



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Whole Exome Sequencing

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 11/20/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers whole exome sequencing (WES) to be **investigational*** for all indications.

Background/Overview

Whole exome sequencing is defined as targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding deoxyribonucleic acid (DNA). Whole exome sequencing has 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 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 profile 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.



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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.

Limitations of Whole Exome Sequencing

At this time, the limitations of WES 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.

There are also ethical questions about reporting incidental findings, such as identifying medically relevant mutations in genes unrelated to the diagnostic question, sex chromosome abnormalities and non-paternity when family studies are performed.

Results of testing with Whole Exome Sequencing

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 3 to 8 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



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prove it is pathogenic. Currently, nearly all of the variants among the tens of thousands must be considered of uncertain significance.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

No U.S. FDA-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Examples of laboratories offering 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."
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	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 proband's manifestations."

Centers for Medicare and Medicaid Services (CMS)

No national coverage determination is identified.



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Rationale/Source

Literature Review

Analytic Validity

Whole exome sequencing has not yet been well-standardized for the clinical laboratory and has not been fully characterized in publicly available documents with regard to the analytic validity for the various types of relevant mutations. The few existing professional guidelines give only high-level direction.

Technical limitations include error rates due to uneven sequencing coverage and gaps in exon capture prior to sequencing, and the variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

Clinical Utility

The clinical utility of exome sequencing 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.

- Whole exome sequencing may detect additional mutations that are missed by other testing methods, thus leading to a definitive diagnosis.
 - o If the establishment of a definitive diagnosis leads to management changes that improve outcomes, then clinical utility has been established.
 - o 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 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.

Whole Exome Sequencing in Characterizing Mendelian Disorders

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 include facilitating the accurate diagnosis of individuals 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 (e.g., 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.

An additional potential use of WES 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, also considering whether management changes occur that improve outcomes.

As cited in a 2013 Technology Evaluation Center (TEC) Special Report, 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



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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. The publication of a large number of small diagnostic studies with positive results but few with negative results, raise the possibility of publication bias—the impact of which is unknown.

Summary

Whole exome sequencing using next-generation sequencing has been recently introduced as a laboratory-developed diagnostic clinical laboratory test. A potential major indication for use is molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder or for patients with known genetic disorders that have a large degree of genetic heterogeneity involving substantial gene complexity. Such patients may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic work-up involving a variety of traditional molecular and other types of conventional diagnostic tests. For some of these patients, WES, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant.

However, at this time, there are many technical limitations to WES that prohibit its use in routine clinical care. The limited experience with WES on a population level leads to gaps in understanding and interpreting ancillary information and variants of uncertain significance. As a result, the risk/benefit ratio of WES testing is poorly defined. Therefore, the use of WES is considered investigational for all indications.

References

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479
HCPCS	No code
ICD-9 Diagnosis	All diagnoses
ICD-9 Procedure	No code

Policy History

Original Effective Date: 11/20/2013

Current Effective Date: 11/20/2013

11/07/2013 Medical Policy Committee review

11/20/2013 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 11/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. reference to federal regulations.

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