterogeneous diseases		3: Results of standard diagnostic methods not discussed		
Gilissen et al (2014)[42]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
rWGS: rapid whole genome sequencing.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 13. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Wu et al (2019)[51]	1: Criteria for selection unclear					
Elliott et al (2019)[52]	2: Potential enrollees selected by a panel					
Gubbels et al (2019)[53]	2: New ICU admissions were triaged by 1 team and enrollment criteria were applied by a panel					
Stark et al (2018)[16]	2: Eligibility determined by panel; a minimum of 2 clinical geneticists had to agree rWES was appropriate for a					

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
	patient to be enrolled					
Meng et al (2017)[54.]	1,2 Unclear if the patients were randomly or consecutively chosen from those who were eligible					
French et al (2019)[55.]	1,2. Unclear how patients were selected from those eligible					
Sanford et al (2019)[56.]						
Hauser et al (2018)[57.]						
Farnaes et al (2018)[58.]	2: Patients nominated by clinicians					
Mestek-Boukhibar et al (2018)[59.]	2: Eligibility criteria established after first 10 enrolled.					
Van Diemen (2018)[60.]	2: Decision to include a patient was made by a multidisciplinary team					
Willig et al (2015)[61.]	2: Nominated by treated physician, reviewed by panel of experts for inclusion					
Gilissen et al (2014)[42.]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ICU: intensive care unit; rWES: rapid whole exome sequencing. .
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b]Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c]Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Kingsmore et al (2019) reported early results of A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting (NSIGHT2) trial[62]. NSIGHT2 was a randomized, controlled, blinded trial of the effectiveness of rapid whole-genome or -exome sequencing (rWGS or rWES, respectively) in seriously ill infants with diseases of unknown etiology primarily from the NICU, pediatric intensive care unit (PICU), and cardiovascular intensive care unit (CVICU) at a single hospital in San Diego. Details of the study are provided in Table 14 and results are shown in Table 15. Ninety-five infants were randomized to rWES and 94 to rWGS. In addition 24 infants who were gravely ill received ultrarapid whole-genome sequencing (urWGS). The initial Kingsmore et al (2019) publication included only the diagnostic outcomes. Other outcomes are expected in future publications. The registration for the study (NSIGHT2; NCT03211039) indicates that 1000 infants are expected to be enrolled. The Kingsmore et al (2019) publication does not specify whether enrollment is continuing. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). Although the urWGS was not part of the randomized portion of the study, the proportion diagnosed by urWGS was (11 of 24 [46%]) and time to result was a median of 4.6 days. The incremental diagnostic yield of reflexing to trio testing after inconclusive proband analysis was 0.7% (1 of 147).

Petrikin et al (2018) reported on the Prospective Randomized Trial of the Clinical Utility of Rapid Next Generation Sequencing in Acutely Ill Neonates (NSIGHT1; NCT02225522) RCT of rWGS to diagnose suspected genetic disorders in critically ill infants.[50] In brief, NSIGHT1 was an investigator-initiated (funded by the National Human Genome Research Institute and Eunice Kennedy Shriver National Institute of Child Health and Human Development), blinded, and pragmatic trial comparing trio rWGS with standard genetic tests to standard genetic tests alone with a primary outcome of the proportion of NICU/PICU infants receiving a genetic diagnosis within 28 days. Parents of patients and clinicians were unblinded after 10 days and compassionate cross-over to rWGS occurred in 5 control patients. The study was designed to enroll 500 patients in each group but was terminated early due to loss of equipoise on the part of study clinicians who began to regard standard tests alone as inferior to standard tests plus trio rWGS. Intention-to-treat analyses were reported, i.e., crossovers were included in the group to which they were randomized. The trial required confirmatory testing of WGS results, which lengthened the time to rWGS diagnosis by 7–10 days. Study characteristics are shown in Table 14 and results are shown in Table 15.

Table 14. Characteristics of RCTs of Rapid Whole Genome Sequencing in Critically Ill Infants

Study; Trial	Countries	Sites	Dates	Participants	Interventions[1]	
					Active	*Comparator*
Kingsmore et al (2019)[62];NSIGHT2 (NCT03211039)	U.S.	1	2017 to 2018	Acutely ill infants, primarily from the NICU, PICU, and CVICU; age <4 mos; time from admission or time from development of a feature suggestive of a genetic condition of <96 h; excluding infants in whom there was a very low likelihood that a genetic disease diagnosis would change management.	N=94, rWGS initially performed with proband sequences alone; if diagnosis was not made, analysis was performed again, with parental samples	N=95, rWES initially performed with proband sequences alone; if diagnosis was not made, analysis was performed again, with parental samples
Petrikin (2018)[50];NSIGHT1 (NCT02225522)	U.S.	1	2014 to 2016	Infants (<4m) in the NICU/PICU with illnesses of unknown	N=32 rWGS on specimens	N=33 Standard clinical testing for genetic

	etiology and: 1. genetic test order or genetic consult; 2. major structural congenital anomaly or at least 3 minor anomalies; 3. abnormal laboratory test suggesting genetic disease; or 4. abnormal response to standard therapy for a major underlying condition. Primary system involved: CA/musculoskeletal, 35%; Neurological, 25%; Cardiovascular, 17%; Respiratory, 6%	from both biological parents and affected infants simultaneously	disease etiologies was performed in infants based on physician clinical judgment, assisted by subspecialist recommendations

CA: congenital anomalies; CVICU: cardiovascular intensive care unit; NICU: neonatal intensive care unit ; NSIGHT1: Prospective Randomized Trial of the Clinical Utility of Rapid Next Generation Sequencing in Acutely Ill Neonates; NSIGHT2; A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting; PICU: pediatric intensive care unit; RCT: randomized controlled trial; rWES: rapid whole exome sequencing; rWGS: rapid whole genome sequencing.

Table 15. Results of RCTs of Rapid Whole Genome Sequencing in Critically Ill Infants

Study	Diagnostic yield	Time to diagnosis	Age at at discharge	Changes in management	Mortality
Kingsmore et al (2019) [62.] NSIGHT2	Genetic diagnosis, timing unspecified (%)	Proportion of results reported within 7 days (%)			Mortality at 28 days (%)
N	189	189	NR	NR	189
rWGS	20%	11%			3%
rWES	19%	4%			0%
Treatment effect (95% CI)	p=0.88	p=0.10			p=0.25
Petrikin et al (2018)[50.]; NSIGHT1	Genetic diagnosis within 28 days of enrollment (%)	Time (days) to diagnosis from enrollment, median	Age (days) at hospital discharge, mean	Change in management related to test results (%)	Mortality at 180 days (%)
N	65	65	65	65	65
rWGS	31%	13	66.3	41%[1]	13%
Standard testing	3%	107	68.5	24%[1]	12%
Treatment effect (95% CI)	p=0.003	p=0.002	p=0.91	p=0.11	NR

CI: confidence interval; NR: not reported; NSIGHT1: Prospective Randomized Trial of the Clinical Utility of Rapid Next Generation Sequencing in Acutely Ill Neonates;
NSIGHT2; A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting; RCT: randomized controlled trial;
rWES: rapid whole exome sequencing; rWGS: rapid whole genome sequencing.
[1] Includes changes related to positive result (diagnosis); does not include impact of negative test results on management.

Tables 16 and 17 display notable limitations identified in each study.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kingsmore et al (2019) [62.] NSIGHT2				1: Initial publicaion includes only diagnostic outcomes5: No discussion of clinically significant differences	1,2: Follow-up unclear
Petrikin et al (2018)[50.]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Kingsmore et al (2019)[62.]NSIGHT2	3: Allocation concealment not described				1: Power calculations not reported; clinicaltrials.gov listing indicates that 1000 infants were expected but only 189 were reported in the initial report	4 :Only p-values reported; no treatment effects
Petrikin et al (2018)[50.]NSIGHT1		1: Parents/clinicians unblinded at day 10 but analyses were intention-to-treat so crossovers would bias toward null			4: Trial stopped early, power for secondary outcomes will be very low	3, 4: Only p-values reported with no treatment effects or CIs

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4: Target sample size not achieved.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event;

2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Two case series with approximately 100 infants are available to estimate performance characteristics of rWES in the NICU setting.

Studies on rapid WGS report changes in management that would improve health outcomes. The effect of WGS results on health outcomes are the same as those with WES, 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 WGS for critically ill infants.
Section Summary: Rapid Whole Exome or Genome Sequencing in Critically Ill Infants or Children
For critically ill infants, disease may progress rapidly and genetic diagnoses must be made quickly. Results of rWES have been reported in 2 cases including approximately 100 infants and children. Due to the limited data available, diagnostic yield and management changes are not well characterized.

Rapid WGS has increased coverage compared to WES. One RCT comparing trio rWGS with standard genetic tests to diagnose suspected genetic disorders in critically ill infants funded by the National Institutes of Health has been conducted. The study was terminated early due to loss of equipoise on the part of study clinicians who began to regard standard tests alone as inferior to standard tests plus trio rWGS. The rate of genetic diagnosis within 28 days of enrollment was higher for rWGS versus standard tests (31% vs. 3%; p=0.003) and the time to diagnosis was shorter (13 days vs. 107 days; p=0.002). The age at hospital discharge and mortality rates were similar in the 2 groups. However, many of the conditions are untreatable and diagnosis of an untreatable condition may lead to earlier transition to palliative care, but may not prolong survival. A second RCT compared rWGS to rWES in seriously ill infants with diseases of unknown etiology from the NICU, PICU, and CVICU. Only the diagnostic outcomes have currently been reported. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days).. Several retrospective and prospective observational studies with sample sizes ranging from about 20 to more than 275 (in total including more than 450 critically ill infants or children) 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% and reports of changes in management such as avoidance of invasive procedures, medication changes, discontinuation of or additional testing, and initiation of palliative care.

Summary of Evidence
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 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 a 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 an 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 a 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 that the technology results in an improvement in the net health outcome.

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 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. In studies of children with congenital abnormalities and developmental delays of unknown etiology following a standard clinical workup, the yield of WGS has been between 20% and 40%. Additional indirect evidence is available from studies reporting diagnostic yield and change in management results of WES in a similar population. Whole genome sequencing may result in a similar or better diagnostic yield for pathogenic or likely pathogenic variants as compared with WES but few direct comparisons are available. 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 a standard workup 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. Whole genome sequencing 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 that the technology results in an improvement in the net health outcome.

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rWGS or rWES with trio testing when possible, the evidence includes RCTs and case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. One RCT comparing 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 versus 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 NICU , PICU , and CVICU. Only the diagnostic outcomes have currently been reported. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). 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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Medical Genetics and Genomics
In 2012, the American College of Medical Genetics and Genomics (ACMG) recommended that *diagnostic testing* with whole exome sequencing (WES) and whole genome sequencing (WGS) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:[63]

a. "The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
b. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
c. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
d. A fetus 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."

ACMG has recommended that for *screening* purposes:
WGS/WES may be considered in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.

ACMG has also recommended that WGS and WES not be used at this time as an approach to prenatal screening or as a first-tier approach for newborn screening.

In 2014, ACMG guidelines on the clinical evaluation and etiologic diagnosis of hearing loss stated that for individuals with findings suggestive of a syndromic genetic etiology for hearing loss, "pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing, if available, should be ordered to confirm the diagnosis—this testing may include single-gene tests, hearing loss sequencing panels, WES, WGS, chromosome analysis, or microarray-based copy number analysis, depending on clinical findings."[64]

In 2016, ACMG updated its recommendations on reporting incidental findings in WGS and WES testing.[65] ACMG determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum

list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician. The 2016 update added 4 genes and removed 1 gene resulting in an updated secondary findings minimum list including 59 medically actionable genes recommended for return in clinical genomic sequencing.

American Academy of Neurology et al

In 2014, the American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine issued evidence-based guidelines on the diagnosis and treatment of limb-girdle and distal dystrophies, which made the following recommendations (Table 18).[66,]

Table 18. Guidelines on Limb-Girdle Muscular Dystrophy

Recommendation	LOE
Diagnosis	
• For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement).	B
• In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality.	C
Management of cardiac complications	
• Clinicians should refer newly diagnosed patients with (1) limb-girdle muscular dystrophy (LGMD)1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, … or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including electrocardiogram (ECG) and structural evaluation (echocardiography or cardiac magnetic resonance imaging [MRI]), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management.	B
• If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management.	B
• Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.	B
• It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms.	B
Management of pulmonary complications	
• Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course.	B
• In patients with a known high risk of respiratory failure (e.g., those with LGMD2I …), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency.	B
• It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.	C
• Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life.	B

LOE: level of evidence; LGMD: limb-girdle muscular dystrophy.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03211039	Prenatal Precision Medicine (NSIGHT2): A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting	1000	Aug 2019
NCT02699190	LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies	450	Aug 202 1
NCT02422511	Genomic Sequencing for Childhood Risk and Newborn Illness (The BabySeq Project)	1440	Apr 2020
NCT03525431	Genomic Sequencing to Aid Diagnosis in Pediatric and Prenatal Practice: Examining Clinical Utility, Ethical Implications, Payer Coverage, and Data Integration in a Diverse Population	800	May 2021
NCT03548779	North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2	1700	May 2021
NCT03918707	Utility of Rapid Whole Genome Sequencing in the NICU: A Pilot Study	115	Jan 2022
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	213	Aug 2022
NCT04170985	NeuroSeq: A Prospective Trial to Evaluate the Diagnostic Yield of Human Whole Genome Sequencing (WGS) Compared to Standard of Care in Adults With Suspected Genetic Neurological Disorders	100	Jun 2022
NCT04154891	Genome Sequencing Strategies for Genetics Diagnosis of Patients With Intellectual Disability (DEFIDIAG)	3825	Mar 2023
NCT03632239	The Genomic Ascertainment Cohort (TGAC)	1000	Dec 2028
NCT03385876	Rapid Whole Genome Sequencing (rWGS): Rapid Genomic Sequencing for Acutely Ill Patients and the Collection, Storage, Analysis, and Distribution of Biological Samples, Genomic and Clinical Data	100000	Dec 2050
Unpublished			
NCT02380729	Mutation Exploration in Non-acquired, Genetic Disorders and Its Impact on Health Economy and Life Quality	200	Dec 2017 (completed)
NCT02826694	North Carolina Newborn Exome Sequencing for Universal Screening	400	Jun 2019
NCT03290469	NICUSeq: A Prospective Trial to Evaluate the Clinical Utility of Human Whole Genome Sequencing (WGS) Compared to Standard of Care in Acute Care Neonates and Infants	355	Jan 2020
NCT03829176	Investigating the Feasibility and Implementation of Whole Genome Sequencing in Patients With Suspected Genetic Disorder	200	Oct 2020

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation for standard whole exome or whole genome testing:

- History and physical and/or consultation notes including:
  - Type of test and reason for test including why a genetic cause for problems is considered to be likely
  - Family history and phenotype
  - Any invasive procedures that could be avoided by whole exome or genome testing
- Previous lab results pertaining to genetic testing, including CMA (chromosomal microarray)

Post Service (in addition to the above, please include the following):

- Laboratory report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0036U	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
	0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
	0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood

Type	Code	Description
		or saliva, identification and categorization of genetic variants, proband ***(Code effective 10/1/2020)***
	0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling) ***(Code effective 10/1/2020)***
	0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband ***(Code effective 10/1/2020)***
	0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling) ***(Code effective 10/1/2020)***
	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) (List separately in addition to code for primary procedure
	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) (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)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/30/2015	BCBSA Medical Policy adoption
08/01/2016	Policy revision without position change
03/01/2017	Policy revision with position change
12/01/2017	Policy revision without position change
05/01/2018	Coding update
12/01/2018	Policy revision without position change
07/01/2019	Policy revision with position change

Effective Date	Action
	Coding Update
06/01/2020	Administrative update. Policy statement and guidelines updated.
07/01/2020	Annual review. Policy statement, guidelines and literature updated. Coding update.
11/01/2020	Administrative update. Policy statement updated.
12/01/2020	Coding update.
05/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders 2.04.102 **Policy Statement:** A standard whole exome sequencing (WES), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. Testing is for the evaluation of unexplained congenital or neurodevelopmental disorder in children when **all** of the following criteria are met: A. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, and **all** of the following: 1. Evaluation includes at least a family history and phenotype description 2. Patient and family (if applicable) have been counseled about the potential risks of genetic testing II. Previous genetic testing (e.g., chromosomal microarray analysis [CMA] and/or targeted single-gene testing) has failed to yield a diagnosis III. Documentation of **one or more** of the following: A. A genetic etiology is considered the most likely explanation for the phenotype B. The affected individual is faced with invasive procedures or testing (e.g., muscle biopsy) as the next diagnostic step Rapid whole exome or rapid whole genome sequencing (rWES or rWGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. For the evaluation of critically ill infants or children less than 18 years of age II. Hospitalized in neonatal or pediatric intensive care with illness of unknown etiology III. Documentation that supports **both** of the following: A. At least **one** of the following:	**Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders 2.04.102** **Policy Statement:** A standard whole exome sequencing (WES), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. Testing is for the evaluation of unexplained congenital or neurodevelopmental disorder in children when **all** of the following criteria are met: A. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, and **all** of the following: 1. Evaluation includes at least a family history and phenotype description 2. Patient and family (if applicable) have been counseled about the potential risks of genetic testing II. Previous genetic testing (e.g., chromosomal microarray analysis [CMA] and/or targeted single-gene testing) has failed to yield a diagnosis III. Documentation of **one or more** of the following: A. A genetic etiology is considered the most likely explanation for the phenotype B. The affected individual is faced with invasive procedures or testing (e.g., muscle biopsy) as the next diagnostic step Rapid whole exome or rapid whole genome sequencing (rWES or rWGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. For the evaluation of critically ill infants or children less than 18 years of age II. Hospitalized in neonatal or pediatric intensive care with illness of unknown etiology III. Documentation that supports **both** of the following: A. At least **one** of the following:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
1. Multiple congenital anomalies 2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: a. Choanal atresia b. Coloboma c. Hirschsprung disease d. Meconium ileus 3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: a. Abnormal newborn screen b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis c. Hyperammonemia d. Lactic acidosis not due to poor perfusion e. Refractory or severe hypoglycemia 4. An abnormal response to standard therapy for a major underlying condition 5. Significant hypotonia 6. Persistent seizures 7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: a. Recurrent events without respiratory infection b. Recurrent witnessed seizure like events c. Required Cardiopulmonary Resuscitation (CPR) d. 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 e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease f. Family history of **one or more** of the following: i. Arrhythmia	1. Multiple congenital anomalies 2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: a. Choanal atresia b. Coloboma c. Hirschsprung disease d. Meconium ileus 3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: a. Abnormal newborn screen b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis c. Hyperammonemia d. Lactic acidosis not due to poor perfusion e. Refractory or severe hypoglycemia 4. An abnormal response to standard therapy for a major underlying condition 5. Significant hypotonia 6. Persistent seizures 7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: a. Recurrent events without respiratory infection b. Recurrent witnessed seizure like events c. Required Cardiopulmonary Resuscitation (CPR) d. 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 e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease f. Family history of **one or more** of the following: i. Arrhythmia

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
ii. BRUE in sibling iii. Developmental delay iv. Inborn error of metabolism or genetic disease v. Long QT syndrome (LQTS) vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant B. **All** of the following have been excluded a reason for admission: 1. An infection with normal response to therapy 2. Confirmed genetic diagnosis explains illness 3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event 4. Isolated prematurity 5. Isolated Transient Tachypnea of the Newborn (TTN) 6. Isolated unconjugated hyperbilirubinemia 7. Nonviable neonates Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **all** of the following are met: I. Performed at the same time as rWES or later II. The results of the rWES are insufficient to explain the clinical presentation Rapid whole exome sequencing and rapid whole genome sequencing (rWES and rWGS) is considered **investigational** for the diagnosis of genetic disorders in all other situations. Standard whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations. Standard and rapid whole exome sequencing (WES and rWES) and standard and rapid whole genome sequencing (WGS and rWGS)are considered **investigational** when screening for genetic disorders.	ii. BRUE in sibling iii. Developmental delay iv. Inborn error of metabolism or genetic disease v. Long QT syndrome (LQTS) vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant B. **All** of the following have been excluded a reason for admission: 1. An infection with normal response to therapy 2. Confirmed genetic diagnosis explains illness 3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event 4. Isolated prematurity 5. Isolated Transient Tachypnea of the Newborn (TTN) 6. Isolated unconjugated hyperbilirubinemia 7. Nonviable neonates Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **all** of the following are met: I. Performed at the same time as rWES or later II. The results of the rWES are insufficient to explain the clinical presentation Rapid whole exome sequencing and rapid whole genome sequencing (rWES and rWGS) is considered **investigational** for the diagnosis of genetic disorders in all other situations. Standard whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations. Standard and rapid whole exome sequencing (WES and rWES) and standard and rapid whole genome sequencing (WGS and rWGS)are considered **investigational** when screening for genetic disorders.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Standard whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders. Separate CMA testing is considered **not medically necessary** with rWGS analysis.	Standard whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders. Separate CMA testing is considered **not medically necessary** with rWGS analysis.