Corporate Medical Policy

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

File Name:	whole_exome_and_whole_exome_sequencing_for_diagnosis_of_genetic_disorders
Origination:	10/2013
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Next CAP Review:	3/2019
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Description of Procedure or Service

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 (NGS) techniques to sequence both coding and non-coding 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 impacting the search for a diagnosis, informing follow-up that can benefit a child by reducing morbidity, and 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 can become a time-consuming and expensive process. WES or WGS using NGS technology may facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual (approximately 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; duplictions; 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 to WES, but requires greater data analytics. Technical aspects of WES and WGS are evolving, including 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 types of data into 5 categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

Available WES/WGS Testing Services

Although WES/WGS have been used as research tools, they are less well-developed as a clinical service. Several laboratories offer WES/WGS as a clinical service. Illumina offers 3 TruGenome tests: the TruGenome Undiagnosed Disease Test (indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology), TruGenome™ Predisposition Screen (indicated for healthy patients interested in learning about their carrier status and genetic predisposition toward adult-onset conditions), and the TruGenome™ Technical Sequence Data (WGS for labs and physicians who will make their own clinical interpretations). Ambry Genetics offers 2 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/WGS as a clinical service.

Examples of laboratories offering WES as a clinical service and their indications for testing are summarized in the table below:

Examples of laboratories offering exome sequencing as a clinical service

Laboratory	Laboratory Indication 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, even if available and sequencing 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 underling 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 work-up 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 probands manifestations."

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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 Amendment (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.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Whole Exome Sequencing may be considered medically necessary for the evaluation of unexplained congenital or neurodevelopment disorder in children as indicated below.

Whole Exome Sequencing is considered investigational for the diagnosis of genetic disorders in all other situations. Whole Genome Sequencing is considered investigational for the diagnosis of genetic disorders. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is covered

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

1. The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing.
2. There is potential for a change in management and clinical outcome for the individual being tested.
3. A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing, such as 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 invasisve procedures/testing as the next diagnostic step, such as muscle biopsy.

When Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is not covered

Whole exome sequencing is considered investigational for the diagnosis of genetic disorders in all other situations.

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

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Policy Guidelines

The policy statement is intended to address the use of whole exome and whole genome sequencing for diagnosis 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.

The evidence for individuals who have multiple unexplained congenital anomalies or a neurodevelopmental disorder who receive whole exome sequencing (WES), includes large case series and a within-subject comparison. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilitzation. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but the 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 age of the individual, 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.

The evidence for the use of WES for individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder who receive WES, includes small case series and prospective research studies. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilitzaiton. There are increasing reports regarding the use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yield in these studies ranges from as low as 3% to 60%, with the possibility of incidental findings a concern with WES. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and 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 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.

The evidence for the use of whole genome sequencing (WGS) in individuals with suspected genetic disorders 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 to WES, however, the technology is limited by the amount of data generated and greater need for storage and analytic capability. Currently, there is limited data on the clinical use of WGS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *81415*, *81416*, *81417, 81425, 81426, 81427, 0010U, 0012U*

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For policy titled, "Whole Exome Sequencing"

Dixon-Salazar TJ, Silhavy JL, Udpa N et al. Exome sequencing can improve diagnosis and alter patient management. Science translational medicine 2012; 4(138):138ra78.

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. Volume 28 T.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 9/12/13

Medical Director review 10/2013

Specialty Matched Consultant Advisory Panel review 1/2014

For policy titled, "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders"

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 11/13/14

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 10/15/15

Specialty Matched Consultant Advisory Panel review 3/2106

Medical Director review 3/2016

Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. Front Pediatr, 2015; 3:67. PMID 26284228.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 11/2016

Medical Director review 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 11/2016

Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.102, 10/2017

Medical Director review 10/2017

Specialty Matched Consultant Advisory Panel review 3/2018

Medical Director review 3/2018

Policy Implementation/Update Information

For policy titled, "Whole Exome Sequencing"

10/15/13New policy developed. Whole exome sequencing is considered investigational. Medical Director review 10/2013. (mco)

2/25/14 Specialty Matched Consultant Advisory Panel review 1/2014. No changes to PolicyStatements. (mco)

For policy titled, "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders"

12/30/14 References updated. Policy retitled from "Whole Exome Sequencing" to "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders". Description section revised. Policy Statement updated to include whole genome sequencing. Policy Guidelines section revised. CPT codes 81415, 81416, 81417, 81425, 81426, 81427 added to Billing/Coding section for effective date 1/1/2015. (td)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/2015. Medical Director review 4/2015. Policy Statements remain unchanged. (td)

12/30/15 Description section updated. Policy Guidelines section updated. Billing/Coding section updated. References updated. (td)

4/29/16 References updated. Specialty Matched Consultant Advisory Panel review 3/2016. Medical Director review 3/2016. (td)

12/30/16 Policy statement extensively revised to add coverage for whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children, if all indicated criteria are met. References updated. Medical Director review 11/2016.(jd)

4/28/17 Description section updated. Added laboratory, Illumina to the table titled: "Examples of laboratories offering exome sequencing as a clinical service". Policy guidelines updated. Specialty Matched Consultant Advisory Panel review 3/2107. Medical Director review 3/2017. (jd)

7/28/17 Code section updated with the following additions: 0010U, 0012U; effective 8/1/17. (jd)

11/10/17 Policy guidelines revised. Refernces updated. Medical Director review 10/2017. (jd)

4/13/18 Specialty Matched Consultant Advisory Panel review 3/2108. Medical Director review 3/2018. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.