Medical Policy

MP 2.04.102
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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Last Review: 10/24/2019
Effective Date: 10/24/2019
Section: Medicine

Related Policies
2.04.89 Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies
2.04.105 Genetic Testing for Facioscapulohumeral Muscular Dystrophy
2.04.109 Genetic Testing for Epilepsy
2.04.132 Genetic Testing for Limb-Girdle Muscular Dystrophies
2.04.570 Genetic Counseling

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POLICY

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

1. The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing.
2. There is potential for a change in management and clinical outcome for the individual being tested.
3. A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (eg, 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 (eg, muscle biopsy).
Whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations.

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

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

**Genetic Counseling**

Documentation of individualized genetic counseling is required, before any genetic testing will be considered medically necessary. See MP 2.04.570.

**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.

**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</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></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>
</tbody>
</table>
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Variant of uncertain significance  | Change in DNA sequence with uncertain effects on disease
 Likely benign                  | Likely benign change in the DNA sequence
 Benign                         | Benign change in the DNA sequence

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

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

CODING
A new PLA code was effective April 1, 2018:

0036U Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses.

See the Codes table for details.

BENEFIT APPLICATION

BLUE CARD/NATIONAL ACCOUNT ISSUES
Some Plans may have contract or benefit exclusions for genetic testing.

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.¹ 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
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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.²

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.

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</td>
<td>“This test is intended for use in conjunction with the clinical presentation of the patient.”</td>
</tr>
</tbody>
</table>
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Los Angeles Health System

and other markers of disease progression for the management of patients with rare genetic disorders.”

EdgeBio

Recommended “In situations where there has been a diagnostic failure with no discernible path. In situations where there are currently no available tests to determine the status of a potential genetic disease. In situations with atypical findings indicative of multiple disease[s].”

Children’s Mercy Hospitals and Clinics (Kansas City, MO)

Provided as a service to families with children who have had an extensive negative workup for a genetic disease; also used to identify novel disease genes.

Emory Genetics Laboratory

“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”

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

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. 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.

RATIONALE

The evidence review was created in September 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through August 6, 2018.

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

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

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

WHOLE EXOME SEQUENCING 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:
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- 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.

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.

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.4

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</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 evidence-based filtering strategies,</td>
</tr>
</tbody>
</table>
### Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
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<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nambot et al (2018)⁶</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 and newly discovered disease-associated genes</td>
</tr>
<tr>
<td>Tsuchida et al (2018)⁷</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>
</tbody>
</table>
| Evers et al (2017)⁸     | Children with undiagnosed NDDs (63%), neurometabolic disorders, and dystonias          | 72  | Prospective study, referral and selection unclear                      |              | • 36% in NDD  
• 43% in neurometabolic disorders  
• 25% in dystonias  
Results reported to be important for family planning, used for a prenatal diagnostic procedure in 4 cases, management changes reported in 8 cases; surveillance for other disease-associated complications initiated in 6 cases |
| Vissers et al (2017)⁴   | Children with complex neurologic disorders of suspected genetic origin                | 150 | Prospective comparative study at a tertiary center                    | 44 (29) conclusive  
41 (27) possible | First-line WES had 29% yield vs 7% yield for standard diagnostic workup⁸                                                            |
<p>| Nolan and Carlson (2016)⁹ | Children with unexplained NDDs                                                       | 50  | Pediatric neurology clinic                                             | 41 (48)      | Changed medication, systemic investigation, and family planning                                                                                     |
| Allen et al (2016)¹⁰    | Patients with unexplained early-onset epileptic encephalopathy                        | 50 (95% &lt;1 y) | Single center                                                          | 11 (22)      | 2 VUS for follow-up, 11 variants identified as de novo                                                                                        |</p>
<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>Stark et al (2016)</td>
<td>Infants (≤2 y) with suspected monogenic disorders with multiple congenital anomalies 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>Tarailo-Graovac et al (2016)</td>
<td>Intellectual developmental disorders and unexplained metabolic phenotypes (all ages)</td>
<td>41</td>
<td>Consecutive ly 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); 31 (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.-wide patient recruitment network</td>
<td>311 (27)</td>
<td>Part of the DDD study</td>
</tr>
<tr>
<td>Yang et al (2014)</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)</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>
<tr>
<td>Soden et al (2014)</td>
<td>Children with unexplained NDDs</td>
<td>119 (100 families)</td>
<td>Single-center database&lt;sup&gt;a&lt;/sup&gt;</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>
### Clinical Usefulness of Whole Exome Sequencing

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.

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**Table 2: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders**

<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>Yang et al (2013)²⁰</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>
</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.

²⁰ Included both WES and whole genome sequencing.

² 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.
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 development 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 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 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.

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>
</table>
| Hauer et al (2018)²¹ | Short stature in whom common nongenetic causes had been excluded (mostly children) | 200 | Randomly selected from a consecutive series of patients referred for workup; trio testing performed | 33 (17) | • Standard diagnostic approach yield: 13.6% in original cohort of 565  
• WES results had possible impact on treatment or additional preventive measurements in 31 (16%) families |
<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>Rossi et al (2017)²²</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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• VUS in 12%</td>
</tr>
<tr>
<td>Walsh et al (2017)²³</td>
<td>Peripheral neuropathy in patients ranging from 2-68 y</td>
<td>23</td>
<td>Prospective research study at tertiary pediatric and adult centers</td>
<td>19 (38)</td>
<td>Initial targeted analysis with virtual gene panel, followed by WES</td>
</tr>
<tr>
<td>Miller et al (2017)²⁴</td>
<td>Craniosynostosis in patients who tested negative on targeted genetic testing</td>
<td>40</td>
<td>Research study of referred patients²</td>
<td>15 (38)</td>
<td>Altered management and reproductive decision making</td>
</tr>
<tr>
<td>Posey et al (2016)²⁵</td>
<td>Adults (overlap of 272 patients reported by Yang et al [2014]),¹⁵ includes neurodevelopmental and other phenotypes</td>
<td>486</td>
<td>Review of lab findings in consecutive retrospective series of adults</td>
<td>85 (18)</td>
<td>Yield in patients 18-30 y (24%) vs those &gt;30 y (10.4%)</td>
</tr>
<tr>
<td>Ghaoui et al (2015)²⁶</td>
<td>Unexplained limb-girdle muscular dystrophy</td>
<td>60</td>
<td>Prospective study of patients identified from specimen bank</td>
<td>27 (60)</td>
<td>Trio (60% yield) vs proband only (40% yield)</td>
</tr>
<tr>
<td>Valencia et al (2015)²⁷</td>
<td>Unexplained disorders: congenital anomalies (30%), neurologic (22%), mitochondrial (25%), endocrine (3%), immunodeficiencies (17%)</td>
<td>40</td>
<td>Consecutive patients in a single center</td>
<td>12 (30)</td>
<td>• Altered management including genetic counseling and ending diagnostic odyssey</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• VUS in 15 (38%) patients</td>
</tr>
<tr>
<td>Wortmann et al (2015)²⁸</td>
<td>Suspected mitochondrial disorder</td>
<td>109</td>
<td>Patients referred to a single center</td>
<td>42 (39)</td>
<td>57% yield in patients with high suspicion of mitochondrial disorder</td>
</tr>
<tr>
<td>Neveling et al (2013)²⁹</td>
<td>Unexplained disorders: blindness, deafness, movement disorders, mitochondrial disorders, hereditary cancer</td>
<td>186</td>
<td>Outpatient genetic clinic; post hoc comparison with Sanger sequencing</td>
<td>3%-52%</td>
<td>WES increased yield vs Sanger sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest yield for blindness and deafness</td>
</tr>
</tbody>
</table>

WES: whole exome sequencing; VUS: variant of uncertain significance.
²² 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)21</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>Rossi et al (2017)22</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)23</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)24</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)25</td>
<td>3. Included highly heterogeneous diseases</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghaoui et al (2015)26</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valencia et al (2015)27</td>
<td>3. Included highly heterogeneous diseases</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wortmann et al (2015)28</td>
<td>3. Included highly heterogeneous diseases</td>
<td>1. VUS not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neveling et al (2013)29</td>
<td>3. Included highly heterogeneous diseases</td>
<td>1. VUS not reported</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.

ASD: autism spectrum disorder; VUS: variants of uncertain significance; WES: whole exome sequencing.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
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 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>Selectiona</th>
<th>Blindingb</th>
<th>Delivery of Testc</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauer et al (2018)21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</td>
<td></td>
</tr>
<tr>
<td>Rossi et al (2017)22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</td>
<td></td>
</tr>
<tr>
<td>Walsh et al (2017)23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al (2017)24</td>
<td>2. Selection not random or consecutive</td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</td>
<td></td>
</tr>
<tr>
<td>Posey et al (2016)25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</td>
<td></td>
</tr>
<tr>
<td>Wortmann et al (2015)28</td>
<td>1,2. Unclear how patients were selected from those eligible</td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</td>
<td></td>
</tr>
<tr>
<td>Neveling et al (2013)29</td>
<td>1,2. Unclear how patients were selected from those referred</td>
<td></td>
<td></td>
<td></td>
<td>1. No description of indeterminate samples</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.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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.

Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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

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

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

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

A genetic diagnosis for an unexplained disorder can alter management in several ways: such a diagnosis may lead to including genetic counseling and ending the diagnostic odyssey and may affect reproductive decision making.

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

Section Summary: WES 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.
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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.

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 not been found using conventional genetic methods</td>
<td>34</td>
<td>Trio testing for patients recruited from the NICU, PICU, or general inpatient pediatric ward of a single center</td>
<td>2 (6)</td>
<td>VUS in 10 (26%)</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>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; NIHR: National Institute for Health Research; NICU: neonatal intensive care unit; PICU: pediatric intensive care unit; VUS: variant of uncertain significance; WGS: whole genome sequencing; WES: whole exome sequencing.

Tables 7 and 8 display notable gaps identified in each study.

Table 7. Relevance Gaps for Studies of WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparator   c</th>
<th>Outcomesd</th>
<th>Duration of Follow-Upe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lionel et al (2018)</td>
<td>1,2. Unclear how patients were selected from those eligible</td>
<td>3. Proband testing only</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Study Design and Conduct Gaps for Studies of WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Selectiona</th>
<th>Blindingb</th>
<th>Delivery of Testc</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lionel et al (2018)30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauser et al (2018)31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carss et al (2017)32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellingford et al (2016)33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Taylor et al (2015)34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilissen et al (2014)35</td>
<td></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.

VUS: variant of uncertain significance; WGS: whole genome sequencing.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

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e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).
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.

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.


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

No RCTs assessing the use of WGS to diagnose a suspected genetic disorder were identified.

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

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

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

Section Summary: Whole 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.

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:

- 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.
- 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.
- A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
- 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:
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

WGS/WES may be considered in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.

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

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

ACMG (2016) updated its recommendations on reporting incidental findings in WGS and WES testing. ACMG determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician. The 2016 update added 4 genes and removed of 1 gene resulting in an updated secondary findings minimum list including 59 medically actionable genes recommended for return in clinical genomic sequencing.

American Academy of Neurology et al
The American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine (2014) issued evidence-based guidelines on the diagnosis and treatment of limb-girdle and distal dystrophies, which made the following recommendations (see Table 9).

### Table 9. Guidelines on LGMD

<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 syncope, near-syncope, 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...</td>
<td>B</td>
</tr>
</tbody>
</table>
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Recommendation

asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.

- 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.

Management of pulmonary complications

- Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course.

- 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.

- It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.

- 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.

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 10.

Table 10. 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02826694</td>
<td>North Carolina Newborn Exome Sequencing for Universal Screening</td>
<td>400</td>
<td>Aug 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT03211039</td>
<td>Prenatal Precision Medicine (NSIGHT2): A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting</td>
<td>1000</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02699190</td>
<td>LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies</td>
<td>50</td>
<td>Apr 2020</td>
</tr>
<tr>
<td>NCT03548779</td>
<td>North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2</td>
<td>1700</td>
<td>May 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02380729</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 (completed)</td>
</tr>
</tbody>
</table>
NCT: national clinical trial.

**ESSENTIAL HEALTH BENEFITS**

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntary offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

**REFERENCES**


CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81415</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81416</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>81417</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
</tr>
<tr>
<td></td>
<td>81425</td>
<td>Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81426</td>
<td>Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>81427</td>
<td>Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
</tr>
<tr>
<td></td>
<td>0036U</td>
<td>Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>F70.-F79</td>
<td>Intellectual disabilities code range</td>
</tr>
<tr>
<td></td>
<td>F80.0-F89</td>
<td>Pervasive and specific developmental disorders code range</td>
</tr>
<tr>
<td></td>
<td>Q00.0-Q99.9</td>
<td>Congenital malformations, deformations, and chromosomal abnormalities code range (Q89.7 is the specific code for multiple congenital malformations, not elsewhere classified)</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services.</td>
<td></td>
</tr>
</tbody>
</table>
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

There are no ICD procedure codes for laboratory tests.

<table>
<thead>
<tr>
<th>Type of service</th>
<th>Place of service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
</table>
| 09/11/14   | Replace policy | Policy updated with literature review through August 3, 2014. References 2, 4-5, and 8-13 added. Whole genome sequencing added to policy statement; whole genome sequencing considered investigational. Title changed to “Whole Exome and Whole Genome Sequencing for Diagnosis of Patients with Suspected Genetic Disorders”.

| 11/13/14   | Replace policy | The policy statement and Policy Guidelines were revised to clarify that the intent of the policy is limited to the diagnosis of genetic disorders. Title changed to “Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders.”


| 11/10/16   | Replace policy | Policy updated with literature review through August 22, 2016; references 9, 11, 14, 16-18, and 20-22 added. Rationale revised. Whole exome sequencing considered medically necessary for children with multiple congenital anomalies or a neurodevelopmental disorder. All other uses of whole exome and whole genome sequencing are considered investigational. Policy statement added that whole exome and whole genome sequencing are considered investigational for screening.

| 10/30/17   | Replace policy | Blue Cross of Idaho adopted changes to policy noted. Policy updated with literature search through August 23, 2017; references 6-8, 19, 24-25, 27, and 30 added. Policy statements unchanged.                                                                                                                                                                                     |

| 10/18/18   | Replace policy | Blue Cross of Idaho adopted changes as noted, effective 10/18/2018. Policy updated with literature search through August 6, 2018; references 12, 16-20, 28-29, 31, 35, and 37; references 36 and 38 updated. Policy statements unchanged.                                                                                                                                                       |

| 10/24/19   | Replace policy | Blue Cross of Idaho annual review; added genetic counseling statement. No other changes.                                                                                                                                                                                                                                                             |