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

Effective Date: January 15, 2019

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

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Description
Whole exome sequencing (WES) sequences the portion of the genome that contains protein-coding DNA, while whole genome sequencing (WGS) sequences both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

OBJECTIVE
The objective of this evidence review is to determine whether whole exome or whole genome sequencing improves the net health outcome in individuals with suspected genetic disorders.

POLICY STATEMENT
Whole exome sequencing may be considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of 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.

**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>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>

<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>
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**GENETIC COUNSELING**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is

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considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

**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>
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<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...”</td>
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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.

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

#### 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:

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

ACMG has recommended that for screening purposes:

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

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

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 Table2).
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Table 2. Guidelines on LGMD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<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></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></td>
<td>C</td>
</tr>
</tbody>
</table>

Management of cardiac complications

• Clinicians should refer newly diagnosed patients with (1) limb-girdle muscular dystrophy (LGMD)1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, … or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including electrocardiogram (ECG) and structural evaluation (echocardiography or cardiac magnetic resonance imaging [MRI]), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management. | | B |
• If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management. | | B |
• Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation. | | B |
• It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiology evaluation unless they develop overt cardiac signs or symptoms. | | B |

Management of pulmonary complications

• Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course. | | B |
• In patients with a known high risk of respiratory failure (e.g., those with LGMD2I …), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency. | | B |
• It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic. | | C |
• Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life. | | B |

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES


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**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2013</td>
<td>New Policy</td>
<td></td>
</tr>
<tr>
<td>December 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review. References 2, 4, 5, and 8-13 added. Whole genome sequencing added to policy statement; whole genome sequencing considered investigational.</td>
</tr>
<tr>
<td>March 2017</td>
<td>Update Policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2017</td>
<td>Update Policy</td>
<td>Policy updated with literature search through August 23,</td>
</tr>
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<tr>
<th>Date</th>
<th>Update Policy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2018</td>
<td>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.</td>
<td>2017: references 6-8, 19, 24-25, 27, and 30 added. Policy statements unchanged.</td>
</tr>
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