# Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

**Original Policy Date:** January 30, 2015  
**Effective Date:** May 1, 2018  
**Section:** 2.0 Medicine  
**Page:** Page 1 of 19

## Policy Statement

Whole exome sequencing (WES) may be considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorder in children when all of the following criteria are met:

- The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing
- There is potential for a change in management and clinical outcome for the individual being tested
- **One** of the following:
  - A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (e.g., chromosomal microarray analysis and/or targeted single-gene testing)
  - When previous genetic testing has failed to yield a diagnosis, and the affected individual is faced with invasive procedures or testing as the next diagnostic step (e.g., muscle biopsy)

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

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

Whole exome sequencing and whole genome sequencing are considered **investigational** for screening for genetic disorders.

## Policy Guidelines

The policy statement is 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.

**Trio Testing**

Testing of the child and both parents can increase the chance of finding a definitive diagnosis.

**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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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:

- **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 that have not been 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 Epilepsy
- Genetic Testing for Facioscapulohumeral Muscular Dystrophy
- Genetic Testing for Limb-Girdle Muscular Dystrophies
- Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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. Whole exome or genome sequencing tests as a clinical service are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration 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 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 techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

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

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process.
WES and WGS Technology
WES or WGS using next-generation sequencing 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 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 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 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 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 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.2

WES and WGS Testing Services
Several laboratories offer WES and WGS as a clinical service. Illumina offers 3 TruGenome tests: the TruGenome Undiagnosed Disease Test (indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology), the 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 2 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>
<thead>
<tr>
<th>Laboratory (Location)</th>
<th>Laboratory Indications for Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambry Genetics (Aliso Viejo, CA)</td>
<td>“The patient’s clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis.”</td>
</tr>
<tr>
<td>GeneDx (Gaithersburg, MD)</td>
<td>“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.”</td>
</tr>
<tr>
<td>Baylor College of Medicine (Houston, TX)</td>
<td>“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.”</td>
</tr>
<tr>
<td>Illumina (San Diego, CA)</td>
<td>The TruGenome Undiagnosed Disease Test is indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology.</td>
</tr>
</tbody>
</table>
Laboratory Indications for Testing

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of California Los Angeles Health System</td>
<td>“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.”</td>
</tr>
<tr>
<td>EdgeBio (Gaithersburg, MD)</td>
<td>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].”</td>
</tr>
<tr>
<td>Children’s Mercy Hospitals and Clinics (Kansas City, MO)</td>
<td>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.</td>
</tr>
<tr>
<td>Emory Genetics Laboratory (Atlanta, GA)</td>
<td>“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”</td>
</tr>
</tbody>
</table>

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.

**Literature Review**

This review was informed in part by a 2013 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Special Report on exome sequencing for patients with suspected genetic disorders.3

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

**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
These tests are performed when standard clinical workup has failed to arrive at a diagnosis.

Setting
These tests are offered commercially through various manufacturers.

Analytic Validity
There are relatively few data specific to the analytic validity of WES. NGS techniques used for WES are expected to have high accuracy for mutation detection. However, NGS platforms differ regarding the depth of sequence coverage, methods for base calling and read alignment, and other factors. These factors contribute to potential variability across the platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service. The American College of Medical Genetics and Genomics has clinical laboratory standards for NGS, including WES.\(^4\) The guidelines outline the documentation of test performance measures that should be evaluated for NGS platforms, and note that typical definitions of analytic sensitivity and specificity do not apply for NGS.

Depending on the platform and variant call method used, WES may not accurately detect large insertions and deletions, large copy number variants, and structural chromosome rearrangements due to the short sequence read lengths.\(^4\) WES may be less sensitive for the detection of copy number variants than high-resolution microarray testing.\(^5\) NGS also has poorer coverage for A/T-rich, G/C-rich, and pseudogene regions, as well as homopolymer stretches.\(^6,7\)

Clinical Validity
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 populations vary.

Series have been reported with as many as 2000 patients. The largest 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 as many as 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.8

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 the 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 (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.

Table 2. Diagnostic Yields of WES for Congenital Anomalies or a Neurodevelopmental Disorder

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2013)9</td>
<td>Suspected genetic disorder (80% neurologic)</td>
<td>250 (1% fetus; 50% &lt;5 y; 38% 5-18 y; 11% adults)</td>
<td>Consecutive patients at single center</td>
<td>62 (25)</td>
<td>Identification of atypical phenotypes of known genetic diseases and blended phenotypes</td>
</tr>
<tr>
<td>Yang et al (2014)10</td>
<td>Suspected genetic disorder (88% neurologic or developmental)</td>
<td>2000 (45% &lt;5 y; 42% 5-18 y; 12% adults)</td>
<td>Consecutive patients at single center</td>
<td>504 (25)</td>
<td>Identification of novel variants. End of the diagnostic odyssey and change in management</td>
</tr>
<tr>
<td>Lee et al (2014)11</td>
<td>Suspected rare Mendelian disorders (57% of children had developmental delay; 26% of adults had ataxia)</td>
<td>814 (49% &lt;5 y; 15% 5-18 y; 36% adults)</td>
<td>Consecutive patients at single center</td>
<td>213 (26)</td>
<td>Trio (31% yield) vs proband only (22% yield)</td>
</tr>
</tbody>
</table>
### 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 is on neurodevelopmental disorders in children; however, other potential indications for WES have been reported (see Table 3). These include limb-girdle muscular dystrophy, inherited retinal disease, and other disorders including mitochondrial, 

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soden et al (2014)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>119 (100 families)</td>
<td>Single-center database</td>
<td>53 (45)</td>
<td>Change in clinical care or impression in 49% of families</td>
</tr>
<tr>
<td>Srivastava et al (2014)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>78</td>
<td>Pediatric neurogenetics clinic</td>
<td>32 (41)</td>
<td>Changed medical management, prognostication, and family planning</td>
</tr>
<tr>
<td>Farwell et al (2015)</td>
<td>Unexplained neurologic disorders (65% pediatric)</td>
<td>500</td>
<td>WES laboratory</td>
<td>152 (30)</td>
<td>Trio (37.5% yield) vs proband only (20.6% yield); 31 (7.5% de novo)</td>
</tr>
<tr>
<td>Nolan and Carlson (2016)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>50</td>
<td>Pediatric neurology clinic</td>
<td>41 (48)</td>
<td>Changed medication, systemic investigation, and family planning</td>
</tr>
<tr>
<td>Allen et al (2016)</td>
<td>Patients with unexplained early-onset epileptic encephalopathy</td>
<td>50 (95% &lt;1 y)</td>
<td>Single center</td>
<td>11 (22)</td>
<td>2 VUS for follow-up, 11 variants identified as de novo</td>
</tr>
<tr>
<td>Stark et al (2016)</td>
<td>Infants (≤2 y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features</td>
<td>80</td>
<td>Prospective comparative study at a tertiary center</td>
<td>46 (58)</td>
<td>First-line WES increased yield by 44%, changed clinical management and family planning</td>
</tr>
<tr>
<td>Vissers et al (2017)</td>
<td>Children with complex neurologic disorders of suspected genetic origin</td>
<td>150</td>
<td>Prospective comparative study at a tertiary center</td>
<td>• 44 (29) conclusive • 41 (27) possible</td>
<td>First-line WES had 29% yield vs 7% yield for standard diagnostic workup</td>
</tr>
</tbody>
</table>

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.
endocrine, and immunologic disorders. The yield for unexplained limb-girdle muscular dystrophy 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.

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

**Clinical Validity**
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. 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. 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. 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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neveling et al (2013)</td>
<td>Unexplained disorders: blindness, deafness, movement disorders</td>
<td>186</td>
<td>Outpatient genetic clinic; post hoc comparison with</td>
<td>3%-52%</td>
<td>WES increased yield vs Sanger sequencing. Highest yield for</td>
</tr>
</tbody>
</table>
**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.

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

**Analytic Validity**
WGS can detect structural variants and variants in regulatory regions. However, it is subject to many of the same considerations for potential variability in technical performance as WES. In 2014, Dewey et al reported the coverage and concordance of clinically relevant genetic variations provided by WGS technologies in 12 healthy adult volunteers. All subjects underwent WGS with the Illumina platform; 9 subjects also underwent WGS by the Complete Genomics (Mountain View, CA) platform to evaluate the reproducibility of sequence data. Genome sequences were compared with several reference standards. Depending on the sequencing platform, a median of 10% (Illumina; range, 5%-34%) to 19% (Complete Genomics; range, 18%-21%) of genes associated with inherited disease and a median of 9% (Illumina; range, 2%-27%) to 17% (Complete Genomics; range, 17%-19%) of American College of Medical Genetics and Genomics-reportable genes were not covered at a minimum threshold for genetic variant discovery. The genotype concordance between sequencing platforms was high for common genetic variants, for single-nucleotide variants in protein-coding regions of the genome, and among candidate variants for inherited disease risk. However, genotype concordance between sequencing platforms for small insertion or deletion variants was moderate overall (median, 57%; range, 53%-59%) and in protein-coding regions of the genome (median, 66%; range, 64%-70%), but was substantially lower among genetic variants that were candidates for inherited disease risk (median, 33%; range, 10%-75%).

WGS may have improved coverage compared with WES, particularly in GC-rich regions, structural variants, and intronic variants.

**Clinical Validity**
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 4). 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 4. Diagnostic Yields with WGS

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al (2015)</td>
<td>Broad spectrum of suspected genetic disorders</td>
<td>217</td>
<td>Multicenter series</td>
<td>46 (21)</td>
<td>34% yield in Mendelian disorders; 57% yield in trios</td>
</tr>
<tr>
<td>Ellingford et al (2016)</td>
<td>Unexplained inherited retinal disease</td>
<td>46</td>
<td>WGS in patients referred to a single center</td>
<td>24 (52)</td>
<td>Estimated 29% increase in yield vs NGS</td>
</tr>
<tr>
<td>Carss et al (2017)</td>
<td>Unexplained inherited retinal disease</td>
<td>605</td>
<td>NIHR-BioResource Rare Diseases Consortium</td>
<td>331 (55)</td>
<td>Compared with a detection rate of 50% with WES (n=117)</td>
</tr>
<tr>
<td>Lionel et al (2017)</td>
<td>Well-characterized but genetically heterogeneous cohort that had undergone targeted gene sequencing</td>
<td>103</td>
<td>Trio test for patients recruited from pediatric nongenetic subspecialists</td>
<td>42 (41)</td>
<td>Compared with a yield of 24% with standard diagnostic testing and a 25% increase in yield from WES</td>
</tr>
</tbody>
</table>

NGS: Next-Generation Sequencing; NIHR: National Institute for Health Research; WGS: Whole Genome Sequencing; WES: Whole Exome Sequencing.

Clinical Utility

The effect on health outcomes based on WGS results 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.

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 disorder who receive WES, the evidence includes large case series and within-subject comparisons. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60% depending on the individual’s age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who 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. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. There are increasing reports of 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, there are a limited number of patients who 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 WGS, the evidence includes case series. Relevant outcomes are test accuracy and 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.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics (ACMG) has 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:

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

In 2013, ACMG finalized its recommendations for reporting incidental findings in WGS and WES. 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.

**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 (see Table 5).
Table 5. Guidelines on Limb-Girdle Muscular Dystrophy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>• 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).</td>
<td>B</td>
</tr>
<tr>
<td>• 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.</td>
<td>C</td>
</tr>
<tr>
<td><strong>Management of cardiac complications</strong></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
<tr>
<td>• If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncpe, near-syncpe, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management.</td>
<td>B</td>
</tr>
<tr>
<td>• Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.</td>
<td>B</td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
<tr>
<td><strong>Management of pulmonary complications</strong></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
<tr>
<td>• It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.</td>
<td>C</td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
</tbody>
</table>


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 unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Mutation Exploration in Non-acquired, Genetic Disorders and Its Impact on Health Economy and Life Quality</td>
<td>200</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>
Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.102

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td>X</td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Type of test and reason for test
  - How testing will change management and clinical outcome
- Previous lab results pertaining to genetic testing
- Plan of care if genetic testing has failed to diagnose individual

**Post Service**

- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0036U</td>
<td>Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses <em>(Code effective 4/1/2018)</em></td>
</tr>
<tr>
<td>CPT®</td>
<td>81415</td>
<td>Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
<tr>
<td>CPT®</td>
<td>81416</td>
<td>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)</td>
</tr>
<tr>
<td>CPT®</td>
<td>81417</td>
<td>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)</td>
</tr>
<tr>
<td>CPT®</td>
<td>81425</td>
<td>Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
</tbody>
</table>
### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>12/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.