Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 12/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies is addressed separately in medical policy 00378.

Note: Genetic Testing for Facioscapulohumeral Muscular Dystrophy is addressed separately in medical policy 00392.

Note: Genetic Testing for Epilepsy is addressed separately in medical policy 00401.

Note: Genetic Testing for Limb-Girdle Muscular Dystrophies is addressed separately in medical policy 00489.

Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children to be eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be met for whole exome sequencing (WES) 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; and
- There is potential for a change in management and clinical outcome for the individual being tested; and
- 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), OR 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).
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When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers whole exome sequencing (WES) for the diagnosis of genetic disorders in all other situations to be investigational.*

Based on review of available data, the Company considers whole genome sequencing (WGS) for the diagnosis of genetic disorders to be investigational.*

Based on review of available data, the Company considers whole exome sequencing (WES) and whole genome sequencing (WGS) for screening for genetic disorders to be investigational.*

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

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

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.
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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></td>
<td>Variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</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>

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

GENETIC COUNSELING

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

Background/Overview

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.

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

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

The American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists (2013) convened a workgroup to standardize 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.

WES and WGS Testing Services

Several laboratories offer WES and WGS as a clinical service. For example, 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 WES 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.
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Table 1. Examples of Laboratories Offering Whole Exome Sequencing as a Clinical Service

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indications for Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambry Genetics</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</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</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</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>
<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</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) Emory Genetics Laboratory</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. “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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. WES or WGS 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.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source
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
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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 FOR 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 the use of 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 are suspected to have a genetic basis but are not explained by standard clinical workup.

**Intervention**
The relevant intervention of interest is WES.

**Comparators**
The following practice is currently being used to diagnose multiple unexplained congenital anomalies or a neurodevelopmental disorder: 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.

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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**
WES 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 had suspected rare genetic disorders, although the specific populations vary.

Series have been reported with as many as 2000 patients. The most common reason for referral to a tertiary care center was an unexplained neurodevelopmental disorder. Many patients had been through 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.
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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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al (2018)</td>
<td>Children with severe undiagnosed NDDs and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral phenotypes</td>
<td>1133</td>
<td>Consecutive family trios from U.K.-wide patient recruitment network</td>
<td>454 (40)</td>
<td>Reanalysis of existing data from earlier Wright (2015) publication from DDD study using improved variant calling methodologies, novel variant detection algorithms, updated variant annotation, evidence-based filtering strategies, and newly discovered disease-associated genes</td>
</tr>
<tr>
<td>Nambot et al (2018)</td>
<td>Children with congenital anomalies and intellectual disability with negative prior diagnostic workup</td>
<td>461</td>
<td>Consecutive cases meeting criteria referred to specialty clinic in France</td>
<td>31%</td>
<td>Initial yield in year 1: 22%, reanalysis led to increase yield</td>
</tr>
<tr>
<td>Tsuchida et al (2018)</td>
<td>Children with epilepsy (63% with early-onset epileptic encephalopathies) with no causative SNV in known epilepsy-associated genes</td>
<td>168</td>
<td>Consecutive unsolved cases referred to a single center</td>
<td>18 (11)</td>
<td>Performed WES with CNV detection tools</td>
</tr>
<tr>
<td>Evers et al (2017)</td>
<td>Children with undiagnosed NDDs (63%), neurometabolic disorders, and dystonias</td>
<td>72</td>
<td>Prospective study, referral and selection unclear</td>
<td></td>
<td>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</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>
<tr>
<td>Nolan and Carlson</td>
<td>Children with unexplained NDDs</td>
<td>50</td>
<td>Pediatric neurology clinic</td>
<td>41 (48)</td>
<td>Changed medication, systemic investigation,</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Population</td>
<td>N</td>
<td>Design</td>
<td>Yield, n (%)</td>
<td>Additional Information</td>
</tr>
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<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Allen et al (2016)</td>
<td>Patients with unexplained early-onset epileptic encephalopathy</td>
<td>50</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</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>Tarailo-Graovac et al (2016)</td>
<td>Intellectual developmental disorders and unexplained metabolic phenotypes (all ages)</td>
<td>41</td>
<td>Consecutively enrolled patients referred to a single center</td>
<td>28 (68)</td>
<td>WES diagnosis affected the clinical treatment of 18 (44%) probands</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); (7.5% de novo)</td>
</tr>
<tr>
<td>Wright et al (2015)</td>
<td>Children with severe undiagnosed NDDs and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral phenotypes</td>
<td>1133</td>
<td>Consecutive family trios from U.K.-wi patient recruiter network</td>
<td>311 (27)</td>
<td>Part of the DDD study</td>
</tr>
<tr>
<td>Lee et al (2014)</td>
<td>Suspected rare Mendelian disorders (57% of children had developmental delay; 28% of adults had ataxia)</td>
<td>814</td>
<td>Consecutive patients at single center</td>
<td>213 (26)</td>
<td>Trio (31% yield) vs proband only (22% yield)</td>
</tr>
<tr>
<td>Iglesias et al (2014)</td>
<td>Birth defects (24%); developmental delay (25%); seizures (32%)</td>
<td>115</td>
<td>Single-center tertiary clinic</td>
<td>37 (32)</td>
<td>Discontinuation of planned testing, changed medical management, and family planning</td>
</tr>
<tr>
<td>Soden et al (2014)</td>
<td>Children with unexplained NDDs</td>
<td>119</td>
<td>Single-center database(^a)</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 NDDs</td>
<td>78</td>
<td>Pediatric neurogenetics clinic</td>
<td>32 (41)</td>
<td>Change in medical management, prognostication, and family planning</td>
</tr>
</tbody>
</table>

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.

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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 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 (eg, by including parent testing), future reproductive decisions can be affected. Early use of WES can reduce the time to diagnosis and reduce the financial and psychological burdens associated with prolonged investigation.

Section Summary: Whole Exome Sequencing for 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
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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 FOR 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, 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 stated above.

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

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 following practice is currently being used to diagnose a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder: 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
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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**
WES 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 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.
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauer et al (2018)</td>
<td>Short stature in whom common nongenetic causes had been excluded</td>
<td>200 (mostly children)</td>
<td>Randomly selected from a consecutive series of patients referred for workup; trio testing performed</td>
<td>33 (17)</td>
<td>• Standard diagnostic approach yield: 13.6% in original cohort of 565 families&lt;br&gt;• WES results had possible impact on treatment or additional preventive measurements in 31 (16%) families</td>
</tr>
<tr>
<td>Rossi et al (2017)</td>
<td>Patients with autism spectrum disorder diagnosis or autistic features referred for WES</td>
<td>163</td>
<td>Selected from 1200 consecutive retrospective samples from commercial lab</td>
<td>42 (26)</td>
<td>• 66% of patients already had a clinician-reported autism diagnosis&lt;br&gt;• VUS in 12%</td>
</tr>
</tbody>
</table>
| Walsh et al (2017)     | Peripheral neuropathy in patients ranging from 2-68 y  
• 23 children  
• 27 adults | Prospective research study at tertiary pediatric and adult centers | 19 (38)                | Initial targeted analysis with virtual gene panel, followed by WES |
| 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 y; 47% >30 y) | Review of lab findings: consecutive retrospective series of adults | 85 (18)      | Yield in patients 18-30 y (24%) vs those >30 y (10.4%) |
60 families | Prospective study of patients identified from 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 a single center | 12 (30)      | • Altered management<br>• including genetic<br>• counseling and ending diagnostic odyssey<br>• VUS in 15 (38%) patients |
| Wortmann et al (2015)  | Suspected mitochondrial disorder | 109     | 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<br>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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauer et al (2018)</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossi et al (2017)</td>
<td>4. Most patients had a clinical diagnosis; only 33% had testing for specific ASD genes before WES</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walsh et al (2017)</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al (2017)</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posey et al (2016)</td>
<td>3. Included highly heterogeneous diseases</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghaoui et al (2015)</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wortmann et al (2015)</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neveling et al (2013)</td>
<td>3. Included highly heterogeneous diseases</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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Table 5. Study Design and Conduct Gaps for Studies Assessing WES for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection*</th>
<th>Blinding*</th>
<th>Delivery Test†</th>
<th>Selective Reporting‡</th>
<th>Data Completeness§</th>
<th>Statistical¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauer et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walsh et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al (2017)</td>
<td>2. Selection not random or consecutive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posey et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wortmann et al (2015)</td>
<td>1,2. Unclear how patients were selected from those eligible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neveling et al (2013)</td>
<td>1,2. Unclear how patients were selected from those referred</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

* Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

† Blinding key: 1. Not blinded to results of reference or other comparator tests.

‡ 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.


¶ 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.

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

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 12/19/2018

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 for a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder**
There is an increasing number of reports assessing use of WES 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 have reported 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, a limited number of patients have been studied for any specific disorder, and study of WES in these disorders is at an early stage.

**WHOLE GENOME SEQUENCING FOR 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 stated 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 suspected to have a genetic basis but not explained by standard clinical workup.

**Intervention**
The relevant intervention of interest is WGS.
Comparators
The following practice is currently being used to diagnose a suspected genetic disorder: standard clinical workup without WGS.

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

Timing
Follow-up is 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 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 sequenced with WGS are available for future review when new variants associated with clinical diseases are discovered.
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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Table 6. Diagnostic Yields With WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lionel et al (2018)</td>
<td>Well-characterized but genetically heterogeneous cohort that had undergone targeted gene sequencing</td>
<td>103</td>
<td>Trio testing for patients recruited from pediatric nongenetic subspecialists</td>
<td>42 (41)</td>
<td>Compared with a 24% yield with standard diagnostic testing and a 25% increase in yield from WES</td>
</tr>
<tr>
<td>Hauser et al (2018)</td>
<td>Neonatal and pediatric patients born with a cardiac defect in whom the suspected genetic disorder had been found using conventional genetic methods</td>
<td>34</td>
<td>Trio testing for patients recruited from the NICU, PICU, or general in patient pediatric ward of a single center</td>
<td>2 (6)</td>
<td>VUS in 10 (26%)</td>
</tr>
<tr>
<td>Canss 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>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>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>Gilissen et al (2014)</td>
<td>Children with severe intellectual disability who did not have a diagnosis after extensive genetic testing that included exome sequencing</td>
<td>50</td>
<td>Trio testing including unaffected parents</td>
<td>201 (42)</td>
<td>Of 21 with positive diagnosis, 20 had de novo variants</td>
</tr>
</tbody>
</table>

NGS: next-generation sequencing; NIH: 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.

Table 7. Relevance Gaps for Studies of WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lionel et al (2018)</td>
<td>1. Unclear how patients were selected from those eligible</td>
<td>2. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauser et al (2018)</td>
<td>25% had no prescreening performed</td>
<td>3. Proband testing only</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canss et al (2017)</td>
<td>3. Included highly heterogeneous diseases</td>
<td>1. VUS not reported</td>
<td></td>
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<tr>
<td>Gilissen et al (2014)</td>
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<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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.

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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.

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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lionel et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauser et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cars et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellingford et al (2016)</td>
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</tbody>
</table>


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.

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.
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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 Genome Sequencing for 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 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 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 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.

References


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Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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Policy History
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Current Effective Date: 12/19/2018

11/07/2013 Medical Policy Committee review
12/04/2014 Medical Policy Committee review

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12/17/2014 Medical Policy Implementation Committee approval. Title changed from “Whole Exome Sequencing” to “Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders.” The policy investigational section was revised to clarify that the intent of the policy is limited to the diagnosis of genetic disorders.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. No change to coverage eligibility.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Added eligibility statement for WES with criteria and INV statement for WES and WGS in screening for genetic disorders.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/01/2017 Coding update
12/07/2017 Medical Policy Committee review
12/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2019

**Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0012U, 81415, 81416, 81417, 81425, 81426, 81427, 81479</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

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Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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