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
Last CAP Review: 3/2016
Next CAP Review: 3/2017
Last Review: 3/2016

Description of Procedure or Service

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 techniques to sequence both coding and non-coding regions of the genome. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases.

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, electrophysiological, 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 gold 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 an individual’s exomic variation in a single assay. This profile 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 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
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

increased above that of traditional Sanger sequencing, and exome sequencing has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes.

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 and WGS include technical and implementation challenges. There are issues of error rates due to uneven sequencing coverage, gaps in exon capture prior to 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 (i.e. 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; e.g., 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.

**Results of testing with WES and 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 (i.e. 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 upon 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 30,000-40,000 variants that reside in the protein-coding portions of the genome, the typical subject will have three to eight actionable variants. (Most of these relate to reproductive risks, that is, 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
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

tens of thousands must be considered of uncertain significance.

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 (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, which sequence both the nuclear and the 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 the table below:

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indication for Testing</th>
</tr>
</thead>
<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, even if available and sequencing 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 probands manifestations.”</td>
</tr>
</tbody>
</table>
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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.

***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 and Whole Genome Sequencing are 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

Not Applicable

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

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

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 the use of whole exome sequencing (WES)/whole genome sequencing (WGS) in individuals with suspected genetic disorders includes multiple studies describing detection of novel genetic variants and several relatively large cohort studies reporting on the yield of WES/WGS. Relevant outcomes are test accuracy and 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 the molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder but when a specific mutation is not suspected or patients 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
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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.

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

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”


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.


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”


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Specialty Matched Consultant Advisory Panel review 3/2106

Medical Director review 3/2016

Policy Implementation/Update Information
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

**For policy titled, “Whole Exome Sequencing”**

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


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.