Protocol

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

(204102)

Medical Benefit		**Effective Date**: 07/01/17	**Next Review Date**: 03/19
Preauthorization	No	**Review Dates**: 03/17, 03/18	

This protocol considers this test or procedure to have investigational applications. If the physician feels this service is medically necessary for these applications, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With multiple unexplained congenital anomalies or a neurodevelopmental disorder	Interventions of interest are: • Whole exome sequencing	Comparators of interest are: • Standard clinical workup	Relevant outcomes include: • Test accuracy • Test validity • Functional outcomes • Changes in reproductive decision making • Resource utilization
Individuals: • With a suspected genetic disorder lacking multiple congenital anomalies or a neurodevelopmental phenotype	Interventions of interest are: • Whole exome sequencing	Comparators of interest are: • Standard clinical workup	Relevant outcomes include: • Test accuracy • Test validity • Functional outcomes • Changes in reproductive decision making • Resource utilization
Individuals: • With a suspected genetic disorder	Interventions of interest are: • Whole genome sequencing	Comparators of interest are: • Standard clinical workup	Relevant outcomes include: • Test accuracy • Test validity • Functional outcomes • Changes in reproductive decision making • Resource utilization

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.

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.

Policy

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

- The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing.
- There is potential for a change in management and clinical outcome for the individual being tested.
- A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (e.g., chromosomal microarray analysis and/or targeted single-gene testing), **OR** when previous genetic testing has failed to yield a diagnosis and the affected individual is faced with invasive procedures or testing as the next diagnostic step (e.g., muscle biopsy).

WES is considered **investigational** for the diagnosis of genetic disorders in all other situations.

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

WES and WGS are considered **investigational** for screening for genetic disorders.

Policy Guidelines

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 protocol 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 protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

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

ing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

Whole exome sequencing and whole genome sequencing are unlikely to impact therapeutic decision-making in the clinical management of the patient and are considered **not medically necessary**.

Background

Whole Exome Sequencing and Whole Genome Sequencing

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

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

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations.[1] The search for a diagnosis may thus become a time-consuming and expensive process.

WES and WGS Technology

WES or WGS using next-generation sequencing technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual (≈ 85%), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of 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 five categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.[2]

WES and WGS Testing Services

Several laboratories offer WES and WGS as a clinical service. Illumina offers three 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 two WGS 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

Laboratory	Laboratory Indications for Testing
Ambry Genetics (Aliso Viejo, CA)	"The patient's clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis."
GeneDx (Gaithersburg, MD)	"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"
Baylor College of Medicine (Houston, TX)	"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."
Illumina (San Diego, CA)	The TruGenome Undiagnosed Disease Test is indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology.
University of California Los Angeles Health System	"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."
EdgeBio (Gaithersburg, MD)	Recommended "In situations where there has been a diagnostic failure with no discernible path. In situations where there are currently no available tests to determine the status of a potential genetic disease. In situations with atypical findings indicative of multiple disease[s]."
Children's Mercy Hospitals and Clinics (Kansas City, MO)	Provided as a service to families with children who have had an extensive negative workup for a genetic disease; also used to identify novel disease genes.
Emory Genetics Laboratory (Atlanta, GA)	"Indicated when there is a suspicion of a genetic etiology contributing to the proband's manifestations."

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Whole exome or genome sequencing tests as a clinical service are available under the auspices of the CLIA. 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.

Related Protocols

Genetic Testing for Developmental Delay and Autism Spectrum Disorder

Genetic Testing for Epilepsy

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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