Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy Number: 2.04.102  
Last Review: 12/2015
Origination: 12/2015  
Next Review: 06/2016

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders. This is considered investigational.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered

n/a

When Policy Topic is not covered

Whole exome sequencing and whole genome sequencing are considered investigational for the diagnosis of genetic disorders.

Considerations

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

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

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 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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With suspected genetic disorders</td>
<td>• Whole exome sequencing or whole genome sequencing</td>
<td>• Standard management</td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
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<td></td>
<td>• Other test performance measures</td>
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<td>• Changes in reproductive</td>
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</table>
Whole exome sequencing (WES) is targeted 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 (NGS) techniques to sequence both coding- and noncoding regions of the genome.

The evidence for the use of WES/WGS in individuals with suspected genetic disorders includes multiple studies that describe detection of novel genetic variants and several relatively large cohort studies that report on the yield of WES/WGS. Relevant outcomes include test accuracy, test validity, other test performance measures, changes in reproductive decision making, morbid events, health status measures, and resource utilization. A potential major indication for their use of WES/WGS is for molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder but when a specific mutation is not suspected or with suspected genetic disorders that have a large degree of genetic heterogeneity. Such patients may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup involving a variety of traditional molecular and other types of conventional diagnostic tests. For some of these patients, WES or WGS, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant. There is developing evidence about the use of WES/WGS in clinical practice, with studies describing yields of a molecular diagnosis in approximately 25% of patients without a diagnosis after a previous workup. No studies were identified that directly compared WES/WGS with alternative testing strategies in terms of the yield of testing for pathogenic variants associated with the phenotype being evaluated and variants of uncertain significance and incidental clinically-actionable findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

Currently available clinical assays designed for the molecular diagnosis of rare Mendelian diseases are incomplete. This is due to genetic heterogeneity, the presence of unknown causative genes, and because only a portion of the known genes and mutations can be efficiently tested using conventional molecular methods. Recently, next-generation sequencing technologies have become more accessible in terms of cost and speed and have been adopted by a growing number of molecular genetic clinical laboratories.

Depending on the disorder and the degree of genetic and clinical heterogeneity, the current diagnostic pathway for patients with suspected genetic disorders accompanied by multiple anomalies may depend on various combinations of low-yield radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process. When a disease-causing gene(s) is established, assays based on polymerase chain reaction technology, for example, can be designed to specifically detect known mutations for clinical diagnosis. When many different point mutations in a gene are possible, Sanger sequencing, the current criterion standard for detecting unknown point mutations, can be employed to determine the entire sequence of the coding and intron/exon splice sites of gene regions where mutations are most likely to be found. However, when genes are large and mutations are possible in many or all exons (protein-coding regions of the gene), and when there is genetic (locus) heterogeneity, comprehensive Sanger sequencing may be prohibitively laborious and costly.

Whole exome sequencing (WES) using next-generation sequencing technology is a relatively new approach to obtaining a genetic diagnosis in patients more efficiently compared with traditional methods.

Exome sequencing has the capacity to determine a person’s exomic variation profile in a single assay. This profile 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 whole genome. It is believed that the exome contains about 85% of heritable disease-causing mutations.

Published exome sequencing studies show that the technology can be used to detect previously annotated pathogenic mutations and reveal new likely pathogenic mutations in known and unknown genes. The diagnostic yield, based on a limited number of studies, appears to be significantly increased above that of traditional Sanger sequencing, and exome sequencing has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes.

Whole genome sequencing (WGS) uses similar techniques to WES, but involves the sequencing of noncoding DNA in addition to the protein-coding segments of the genome.

**Limitations of WES/WGS**
At this time, the limitations of WES/WGS include technical and implementation challenges. There are issues of error rates due to 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. It is difficult to filter and interpret potential causative variants from the large number of variants of unknown significance generated for each patient. Variant databases are poorly annotated, and algorithms for annotating variants will need to be automated. Existing databases that catalog variants and putative disease associations are known to have significant entry error rates.

Approaches for characterizing the functional impact of rare and novel variants (ie, achieving full-genome clinical interpretations that are scientifically sound and medically relevant) have to be improved. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown, and detailed guidance from regulatory and professional organizations is still under development. Finally, exome sequencing has some similar limitations as Sanger sequencing; eg, 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 addresses some of these limitations, but is limited by the need for increased analytic power and the likelihood of greater identification of variants of uncertain significance.

There are ethical questions about reporting incidental findings, such as identifying medically relevant mutations in genes unrelated to the diagnostic question, sex chromosome abnormalities, and nonpaternity when family studies are performed. Standards for the required components of informed consent before WES/WGS is performed have been proposed and include a description of confidentiality and a description of how incidental findings will be managed. Methods of reporting findings from WES/WGS are under development. For example, McLaughlin et al, reporting on the MedSeq Project which is testing methods for evaluating and reporting WES/WGS data, described the development of a genome report that highlights results significant to the indication being evaluated.

**Results of Testing With WES/WGS**
1. A variant known to cause human disease is identified. This is a sequence variant that has been shown through prior genetic and clinical research to cause a disease.
2. A variant suspected to cause human disease is identified. Most variants detected by WES sequencing are uncharacterized and some are novel (ie, never known to have been observed in a human sample). Some variants allow for relatively easy and accurate clinical interpretation; however, for most there is little data on which to base an assessment of causality. Tools to facilitate the assessment of causality include bioinformatic analyses, predicted structural changes and others. While these tools may be useful, their predictive power is highly variable.
3. A variant of uncertain significance is identified. Among the known 30,000 to 40,000 variants that reside in the protein-coding portions of the genome, the typical subject will have 3 to 8 actionable variants. (Most of these relate to reproductive risks, ie, heterozygous carrier alleles.) But the remaining thousands are either highly likely to be benign or of uncertain clinical significance. It can be equally as challenging to prove that a variant is benign as it is to prove it is pathogenic.
Currently, nearly all of the variants among the tens of thousands must be considered of uncertain significance.

**Available WES/WGS Testing Services**

Although WES/WGS has been used as a research tool, it is less well-developed as a clinical service. Several laboratories offer WES/WGS as a clinical service. Illumina (San Diego, CA) 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), 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 (Aliso Viejo, CA) offers 2 WGS tests, the ExomeNext and ExomeNext-Rapid, both of which sequence both the nuclear and mitochondrial genomes. GeneDx (Gaithersburg, MD) offers WES with its XomeDx™ test.

Medical centers may also offer WES/WGS as a clinical service. Examples of some of the laboratories offering WES as a clinical service and their indications for testing are summarized in Table 1.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indications for Testing</th>
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<tbody>
<tr>
<td>Ambry Genetics, Aliso Viejo, CA</td>
<td>“The patient’s clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis.”</td>
</tr>
<tr>
<td>GeneDx, Gaithersburg, MD</td>
<td>“a patient with a diagnosis that suggests the involvement of one or more of many different genes, which would, if even available and sequenced individually, be prohibitively expensive”</td>
</tr>
<tr>
<td>Baylor College of Medicine, Houston, TX</td>
<td>“used when a patient’s medical history and physical exam findings strongly suggest that there is an underlying genetic etiology. In some cases, the patient may have had an extensive evaluation consisting of multiple genetic tests, without identifying an etiology.”</td>
</tr>
<tr>
<td>University of California Los Angeles Health System</td>
<td>“This test is intended for use in conjunction with the clinical presentation and other markers of disease progression for the management of patients with rare genetic disorders.”</td>
</tr>
<tr>
<td>EdgeBio, Gaithersburg, MD</td>
<td>Recommended “In situations where there has been a diagnostic failure with no discernible path. In situations where there are currently no available tests to determine the status of a potential genetic disease. In situations with atypical findings indicative of multiple disease[s].”</td>
</tr>
<tr>
<td>Children’s Mercy Hospitals and Clinics, Kansas City</td>
<td>Provided as a service to families with children who have had an extensive negative work-up for a genetic disease; also used to identify novel disease genes.</td>
</tr>
<tr>
<td>Emory Genetics Laboratory, Atlanta, GA</td>
<td>“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”</td>
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</table>

**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.

**Rationale**
The evidence review was created in August 2013 with review of the literature covering the period through August 27, 2013, and updated periodically with literature reviews. The most recent literature review covers the period through September 28, 2015 (see Appendix Table 2 for genetic testing categories).

Analytic Validity

Whole Exome Sequencing
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 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 detection of CNVs than high-resolution microarray testing.

Whole Genome Sequencing
Whole genome sequencing (WGS), is subject to the same considerations related to potential variability in technical performance as WES. In 2014, Dewey et al reported the coverage and concordance of clinically relevant genetic variation 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 platform to evaluate reproducibility of sequence data. Genome sequences were compared with several reference standards. Depending on the sequencing platform, a median of 10% (Illumina Inc.; range, 5%-34%) to 19% (Complete Genomics; range, 18%-21%) of genes associated with inherited disease and a median of 9% (Illumina Inc.; range, 2%-27%) to 17% (Complete Genomics Inc.; range, 17%-19%) of American College of Medical Genetics (ACMG)–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/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%).

Clinical Validity/Clinical Utility

Overview: WES/WGS in Characterizing Mendelian Disorders
The clinical utility of WES and WGS lies in the influence of the results on medical decision making and patient outcomes. There are several ways in which clinical utility can be demonstrated.

- WES/WGS may detect additional mutations that are missed by other testing methods, thus leading to a definitive diagnosis.
  - If the establishment of a definitive diagnosis leads to management changes that improve outcomes, then clinical utility has been established.
  - If the establishment of a definitive diagnosis leads to avoidance of other tests that are unnecessary, then this is another example of clinical utility.
- If WES/WGS is at least as accurate as other methods of sequencing, then an improvement in the efficiency of workup (diagnosis obtained more quickly and/or at less cost), then clinical utility has been established.
Typically, when a phenotype/history suggests a genetic etiology, microdeletions/duplications should be excluded by chromosomal microarray analysis and, if clinically appropriate, other possible disorders like inborn errors of metabolism should also be excluded. If these tests are negative, the potential uses of WES/WGS include facilitating the accurate diagnosis of people with a suspected monogenic (Mendelian) disorder that presents with an atypical presentation or multiple congenital anomalies, is difficult to confirm with clinical or laboratory criteria alone (eg, when disease characteristics are shared among multiple disorders, leading to potentially overlapping differential diagnoses [clinical heterogeneity]), and when there is a long list of possible candidate genes.8

An additional potential use of WES/WGS is when a clinical presentation is suggestive of a specific genetic condition, but targeted testing is negative or unavailable. In this situation, the yield of a definitive diagnosis can be used to evaluate the clinical utility of WES/WGS, also considering whether management changes occur that improve outcomes.

With advances in sequencing capacity, novel sequence variants associated with genetic disorders are rapidly being described. Sequence variants detected on WES/WGS, or any form of NGS, must be classified on a spectrum from almost certainly pathogenic to almost certainly benign. In 2013, the ACMG, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to develop standard terminology for describing sequence variants.9 Guidelines developed by this workgroup, published in 2015, describe criteria for classifying pathogenic and benign sequence variants based on a variety of population, computational and predictive, functional and data, segregation data into 5 categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

WES/WGS for Identifying Novel Mutations
Since publication of the 2013 TEC Special Report, studies continue to demonstrate that WES can be used to identify novel genetic mutations in a range of clinical conditions. In particular, WES/WGS has been evaluated for disorders associated with significant genetic heterogeneity. A sample of such studies is shown in Table 2.

### Table 2: Studies Evaluating WES/WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Condition</th>
<th>No. of Subjects for WES/WGS</th>
<th>Summary of Major Findings</th>
</tr>
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<tbody>
<tr>
<td>Greenway (2014)8</td>
<td>Familial atrial septal defect</td>
<td>2 family members with atrial septal defect</td>
<td>Identification of alpha-cardiac actin (ACTC1) as the candidate disease-causing gene</td>
</tr>
</tbody>
</table>
| Jiang (2013)11     | ASD                                       | 32 patients with ASD        | Identification of deleterious de novo mutations in 6 families (19%) and X-linked or autosomal inherited alterations in 10 families (31%)  
Variants were found in 4 unrecognized, 9 known, and 8 candidate ASD risk genes |
| Kim (2013)12       | Autosomal dominant nonsyndromic hearing loss | 21 family members with AD-NSHL | Identification of a novel mutation in POU4F3 gene as the candidate disease-causing gene                                                                                                                                   |
| Weeke (2014)13     | dLQTS                                     | 65 dLQTS patients and 148 drug-exposed control subjects | Identification of rare variants in KCNE1 and ACN9 as risk factors for dLQTS                                                                                                                                                 |
| Zhou (2014)14      | Syndrome of intermittent fevers, early-onset lacunar strokes, and other neurovascular manifestations, hepato-splenomegaly, and systemic | 3 unrelated subjects with syndrome and unaffected parents | Identification of mutations in CECR1 (cat eye syndrome chromosome region, candidate 1), encoding adenosine deaminase 2 as candidate gene                                                                                                                                 |
vasculopathy

AD-NSHL: autosomal dominant nonsyndromic hearing loss; ASD: autism spectrum disorder; diLQTS: drug-induced long-QT syndrome.

**WES/WGS in Clinical Practice**

Several studies have reported on the use of WES and, less frequently, WGS in clinical practice. Typically the populations included in these studies are those with suspected rare genetic disorders, although the specific patient populations vary.

In 2015, Lee et al reported on a large (n=814) single-center cohort of patients with undiagnosed, suspected genetic conditions who underwent WES. The investigators used a “trio-CES [clinical exome sequencing]” technique which involves sequencing of the proband and 2 family members, typically unaffected parents. For the first approximately 300 cases, all reported variants were confirmed by Sanger sequencing with more than 99% confirmation. After that, variants were evaluated with a QUAL score, a scaled probability of a variant existing at a given site, and only clinically significant mutations with a QUAL score lower than 500 were confirmed. Variants found were annotated to provide information about their effect on protein function, allele frequency in the general population, and prior evidence of disease causality and filtered to select likely pathogenic DNA variants. For variants in probands with family member testing available, variants were categorized as de novo (usually heterozygous in the patient and potentially causing an autosomal dominant condition), homozygous, compound heterozygous, and inherited variants. Variants were evaluated in the context of a “primary gene list” which was determined based on phenotypic key words included in referring clinician notes. Of the 814 patients included, 520 patients (64%) were children, and 254 of those were younger than 5 years at testing. The most common clinical indication for testing was developmental delay in the entire population and in the childhood group (37% and 53%, respectively). In the adult group, ataxia was the most common indication for testing (26%). Overall, a molecular diagnosis with a causative variant in a well-established clinical gene was provided for 213/814 cases (26%; 95% CI 23 to 29%). Of the 264 variants reported in 213 cases, 188 were reported as “likely pathogenic” and 73 were reported as “pathogenic” variants.

In 2014, Yang et al reported on a single-center observational study that included 2000 consecutive patients referred for clinical WES for a suspected genetic disorder. This report excluded 250 patients reported in an earlier publication. The majority of the samples were from pediatric patients, with 900 from children under 5 years (45.0%), 845 from children/adolescents aged 5 to 18 years (42.2%), 244 from adults (12.2%), and 11 fetal samples. The most common indications for testing were neurological disorders or developmental delay (87.8%). Molecular diagnoses were reported for 504 patients (25.2%, 95% CI 23.3% to 27.2%), with a total of 708 presumptive causative variants. Most of the identified disease-associated variants were novel (409/708; 57.8%). Overall, 95 medically-actionable incidental findings were reported in 92 patients (4.6%), most of which (n=59) were included in the American College of Medical Genetics list of 56 genes recommended to be disclosed to patients.

In an earlier study from the same center as reported in Yang et al (2014), Yang et al reported results from the first 250 patients who underwent WES at a single institution. Most patients (80%) were children presenting with phenotypes consistent with a neurologic disorder. Sixty-two patients were identified to have 86 mutated alleles that satisfied criteria for a molecular diagnosis for an overall rate of a positive molecular diagnosis of 25%. Thirty-nine of the patients with a molecular diagnosis had rare genetic diagnoses. In addition to diagnostic findings, 30 patients had medically actionable incidental findings in a total of 16 genes, and 13 had carrier-status mutations in genes from the ACMG-recommended population-screening panel. This study suggests that WES can have a high diagnostic yield in an appropriately-selected population. However, rates of incidental findings were also high, and the impact on clinical outcomes is unknown.
Tammimies et al reported on the results of chromosomal microarray analysis (CMA) and WES in a sample of children with autism spectrum disorders. The patient cohort included 258 consecutively enrolled patients, stratified into three groups based on the presence of major congenital abnormalities and minor physical anomalies (n=168, 37, and 53 considered essential, equivocal, and complex, respectively). All probands underwent CMA testing. WES was performed for 95 proband-parent trios. Among the 95 patients undergoing WES, 8 children (9 mutations) were received an ASD-related molecular diagnosis (8.4%, 95% CI 3.7% to 15.9%). Incidental or medically-actionable findings were reported in 8/95 (8.4%) probands tested with WES, 6 of which were considered medically-actionable.

Other studies have reported the yield of WES/WGS testing in clinical populations, varying depending on the population. Taylor et al report a yield of 21% for disease-causing variants with WES in a population of 217 patients with suspected genetic disorders with no pathogenic variants on prior screening. Among 11 subjects with cardiomyopathy, Golbus et al reported a yield of 82% for pathogenic variants using WGS.

**Clinical Utility: Change in Patient Management with WES/WGS**

As cited in a 2013 TEC Special Report on exome sequencing for patients with suspected genetic disorders, currently there are no published studies that systematically examine potential outcomes of interest such as changes in medical management (including revision of initial diagnoses), and changes in reproductive decision making after a diagnosis of a Mendelian disorder by WES. A small number of studies of patient series, and a larger number of very small series or family studies report anecdotal examples of medical management and reproductive decision-making outcomes of exome sequencing in patients who were not diagnosed by traditional methods. These studies show that over and above traditional molecular and conventional diagnostic testing, exome sequencing can lead to a diagnosis that influences patient care and/or reproductive decisions, but give no indication of the proportion of patients for which this is true.

Since the publication of the 2013 TEC Special Report, several studies have reported on potential benefits, in terms of medical management changes or avoidance of alternative testing, following WES/WGS. Soden et al reported on the use of WGS and/or WES in parent-child trios for 119 children with neurodevelopmental disorders. A definitive molecular diagnostic of an established genetic disorder was identified in 45 of the 100 families with children affected by neurodevelopmental disorders (53 of 119 affected children). Chart reviews and interviews with referring physicians were used to assess changes in short-term management following WES/WGS, and changed patient management and/or clinical impression was reported in 22/45 families (49%). In a retrospective study of 78 children with neurodevelopmental disorders with a prior unrevealing workup who underwent WES, Srivastava et al reported a presumptive diagnostic testing rate of 41%. Results of WES changed patient management in all cases, most often related to reproductive planning (n=27), along with additional disease monitoring in 4 cases, further workup for systemic involvement in 6 cases, and 7 medication changes.

Iglesias et al reported on clinical changes that occurred after WES/WGS in a broader population of 115 patients with a genetically undefined disorder. The most common indications for WES evaluation were birth defects, developmental delay, and seizures, in 24.3%, 25.2%, and 14% of patients, respectively. A definitive diagnosis was made in 37 cases (32.2%). The clinical implications of testing are described qualitatively for patients with a genetic diagnosis. In 6 cases, it was noted that genetic information was used for reproductive planning; in 11 cases, patients were noted to have a change in medical management or surveillance or testing for related conditions.

With wider genome coverage in sequencing comes an increased likelihood that testing will identify potentially clinically-significant gene mutations that may be unrelated to the phenotype being evaluated. The ACMG issued recommendations in 2013 outlining 56 genes associated with 24 conditions that should be reported to patients when known or likely pathogenic variants are detected. The risks and benefits of WES/WGS in terms of detection of clinically actionable incidental findings should be evaluated on an individual basis.
Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. 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>NCT02175264</td>
<td>Genetic Basis of Non Syndromic Congenital Diaphragmatic Hernia</td>
<td>78</td>
<td>Jul 2016</td>
</tr>
<tr>
<td>NCT02067962</td>
<td>Identification of Genes Involved in Juvenile Idiopathic Arthritis by Whole Exome Sequencing</td>
<td>30</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02077894</td>
<td>Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Cond</td>
<td>150</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT01087320</td>
<td>Whole Genome Medical Sequencing for Gene Discovery</td>
<td>400</td>
<td>No date</td>
</tr>
<tr>
<td>NCT00340626</td>
<td>Genetic Analysis of Hereditary Non-Syndromic Oral Clefts</td>
<td>1000</td>
<td>No date</td>
</tr>
<tr>
<td>NCT01952275</td>
<td>Assessment of the Enrichment of Rare Coding Genetic Variants in Patients Affected by Neutrophil-Mediated Inflammatory Dermatoses</td>
<td>660</td>
<td>Jan 2020</td>
</tr>
<tr>
<td>NCT01858285</td>
<td>Genetics of Epilepsy and Related Disorders</td>
<td>500</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02014961</td>
<td>Worm Study: Identification of Modifier Genes in a Unique Founder Population With Sudden Cardiac Death</td>
<td>223</td>
<td>Apr 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Summary of Evidence
The evidence for the use of WES/WGS in individuals with suspected genetic disorders includes multiple studies that describe detection of novel genetic variants and several relatively large cohort studies that report on the yield of WES/WGS. Relevant outcomes include test accuracy, test validity, other test performance measures, changes in reproductive decision making, morbid events, health status measures, and resource utilization. A potential major indication for the use of WES/WGS is for molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder but when a specific mutation is not suspected or with suspected genetic disorders that have a large degree of genetic heterogeneity. Such patients may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup involving a variety of traditional molecular and other types of conventional diagnostic tests. For some of these patients, WES or WGS, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant. There is developing evidence about the use of WES/WGS in clinical practice, with studies describing yields of a molecular diagnosis in approximately 25% of patients without a diagnosis after a previous workup. No studies were identified that directly compared WES/WGS with alternative testing strategies in terms of the yield of testing for pathogenic variants associated with the phenotype being evaluated and variants of uncertain significance and incidental clinically-actionable findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION
The American College of Medical Genetics (ACMG) states that diagnostic testing with WES (and 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.

The ACMG states 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 states that WGS/WES should not be used at this time as an approach to prenatal screening, or as a first-tier approach for newborn screening.

In March 2013, an ACMG board finalized approval of their recommends for reporting incidental findings in WGS and WES. A working group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing and recommended 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.

**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:


**Billing Coding/Physician Documentation Information**

81415 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis

81416 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)

81417 Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)

81425 Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis

81426 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)

81427 Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
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