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Medical Policy Manual

Topic: Whole Exome Sequencing

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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 (NGS) 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 (PCR) 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.

WES using NGS 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, and constitutes approximately 1% of the whole genome. It is believed that the exome contains about 85% of heritable disease-causing mutations.

Published studies have shown that exome sequencing can be used to detect previously annotated pathogenic mutations and reveal new likely pathogenic mutations in known and unknown genes. A limited number of studies have reported that the diagnostic yield of exome sequencing appears to be significantly increased above that of traditional Sanger sequencing, while also being faster and more efficient 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.

Regulatory Status

No U.S. Food and Drug Administration (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	"The patient's clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis."
GeneDx	"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	"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	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	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	"Indicated when there is a suspicion of a genetic etiology contributing to the proband's manifestations."

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and

3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of the literature search was on evidence related to the ability of genetic test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

Literature Review

Analytic Validity

Whole exome sequencing (WES) 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.

Technical limitations include error rates due to uneven sequencing coverage and gaps in exon capture prior to sequencing. In addition, the variability due to 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. In order for clinical utility to be established, evidence would be needed of the ability of WES to provide the following improvements over other sequencing methods:

- Ability to establish a definitive diagnosis by detection of additional mutations not found by other testing methods and leading to management changes that improve outcomes and/or eliminate the need for additional testing
- Equivalent or superior accuracy attained with superior efficiency of workup (e.g., diagnosis obtained more quickly) compared with other methods of sequencing.

Systematic Reviews

A 2013 BlueCross BlueShield Association Technology Evaluation Center (TEC) Special Report found no published studies that systematically examined 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.[2] The evidence was limited to a small number of studies of patient series and a larger number of very small series or family studies that reported anecdotal examples of medical management and reproductive decision-making outcomes of exome sequencing in patients who were not diagnosed by traditional methods. These studies showed that, over and above traditional molecular and conventional diagnostic testing, exome sequencing could lead to a diagnosis that influenced patient care and/or reproductive decisions, but gave no indication of the proportion of patients for which this was true. The report noted that 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.

Nonrandomized Studies

Evidence published since the publication of the 2013 TEC Special Report continues to be limited to case series and nonrandomized studies.[3-6]

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were found that recommended the use of WES for any indication.

American College of Medical Genetics (ACMG)[7]

- A 2012 consensus-based Policy Statement from the ACMG noted the following potential indications and disadvantages for genomic sequencing:
    - Diagnostic testing with WES (and whole genome sequencing [WGS]) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:
        1. The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
        2. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
        3. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
        4. A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.
    - WGS/WES for screening:
        1. WGS/WES may be considered in preconception carrier screening using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.
        2. WGS/WES should not be used at this time as an approach to prenatal screening, or as a first-tier approach for newborn screening.
    - Disadvantages of WGS/WES
        1. WES may miss some clinically significant mutations due to inefficient capture of certain exons.
        2. Overall analytical sensitivity is still being defined for both WES and WGS.
        3. WGS/WES are highly likely to reveal secondary findings (also called incidental or unanticipated findings) such as finding a previously unsuspected high risk of future disease or an unrecognized disorder in an asymptomatic patient. “When interpreting secondary findings, or results that are generated in the course of screening asymptomatic individuals, it is critical that the standards for what is reportable be high to avoid burdening the health care system and consumers with what could be very large numbers of false positive results.”

- In March 2013, an ACMG board finalized approval of their recommendations for reporting incidental findings in whole genome and whole exome sequencing. [8] A working group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing and recommended that when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician.

Summary

The current evidence is insufficient to determine whether whole exome sequencing (WES) can be used to improve patient health outcomes. In addition, there are technical limitations that prohibit the use of WES in routine clinical care such as the lack of standardized laboratory procedures, gaps in interpreting ancillary information, and the detection of variants of uncertain significance. Test results related to variants of uncertain significance may potentially cause harm by leading to additional unnecessary interventions that would not otherwise be considered based on the patient's clinical presentation and/or family history. As a result the benefits of WES testing is unknown. Therefore, the use of WES is considered investigational for all indications.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
HCPCS	None	