BlueCross BlueShield of Alabama

Name of Policy:

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy #: 539
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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.

Whole Exome Sequencing and Whole Genome Sequencing

Whole exome sequencing (WES) is targeted next generation sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing (NGS) techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients, particularly children, 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, proposed are several potential positive health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

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

WES and WGS Technology

WES or WGS using NGS technology has been proposed to facilitate obtaining a genetic diagnosis in patients more efficiently. WES is limited to most of the protein-coding sequence of an individual (≈85%), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing mutations. 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: 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 greater ability to detect large deletions or duplications in protein-coding regions compared to WES, but such testing requires greater data analytics.

Technical aspects of WES and WGS are evolving, including databases such as the National Institutes of Health's ClinVar database (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 develop standard terminology for describing sequence variants. Guidelines developed by this workgroup, published in 2015, describe criteria for classifying pathogenic and benign sequence variants based on types of data into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

WES and WGS Testing Services

Several laboratories offer WES and WGS as a clinical service. Illumina offers three TruGenome tests: the TruGenome Undiagnosed Disease Test (indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology), TruGenome Predisposition Screen (indicated for healthy patients interested in learning about their carrier status and genetic predisposition toward adult-onset conditions), and the TruGenome Technical Sequence Data (WGS for labs and physicians who will make their own clinical interpretations). Ambry Genetics offers two WGS tests, the ExomeNext and ExomeNext-*Rapid*, which sequence both the nuclear and the mitochondrial genomes. GeneDx offers WES with its XomeDx™ test. Medical centers may also offer WES and WGS as a clinical service.

Examples of laboratories offering WES as a clinical service and their indications for testing are summarized in Table 1.

Table 1. Examples of Laboratories Offering Whole Exome Sequencing as a Clinical Service

Laboratory	Laboratory Indications for Testing
Ambry Genetics (Aliso Viejo, CA)	"The patient's clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis."
GeneDx (Gaithersburg, MD)	"a patient with a diagnosis that suggests the involvement of one or more of many different genes, which would, if even available and sequenced individually, be prohibitively expensive"
Baylor College of Medicine (Houston, TX)	"used when a patient's medical history and physical exam findings strongly suggest that there is an underlying genetic etiology. In some cases, the patient may have had an extensive evaluation consisting of multiple genetic tests, without identifying an etiology."
Illumina (San Diego, CA)	The TruGenome Undiagnosed Disease Test is indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology.
University of California Los Angeles Health System	"This test is intended for use in conjunction with the clinical presentation and other markers of disease progression for the management of patients with rare genetic disorders."
EdgeBio (Gaithersburg, MD)	Recommended "In situations where there has been a diagnostic failure with no discernible path. In situations where there are currently no available tests to determine the status of a potential genetic disease. In situations with atypical findings indicative of multiple disease[s]."
Children's Mercy Hospitals and Clinics (Kansas City, MO)	Provided as a service to families with children who have had an extensive negative workup for a genetic disease; also used to identify novel disease genes.
Emory Genetics Laboratory (Atlanta, GA)	"Indicated when there is a suspicion of a genetic etiology contributing to the proband's manifestations."

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

Policy:

Whole exome sequencing (WES) and whole genome sequencing (WGS) do not meet Blue Cross and Blue Shield of Alabama's medical criteria and are considered **investigational** for all indications**.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review covers the period through August 6, 2018.

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.

Whole Exome Sequencing in Patients with Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Clinical Context and Test Purpose

The purpose of whole exome sequencing (WES) in patients who have multiple unexplained congenital anomalies or a neurodevelopmental disorder 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 WES improve health outcomes when used for the diagnosis of patients with multiple unexplained congenital anomalies or a neurodevelopmental disorder?

The following PICOTS were used to select literature to inform this review.

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

Intervention
The relevant intervention of interest is WES.

Comparators
The relevant comparator of interest is standard clinical workup without WES.

Outcomes
The general outcomes of interest are the accuracy of next-generation sequencing (NGS) compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and improvement in health outcomes. Health outcomes include a 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.

Timing
The timing of the diagnostic accuracy outcomes of interest is time to diagnosis.

Setting
These tests are offered commercially through various manufacturers.

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.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 (see Table 2). Typically, the populations included in these studies have suspected rare genetic disorders, although the specific patient 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 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 select infants with multiple congenital abnormalities and dysmorphic features, diagnostic yield rose to 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.

Table 2. Studies Reporting Diagnostic Yield for Congenital Anomalies or Neurodevelopmental Disorders

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
Wright et al (2018)	Children with severe undiagnosed NDDs and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral	1133	Consecutive family trios from U.K.-wide patient recruitment network	454 (40)	Reanalysis of existing data from earlier Wright (2015) publication from DDD study using improved variant

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
	phenotypes				calling methodologies, novel variant detection algorithms, updated variant annotation, evidence-based filtering strategies, and newly discovered disease associated genes
Nambot et al (2018)	Children with congenital anomalies and intellectual disability with negative prior diagnostic workup	461	Consecutive cases meeting criteria referred to specialty clinic in France	31%	Initial yield in year 1: 22%, reanalysis led to increase yield
Tsuchida et al (2018)	Children with epilepsy (≈63% with early-onset epileptic encephalopathies) with no causative SNV in known epilepsyassociated genes	168	Consecutive unsolved cases referred to a single center	18 (11)	Performed WES with CNV detection tools
Evers et al (2017)	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)	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 standard diagnostic workup[b]
Nolan and Carlson (2016)	Children with unexplained neurodevelopmental disorders	50	Pediatric neurology clinic	41 (48%)	Changed medication, systemic investigation, and family planning

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
Allen et al (2016)	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)	Infants (≤2 y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features	80	Prospective comparative study at tertiary center	46 (58%)	First-line WES increased yield by 44%, changed clinical management and family planning
Tarailo-Graovac et al (2016)	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)	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)
Wright et al (2015)	Children with severe undiagnosed NDDs and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral phenotypes	1133	Consecutive family trios from U.K.-wide patient recruitment network	311 (27)	Part of the DDD study
Yang et al (2014)	Suspected genetic disorder (88% neurologic or developmental)	2000 (45% <5 y; 42% 5-18 y; 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)	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)	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)	Children with unexplained neurodevelopmental disorders	119 (100 families)	Single-center database	53 (45%)	Change in clinical care or impression in 49% of families
Srivastava et al (2014)	Children with unexplained neurodevelopmental disorders	78	Pediatric neurogenetics clinic	32 (41%)	Changed medical management, prognostication, and family

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
					planning
Yang et al (2013)	Suspected genetic disorder (80% neurologic)	250 (1% fetus; 50% <5 y;38% 5-18 y; 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: variants 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 the 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 heterogeneity of disorders, rarity, and outcome importance that may differ according to identified pathogenic variants. Actionable items following testing in the reviewed studies (see 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 (eg, by including parent testing), future reproductive decisions could be affected. The early use of WES is proposed to reduce the time to

diagnosis and to reduce the financial and psychological burdens associated with prolonged investigation.

Section Summary: Whole Exome Sequencing in Patients with Multiple Congenital Anomalies or a Neurodevelopmental Disorder

The evidence on WES in patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology 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 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.

WES in Patients with a Suspected Genetic Disorder Other than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Clinical Context and Test Purpose

Most of the literature on WES and WGS is on neurodevelopmental disorders in children, however, other potential indications for WES and WGS have been reported (see Table 3). These include limb-girdle muscular dystrophy (LGMD), inherited retinal disease, and other disorders including mitochondrial, endocrine, and immunologic disorders. The yield for unexplained LGMD and retinal disease is high, but a limited number of patients have been studied to date.

The purpose of WES in patients who have a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder 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 above.

The question addressed in this evidence review is: Does WES improve health outcomes when used for the diagnosis of a suspected genetic condition?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients 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 standard clinical workup.

Intervention

The relevant intervention of interest is WES.

Comparators

The relevant comparator of interest is standard clinical workup without WES.

Outcomes
The general outcomes of interest are the accuracy of NGS compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and clinical health outcomes. Health outcomes include a 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.

Timing
The test is performed when standard clinical workup has failed to arrive at a diagnosis.

Setting
These tests are offered commercially through various manufacturers.

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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 (see Table 3). Some studies used a virtual gene panel that is restricted to genes that are associated with the phenotype, while others have examined the whole exome, either initially or sequentially. A proposed 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. WES has also been reported to be beneficial in patients with atypical presentations.

Table 3. Diagnostic Yields of WES for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Actions
Hauer et al (2018)	Short stature in whom common	200 (mostly	Randomly selected	33 (17)	--Standard diagnostic

	nongenetic causes had been excluded	children)	from a consecutive series of patients referred for workup; trio testing performed		approach yield: 13.6% in original cohort of 565 --WES results had possible impact on treatment or additional preventive measurements in 31 (16%) families
Rossi et al (2017)	Patients with autism spectrum disorder diagnosis or autistic features referred for WES	163	Selected from 1200 consecutive retrospective samples from commercial lab	42 (26)	--66% of patients already had a clinician-reported autism diagnosis --VUS in 12%
Walsh et al (2017)	Peripheral neuropathy in patients ranging from 2-68 y	• 23 children 27 adults	Research study at tertiary pediatric and adult centers	19 (38)	Initial targeted analysis with virtual gene panel, followed by WES
Miller et al (2017)	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)	Adults (overlap of 272 patients reported by Yang et al, 2014), includes neurodevelopmental and other phenotypes	486 (53% 18-30 y; 47% >30 y)	Review of lab findings of WES in adults	85 (18%)	Yield in patients 18-30 y (24%) vs those >30 y (10.4%)
Ghaoui et al (2015)	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)	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)	Suspected mitochondrial disorder	109	WES in patients referred to a single center	42 (39%)	57% yield in patients with high suspicion of mitochondrial disorder
Neveling et al (2013)	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

WES: whole exome sequencing; VUS: variant of uncertain significance. [a] Included both WES and whole genome sequencing.

The purpose of the gaps tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 4. Relevance Gaps for Studies Assessing WES for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Hauer et al (2018)				1. VUS not reported	
Rossi et al (2017)	4. Most patients had a clinical diagnosis; only 33% had testing for specific ASD genes before WES				
Walsh et al (2017)		3. Proband testing only		1. VUS not reported	
Miller et al (2017)				1. VUS not reported	
Posey et al (2016)	3. Included highly heterogeneous diseases	3. Proband testing only		1. VUS not reported	
Ghaoui et al (2015)				1. VUS not reported	
Valencia et al (2015)	3. Included highly heterogeneous diseases	2. Unclear whether WES performed on Parents			
Wortmann et al (2015)		3. Proband testing only		1. VUS not reported	
Neveling et al (2013	3. Included highly heterogeneous diseases	3. Proband testing only		1. VUS not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. ASD: autism spectrum disorder; VUS: variants of uncertain significance; 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 5. Study Design and Conduct Gaps for Studies Assessing WES for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Hauer et al (2018)					1. No description of indeterminate samples	
Rossi et al (2017)					1. No description of indeterminate samples	
Walsh et al (2017)						
Miller et al (2017)	2. Selection not random or consecutive				1. No description of indeterminate samples	
Posey et al (2016)					1. No description of indeterminate samples	
Ghaoui et al (2015)					1. No description of indeterminate samples	
Valencia et al (2015)						
Wortmann et al	1,2. Unclear how patients were selected from those eligible				1. No description of indeterminate samples	
Neveling et al (2013)	1,2. Unclear how patients were selected from those referred				1. No description of indeterminate samples	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
WES: 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 to 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 including 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: WES in Patients with a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder
There are increasing reports of WES being used 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. One concern with WES is the possibility of incidental findings. Some studies report on the use of a virtual gene panel with restricted analysis of disease-associated genes, and the authors noted that WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients that have been studied for any specific disorder, and study of WES in these disorders is at an early stage.

Whole Genome Sequencing in Patients with a Suspected Genetic Disorder
The purpose of whole genome sequencing (WGS) in patients who have a suspected genetic disorder 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 as above.

The question addressed in this evidence review is: Does WGS improve health outcomes when used for the diagnosis of a suspected genetic disorder?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients presenting with any of a variety of disorders and anomalies that are suspected to have a genetic basis but are not explained by standard clinical workup.

Intervention
The relevant intervention of interest is WGS.

Comparators
The relevant comparator of interest is standard clinical workup without WGS.

Outcomes
As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

Timing
As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

Setting
WGS tests are offered commercially through various manufacturers.

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility

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. In some studies the genes examined were those that had previously been associated with the phenotype, while other studies were research-based and conducted more exploratory analysis (see Table 6). It has been noted that genomes that have been sequenced with WGS are available for future review when new variants associated with clinical diseases are discovered.

Table 6. Diagnostic Yields with WGS

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Actions
Lionel et al (2017)	Well-characterized but genetically heterogeneous cohort that had undergone targeted gene sequencing	103	Trio test for patients recruited from pediatric nongenetic subspecialists	42 (41)	Compared with a yield of 24% with standard diagnostic testing and a 25% increase in yield from WES
Hauser et al (2018)	Neonatal and pediatric patients born with a cardiac defect in whom the suspected genetic disorder had not been found using conventional genetic methods	34	Trio testing for patients recruited from the NICU, PICU, or general inpatient pediatric ward of a single center	2 (6)	VUS in 10 (26%)
Carss et al (2017)	Unexplained inherited retinal disease	605	NIHR-BioResource Rare Diseases Consortium	331 (55)	Compared with a detection rate of 50% with WES (n=117)
Ellingford et al (2016)	Unexplained inherited retinal disease	46	WGS in patients referred to a single center	24 (52)	Estimated 29% increase in yield vs NGS
Taylor et al (2015)	Broad spectrum of suspected genetic disorders	217	Multicenter series	46 (21)	34% yield in Mendelian disorders; 57% yield in trios
Gilissen et al (2014)	Children with severe intellectual disability who did not have a diagnosis after extensive genetic testing that included exome sequencing	50	Trio testing including unaffected parents	201 (42)	Of 21 with positive diagnosis, 20 had de novo variants

NGS: next-generation sequencing; NIHR: National Institute for Health Research; NICU: neonatal intensive care unit; PICU: pediatric intensive care unit; VUS: variant of uncertain significance; WGS: whole genome sequencing; WES: whole exome sequencing

Tables 7 and 8 display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 7. Relevance Gaps for Studies of WGS

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lionel et al (2018)	1,2. Unclear how patients were selected from those eligible	3. Proband testing Only			
Hauser et al (2018)					
Carss et al (2017)	4. 25% had no prescreening			1. VUS not reported	

	performed			
Ellingford et al (2016)		3. Proband testing Only		
Taylor et al (2015)	3. Included highly heterogeneous diseases			1. VUS not reported
Gilissen et al (2014)				1. VUS not reported

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. VUS: variant of uncertain significance; 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 8. Study Design and Conduct Gaps for Studies of WGS

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Lionel et al (2018)						
Hauser et al (2018)						
Carss et al (2017)					1. No description of indeterminate findings	
Ellingford et al (2016)						
Taylor et al (2015)					1. No description of indeterminate findings	
Gilissen et al (2014)					1. No description of indeterminate findings	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. VUS: WGS: whole genome sequencing.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., 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 to 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 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.

The effect of WGS results on health outcomes are the same as those with WES, with a possible change in surveillance, management, and/or reproductive planning. A reduction in invasive testing and an end of the diagnostic odyssey are also considered to be significant health outcomes.

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

Section Summary: Whole Exome Sequencing in Patients with a Suspected Genetic Disorder
WGS has increased coverage and diagnostic yield compared with WES, but the technology is limited by the amount of data generated and greater need for storage and analytic capability. Several authors have proposed that, as WGS becomes feasible on a larger scale, it may in the future become the standard first-tier diagnostic test.

Summary of Evidence
For individuals who have multiple unexplained congenital anomalies or a neurodevelopmental phenotype who receive whole exome sequencing (WES), the evidence includes large case series and a within-subject comparison. 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 the specific genetic alteration is unclear or unidentified by standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. However, analytic validity concerns give pause to consider if WES testing may further add to an already precarious diagnostic odyssey. There is no reference standard available for determining

diagnostic yield thresholds. Depending on the platform and variant call method used, WES may not accurately detect large insertions and deletions, large copy number variants (CNVs), and structural chromosome rearrangements due to the short sequence read lengths. WES may be less sensitive for the detection of CNVs than high-resolution microarray testing. Therefore at this time, the evidence is considered to remain insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder who receive WES, the evidence includes small case series and prospective research studies. The 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%. One concern with WES is the possibility of incidental findings. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a suspected genetic disorder who receive whole genome sequencing (WGS), the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. WGS has increased coverage and diagnostic yield compared with WES, but the technology is limited by the amount of data generated and greater need for storage and analytic capability. Several authors have proposed that as WGS becomes feasible on a larger scale, it may in the future become the standard first-tier diagnostic test. At present, there is limited data on the clinical use of WGS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG) states that diagnostic testing with WES (and whole genome sequencing [WGS]) should be considered In the clinical diagnostic assessment of a phenotypically affected individual when:

"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 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/WES should not be used at this time as an approach to prenatal screening, or as a first-tier approach for newborn screening.

The ACMG guidelines (2014) 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."

In 2016, ACMG updated its recommendations for reporting incidental findings in whole genome and whole exome sequencing. A working group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing and recommended 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 of 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 evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies, which made the following recommendations (see Table 9).

Table 9. Guidelines on LGMD

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	B

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.	
• 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.

Key Words:

Clinical diagnostic exome, Healthy exome sequencing, EmExone, ExomeNext, ExomeNext-Rapid, TruGenome, TruGenome Predisposition Screen, TruGenome Technical Sequence Data, TruGenome Undiagnosed Disease Test, Whole exome sequencing, WES, whole genome sequencing, WGS, XomeDx Plus, XomeDx Slice

Approved by Governing Bodies:

Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Whole exome or genome sequencing tests as a clinical service are available under the auspices of the Clinical Laboratory Improvement Amendments. The laboratory offering the service must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81417	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	sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81427	re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
0010U	Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate **(Effective 08/01/17)**
0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gen rearrangement(s) **(Effective 08/01/17)**
0036U	Exome (i.e. somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses **(Effective 04/01/2018)**

Previous Coding:

Prior to 2015, there are no specific CPT codes for whole exome sequencing. It would likely be reported with **81400-81408** or the unlisted molecular pathology code **81479**.

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Policy History:

Medical Policy Panel, August 2013
Medical Policy Group, October 2013 **(1):** New policy
Medical Policy Administration Committee, October 2013
Available for comment October 4 through November 18, 2013
Medical Policy Panel, September 2014 and November 2014

Medical Policy Group November 2014 **(1):** 2015 Annual Coding update and update to Policy to include whole genome sequencing. Update to Description, Key Points, and References. CPT codes **81415-81417** and **81425-81427** added, effective 01/01/15.
Available for comment November 28 through January 11, 2015
Medical Policy Panel, October 2015
Medical Policy Group, October 2015 **(3)**: 2015 Updates to Description, Key Points, Key Words & References; no change in policy statement
Medical Policy Panel, November 2016
Medical Policy Group, November 2016 **(3)**: 2016 Updates to Description, Key Points, & References; no change in intent of policy statement – WGS and WES testing remain investigational – added abbreviations to statement for clarity
Medical Policy Group, July 2017: Ad hoc coding update. Added new CPT codes 0010U and 0012U to the Current Coding section
Medical Policy Panel, October 2017
Medical Policy Group, December 2017 **(3)**: 2017 Updates to Description, Key Points & References; no changes in policy statement
Medical Policy Group, March 2018: Quarterly Coding Update, April 2018. Added new CPT code 0036U to Current Coding
Medical Policy Panel, October 2018
Medical Policy Group, October 2018 **(9)**: 2018 Updates to Description, Key Points, References. No change in policy statement.
