Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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Section: Diagnostic Testing
Place(s) of Service: Outpatient

I. Description

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

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

For individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder who receive WES, the evidence includes small case series and prospective research studies. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. There are increasing reports of use of WES to identify a molecular basis for disorders other than multiple congenital
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anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. One concern with WES is the possibility of incidental findings. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients who have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

Background

WHOLE EXOME SEQUENCING AND WHOLE GENOME SEQUENCING

Whole exome sequencing (WES) is targeted next-generation sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

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

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

WES and WGS Technology

WES or WGS using next-generation sequencing technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual (≈85%), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing mutations. WES has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. WES shares some limitations with Sanger
sequencing. For example, it will not identify the following: intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications; or rearrangements within genes, nucleotide repeats, or epigenetic changes. WGS uses techniques similar to WES, but includes noncoding regions. WGS has greater ability to detect large deletions or duplications in protein-coding regions compared with WES, but requires greater data analytics. Technical aspects of WES and WGS are evolving, including the development of databases such as the National Institutes of Health’s ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) to catalog variants, uneven sequencing coverage, gaps in exon capture before sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate mutations. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to develop standard terminology for describing sequence variants. Guidelines developed by this workgroup, published in 2015, describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

II. Criteria/Guidelines

1. Whole exome sequencing (WES) is covered for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of the following criteria are met:
   a. The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing.
   b. There is potential for a change in management and clinical outcome for the individual being tested.
   c. 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).

2. The policy statement is intended to address the use of whole exome and whole genome sequencing for the diagnosis of genetic disorders in patients with suspected genetic disorders and for population-based screening.
3. 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.
4. The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state.
5. The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood.

III. Limitations/Exclusions

1. WES is not covered for the diagnosis of genetic disorders in all other situations.
2. WGS is not covered for the diagnosis of genetic disorders.
3. WES and WGS are not covered for screening for genetic disorders.

IV. Administrative Guidelines

A. Precertification is required for all non-emergent conditions. To pre-certify, complete HMSA’s Precertification Request form and fax or mail the form, or use iExchange with the following documentation:
   1. Specify the condition for which the genetic test is being performed and if there are any known first- or second-degree relatives with the condition
   2. Other types of biochemical testing apart from molecular genetic testing (enzyme activity assays, hemoglobin electrophoresis, blood chemistries, etc.), phenotypic findings and relevant clinical history and exam details
   3. Specify how the results of the genetic test will impact the clinical management of the patient in terms of improving health outcomes

B. If precertification is not sought, the member will not be held responsible for payment of denied services unless an Agreement of Financial Responsibility is completed and signed.

C. Applicable codes:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81415</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
<tr>
<td>81416</td>
<td>sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>81417</td>
<td>re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
</tr>
<tr>
<td>81425</td>
<td>Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
</tr>
<tr>
<td>81426</td>
<td>sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>81427</td>
<td>re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
</tr>
</tbody>
</table>
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D. ICD-10 codes are provided for your information.

<table>
<thead>
<tr>
<th>ICD-10-CM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F70.-F79</td>
<td>Intellectual disabilities code range</td>
</tr>
<tr>
<td>F80.0-F89</td>
<td>Pervasive and specific developmental disorders code range</td>
</tr>
<tr>
<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>
</tbody>
</table>

| ICD-10-PCS | Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests. |

V. Scientific Background

This policy has been updated periodically with literature reviews. The most recent literature review covers the period through August 23, 2017. This review was informed in part by a 2013 TEC Special Report on exome sequencing for patients with suspected genetic disorders.

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

WHOLE EXOME SEQUENCING IN PATIENTS WITH MULTIPLE CONGENITAL ANOMALIES OR A NEURODEVELOPMENTAL DISORDER

Clinical Context and Test Purpose
The purpose of whole exome sequencing (WES) in patients who have multiple unexplained congenital anomalies or a neurodevelopmental disorder is to establish a molecular diagnosis. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests;
- The clinical utility of a diagnosis has been established (eg, by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes); and
- Establishing the diagnosis by genetic testing will end the clinical workup for other disorders.

The question addressed in this evidence review is: Does WES improve health outcomes when used for the diagnosis of patients with multiple unexplained congenital anomalies or a neurodevelopmental disorder?
The following PICOTS were used to select literature to inform this review.

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

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

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

**Outcomes**
The general outcomes of interest are the accuracy of next-generation sequencing (NGS) compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and improvement in health outcomes. Health outcomes include a reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

False-positive test results can lead to misdiagnosis and inappropriate clinical management. False-negative test results can lead to a lack of a genetic diagnosis and continuation of the diagnostic odyssey.

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

**Setting**
These tests are offered commercially through various manufacturers.

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

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

Clinical Validity
A number of studies have reported on the use of WES in clinical practice (see Table 2). Typically, the populations included in these studies have suspected rare genetic disorders, although the specific populations vary.

Series have been reported with as many as 2000 patients. The largest reason for referral to a tertiary care center was an unexplained neurodevelopmental disorder. Many patients had been through standard clinical workup and testing without identification of a genetic variant to explain their condition. Diagnostic yield in these studies, defined as the proportion of tested patients with clinically relevant genomic abnormalities, ranged from 25% to as many as 48%. Because there is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies, clinical confirmation may be the only method for determining false-positive and false-negative rates. No reports were identified of incorrect diagnoses, and how often they might occur is unclear.

When used as a first-line test in infants with multiple congenital abnormalities and dysmorphic features, diagnostic yield may be as high as 58%. Testing parent-child trios has been reported to increase diagnostic yield, to identify an inherited variant from an unaffected parent and be considered benign, or to identify a de novo variant not present in an unaffected parent. First-line trio testing for children with complex neurologic disorders was shown to increase the diagnostic yield (29%, plus a possible diagnostic finding in 27%) compared with a standard clinical pathway (7%) performed in parallel in the same patients.

Clinical Utility
Cohort studies following children from presentation to outcomes have not been reported. There are considerable challenges conducting studies of sufficient size given the underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes. Studies addressing clinical utility have reported mainly diagnostic yield and management changes. Thus, it is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to heterogeneity of disorders, rarity, and outcome importance that may differ according to identified pathogenic variants. Actionable items following testing in the reviewed studies (see Table 2) included family planning, change in management, change or avoidance of additional testing, surveillance for associated morbidities, prognosis, and ending the diagnostic odyssey.

The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can: (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. When recurrence risk can be estimated for an identified variant (eg, by including parent testing), future reproductive
decisions can be affected. Early use of WES can reduce the time to diagnosis and reduce the financial and psychological burdens associated with prolonged investigation.

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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2013)</td>
<td>Suspected genetic disorder (86% neurologic)</td>
<td>250 (1% fetus; 50% &lt;5 y; 38% 5-18 y; 11% adults)</td>
<td>Consecutive patients at single center</td>
<td>62 (25)</td>
<td>Identification of atypical phenotypes of known genetic diseases and blended phenotypes</td>
</tr>
<tr>
<td>Yang et al (2014)</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 neurodevelopmental disorders</td>
<td>119 (100 families)</td>
<td>Single-center database</td>
<td>53 (45)</td>
<td>Change in clinical care or impression in 49% of families</td>
</tr>
<tr>
<td>Srivastava et al (2014)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>78</td>
<td>Pediatric neurogenetics clinic</td>
<td>32 (41)</td>
<td>Changed medical management, prognostication, and family planning</td>
</tr>
<tr>
<td>Farwell et al (2015)</td>
<td>Unexplained neurologic disorders (65% pediatric)</td>
<td>500</td>
<td>WES laboratory</td>
<td>152 (30)</td>
<td>Trio (37.5% yield) vs proband only (20.6% yield); 31 (7.5% de novo)</td>
</tr>
<tr>
<td>Nolan and Carlson (2016)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>50</td>
<td>Pediatric neurology clinic</td>
<td>41 (48)</td>
<td>Changed medication, systemic investigation, and family planning</td>
</tr>
<tr>
<td>Allen et al (2016)</td>
<td>Patients with unexplained early-onset epileptic encephalopathy</td>
<td>50 (95% &lt;1 y)</td>
<td>Single center</td>
<td>11 (22)</td>
<td>2 VUS for follow-up, 11 variants identified as de novo</td>
</tr>
<tr>
<td>Stark et al (2016)</td>
<td>Infants (≤2 y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features</td>
<td>80</td>
<td>Prospective comparative study at a tertiary center</td>
<td>46 (58)</td>
<td>First-line WES increased yield by 44%, changed clinical management and family planning</td>
</tr>
<tr>
<td>Vissers et al (2017)</td>
<td>Children with complex neurologic disorders of suspected genetic origin</td>
<td>150</td>
<td>Prospective comparative study at a tertiary center</td>
<td>□ 44 (29) conclude □ 41 (27) possible</td>
<td>First-line WES had 29% yield vs 7% yield for standard diagnostic workup</td>
</tr>
</tbody>
</table>

VUS: variants of uncertain significance; WES: whole exome sequencing.

* Included both WES and whole genome sequencing.
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 in Patients With Multiple Congenital Anomalies or a Neurodevelopmental Disorder**

The evidence on WES in patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology includes case series. These series have reported diagnostic yields of WES ranging from 22% to 58%, depending on the individual’s age, phenotype, and previous workup. Comparative studies have reported an increase in diagnostic yield compared with standard testing strategies. Thus, for individuals who have a suspected genetic etiology but for whom the specific genetic alteration is unclear or unidentified by standard clinical workup, WES may return a likely pathogenic variant. A genetic diagnosis for these patients is reported to change management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning.

**WES IN PATIENTS WITH A SUSPECTED GENETIC DISORDER OTHER THAN MULTIPLE CONGENITAL ANOMALIES OR A NEURODEVELOPMENTAL DISORDER**

**Clinical Context and Test Purpose**

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

The purpose of WES in patients who have a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder is to establish a molecular diagnosis. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as above.

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

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

**Patients**

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

**Intervention**

The relevant intervention of interest is WES.

**Comparators**

The relevant comparator of interest is standard clinical workup without WES.
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Outcomes
The general outcomes of interest are the accuracy of NGS compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and clinical health outcomes. Health outcomes include a reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

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

Setting
These tests are offered commercially through various manufacturers.

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

Clinical Validity
Studies have assessed WES for a broad spectrum of disorders. The diagnostic yield in patient populations restricted to specific phenotypes ranges from 3% for colorectal cancer to 60% for unexplained limb-girdle muscular dystrophy. Some studies used a virtual gene panel that is restricted to genes that are associated with the phenotype, while others have examined the whole exome, either initially or sequentially. An advantage of WES over individual gene or gene panel testing is that the stored data allows reanalysis as new genes are linked to the patient phenotype. WES has also been reported to be beneficial in patients with atypical presentations.

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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neveling et al (2013)¹⁹</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. Highest yield for blindness and deafness</td>
</tr>
<tr>
<td>Ghaoui et al (2015)²⁰</td>
<td>Unexplained limb-girdle muscular dystrophy</td>
<td>60 families</td>
<td>Prospective study of patients identified from a specimen bank</td>
<td>27 (60)</td>
<td>Trio (60% yield) vs proband only (40% yield)</td>
</tr>
<tr>
<td>Valencia et al (2015)²¹</td>
<td>Unexplained disorders: congenital anomalies (30%), neurologic (22%), mitochondrial (25%), endocrine (3%)</td>
<td>40 (&lt;17 y)</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>
</tbody>
</table>
### Clinical Utility

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

### Section Summary: WES in Patients with a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

There are increasing reports of WES being used to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies ranged from 3% for colorectal cancer to 60% for trio (parents and child) analysis of limb-girdle muscular dystrophy. One concern with WES is the possibility of incidental findings. Some studies report on the use of a virtual gene panel with restricted analysis of disease-associated genes, and the authors noted that WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients that have been studied for any specific disorder, and study of WES in these disorders is at an early stage.

### Whole Genome Sequencing in Patients with a Suspected Genetic Disorder

The purpose of whole genome sequencing (WGS) in patients who have a suspected genetic disorder is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as above.

The question addressed in this evidence review is: Does WGS improve health outcomes when used for the diagnosis of a suspected genetic disorder?
The following PICOTS were used to select literature to inform this review.

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

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

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

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

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

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

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

Clinical Validity
Studies have shown that WGS can detect more pathogenic variants than WES, due to an improvement in detecting copy number variants, insertions and deletions, intronic single-nucleotide variants, and exonic single-nucleotide variants in regions with poor coverage on WES. In some studies the genes examined were those that had previously been associated with the phenotype, while other studies were research-based and conducted more exploratory analysis (see Table 4). It has been noted that genomes that have been sequenced with WGS are available for future review when new variants associated with clinical diseases are discovered.

Table 4. Diagnostic Yields With WGS

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

NGS: next-generation sequencing; NIHR: National Institute for Health Research; WGS: whole genome sequencing; WES: whole exome sequencing.

Clinical Utility
The effect on health outcomes based on WGS results are the same as those with WES, with a possible change in surveillance, management and/or reproductive planning. A reduction in invasive testing and an end of the diagnostic odyssey are also considered to be significant health outcomes. Section Summary: Whole Exome Sequencing in Patients With a Suspected Genetic Disorder WGS has increased coverage and diagnostic yield compared with WES, but the technology is limited by the amount of data generated and greater need for storage and analytic capability. Several authors have proposed that, as WGS becomes feasible on a larger scale, it may in the future become the standard first-tier diagnostic test.

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

For individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder who receive WES, the evidence includes small case series and prospective research studies. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. There are increasing reports of use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. One concern with WES is the possibility of incidental findings. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients who have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
American College of Medical Genetics and Genomics
The American College of Medical Genetics and Genomics (ACMG) has recommended that diagnostic testing with whole exome sequencing (WES) and whole genome sequencing (WGS) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

a. "The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis."
b. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.

c. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.

d. A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.

ACMG has recommended that for screening purposes:

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

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

In 2013, ACMG finalized its recommendations for reporting incidental findings in WGS and WES. ACMG determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician.

**American Academy of Neurology et al**

In 2014, the American Academy of Neurology and American Association of Neuromuscular and Electromdiagnostic Medicine issued evidence-based guidelines on the diagnosis and treatment of limb-girdle and distal dystrophies, which made the following recommendations (see Table 5).

**Table 5. Guidelines on Limb-Girdle Muscular Dystrophy**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>- For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement).</td>
<td>B</td>
</tr>
<tr>
<td>- In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality.</td>
<td>C</td>
</tr>
</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 | B   |
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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.

☐ 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.

☐ Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or 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 cardiology 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.

Recommendation

☐ In patients with a known high risk of respiratory failure (e.g., those with LGMD21 ...), 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 ECG: electrocardiogram.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></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</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>
</tbody>
</table>
VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References