MASSACHUSETTS

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Medical Policy

Whole Exome Sequencing

Table of Contents

Policy Number: 457

BCBSA Reference Number: 2.04.102

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Whole exome sequencing is considered **INVESTIGATIONAL** for all indications.

Prior Authorization Information

Commercial Members: Managed Care (HMO and POS)

This is **NOT** a covered service.

Commercial Members: PPO, and Indemnity

This is **NOT** a covered service.

Medicare Members: HMO Blue[SM]

This is **NOT** a covered service.

Medicare Members: PPO Blue[SM]

This is **NOT** a covered service.

CPT Codes / HCPCS Codes / ICD-9 Codes

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

There are no specific codes for this procedure.

Description

Whole exome sequencing (WES) is defined as targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA. WES has been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases.

Background

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. (1) 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 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.

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 WES

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 WES (2)

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

Summary

Whole exome sequencing (WES) 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.

Policy History

Date	Action
3/2014	New medical policy describing investigational indications. Effective 3/1/2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines

Clinical Exception Process
Medical Technology Assessment Guidelines

References

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4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. TEC Assessments 2013; Volume 28 Tab TBD.
5. Green RC, Berg JS, Grody WW et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 2013; 15(7):565-74.