MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**WHOLE EXOME AND WHOLE GENOME SEQUENCING FOR DIAGNOSIS OF GENETIC DISORDERS**
Policy Number	**2.02.46**
Category	**Technology Assessment**
Effective Date	**06/18/15**
Revised Date	**05/25/16, 08/17/17, 05/17/18, 06/20/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

Based upon our criteria and review of the peer-reviewed literature, whole exome sequencing (WES) and whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders.

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.

II. Whole exome sequencing (WES) and whole genome sequencing (WGS) should only be offered in a setting with adequately trained health care providers (e.g., medical geneticist or an affiliated genetic counselor) to provide appropriate pre-and post-test genetic counseling that will guide decisions regarding treatment options.

III. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

IV. If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient or family member then the testing is not medically appropriate.

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

Refer to Corporate Medical Policy #2.02.42 Chromosomal Microarray (CMA) Analysis for the Prenatal Evaulation and Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder

Refer to Corporate Medical Policy #4.01.03 Preconception and Prenatal Genetic Testing/Counseling and Preimplantation Genetic Diagnosis (PGD

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

DESCRIPTION

Diagnostic confirmation of an individual with features suggestive of an inheritable disease (Mendelian disorder) may include traditional molecular and conventional diagnostic tests which may still yield an inconclusive clinical diagnosis after exhaustive and expensive testing. These individuals may be candidates for WES or WGS. WES or WGS utilizes next-generation or massively parallel sequencing technology which allows multiple genes to be analyzed at one time and may return a pathogenic variant that is associated with a gene-causing disease. WGS processes genomic DNA (both coding and non-coding portions of the gene) followed by a series of computational analyses to determine the sequence of

the sample DNA as compared to a reference DNA sequence. WGS is able to evaluate about 90% of the genome. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of the protein-coding DNA and comprises approximately 1.5% of the genome and contains approximately 85% of highly penetrant genetic disease DNA variations. To perform WES testing, the genomic DNA is hybridized to artificial DNA which is then sequenced similarly to WGS. Approximately 85-90% of the exome is covered by WES with less effective coverage in the non-protein-coding portion of the genes. Standards for testing methods, reporting of results, interpretation of results as well as social and ethical questions are areas where additional research is still needed before whole genome or exome sequencing can be incorporated into clinical practice.

Whole genome or whole exome sequencing results include three distinct categories: a variant known to cause human diseases, a variant suspected to cause human disease, and a variant of uncertain significance. Standards, or algorithms still need to be developed to insure accuracy, interpretation of results, continuing assessment of gene variants, as well as, ethical issues. Studies have shown technical difficulties in reproducing and confirming variations by another second testing method. Identification of genetic variants and their significance relies on the database that is used. Current databases are inconsistent with variable information and there is no set standard for updating these databases. There is no standardization in the approach of reporting incidental findings to individuals or the implications of reporting benign or catastrophic disease. More research is needed to expand databases, standardize test methods and interpretation of results and reporting of results for whole exome and whole genome sequencing to be incorporated into clinical practice instead of its use as a research tool.

RATIONALE

Published exome sequencing studies show that the technology can be used to detect previously cataloged pathogenic mutations and reveal new likely pathogenic mutations in known and unknown genes. In addition, WES appears to have a higher diagnostic yield, quicker return of results, and is more efficient compared to traditional Sanger sequencing.

A 2013 Blue Cross Blue Shield Association TEC Special Report on exome sequencing for patients with suspected genetic disorders, stated there are currently 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 whole exome sequencing. A small number of studies of patient series, and a larger number of very small 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 gave 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. Since publication of the 2013 TEC Special Report, studies continue to demonstrate that WES can be used to identify novel genetic mutations in a range of clinical conditions. However, evidence related to the use of WES test results in changes in medical management or reproductive decision making is limited.

The American College of Medical Genetics (ACMG) states that *diagnostic testing* with WES (and WGS) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

I. 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.
II. 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.
III. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
IV. 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.

The ACMG states that for *screening* purposes 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.

ACMG states that WGS/WES should not be used at this time as an approach to prenatal screening, or as a first-tier approach for newborn screening.

In March 2013, an ACMG board finalized approval of their recommends for reporting incidental findings in WGS and WES. 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.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7
81407	Molecular Pathology Procedure Level 8
81408	Molecular Pathology Procedure Level 9
81415 **(E/I)**	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416 **(E/I)**	Exome (e.g, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417 **(E/I)**	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425 **(E/I)**	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426 **(E/I)**	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g, parents, siblings) (List separately in addition to code for primary procedure)
81427 **(E/I)**	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g, updated knowledge or unrelated condition/syndrome)
0036U **(E/I)**	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses (e.g., EXaCT-1 Whole Exome Testing)

Code	Description
0094U (**E/I)**	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)(effective 7/1/2019)

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HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
Numerous Diagnoses	

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*Key Article

KEY WORDS

Exome, genome, WES, WGS

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=128&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAQBAAAA&