2.04.102  Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Section 2.0 Medicine  Effective Date  January 30, 2015

Subsection  Original Policy Date  January 30, 2015  Next Review Date  January 2016

Description
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.

(WES) and WGS using next-generation sequencing have been recently introduced as a laboratory-developed diagnostic clinical laboratory test. A potential major indication for their 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 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 diagnosis, may return a likely pathogenic variant.

Related Policies
•  N/A

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

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.

Coding
There are specific CPT codes for this testing:
•  81415: Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
Medical Policy

• **81416**: Sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)

• **81417**: Re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)

• **81425**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis

• **81426**: Sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)

• **81427**: Re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)

Prior to 2015, there are no specific CPT codes for whole exome sequencing. It would likely be reported with the unlisted molecular pathology code 81479.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**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, electrophysiologic, 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 criterion 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 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 a person’s exomic variation profile in a single assay. This profile is limited to most of the protein coding sequence of an individual (~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.

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/WGS include technical and implementation challenges. There are issues of error rates due to uneven sequencing coverage, gaps in exon capture before 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.
Results of Testing With WES/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 on 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 to 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, i.e., 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.

Regulatory Status

No U.S. Food and Drug Administration–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.

Table 1: Examples of Laboratories Offering Exome Sequencing as a Clinical Service

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indications for Testing</th>
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<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, if even available and sequenced 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”</td>
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</table>
management of patients with rare genetic disorders.”

<table>
<thead>
<tr>
<th>Institution</th>
<th>Description</th>
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<tbody>
<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 proband’s manifestations.”</td>
</tr>
</tbody>
</table>

Although WGS has been used as a research tool, it is less well-developed as a clinical service. Several laboratories offer 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.) AmbryGenetics (Aliso Viejo, CA) offers 2 WGS tests, the ExomeNext and ExomeNext-Rapid, both of which sequence both the nuclear and mitochondrial genomes.

**Analytic Validity**

**Whole Exome Sequencing**

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. 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 before 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. WES may be less sensitive for the detection of copy number variants than high-resolution microarray testing.4

**Whole Genome Sequencing**

For whole genome sequencing (WGS), there are similarly few standards for clinical laboratory testing. In 2014, Dewey et al reported the coverage and concordance of clinically relevant genetic variation provided by WGS technologies in 12 healthy adult volunteers. All subjects underwent WGS with the Illumina platform; 9 subjects also underwent WGS by the Complete Genomics platform to evaluate reproducibility of sequence data. Genome sequences were compared with several reference standards. Depending on the sequencing platform, a median of 10% (Illumina Inc.; range, 5%-34%) to 19% (Complete Genomics Inc.; range, 18%-21%) of genes associated with inherited disease and a median of 9% (Illumina Inc.; range, 2%-27%) to 17% (Complete Genomics Inc.; range, 17%-19%) of American College of Medical Genetics (ACMG)–reportable genes were not covered at a minimum threshold for genetic variant discovery. The
genotype concordance between sequencing platforms was high for common genetic variants, for single nucleotide variants in protein coding regions of the genome, and among candidate variants for inherited disease risk. However, genotype concordance between sequencing platforms for small insertion/deletion variants was moderate overall (median, 57%; range, 53%-59%) and in protein coding regions of the genome (median, 66%; range, 64%-70%) but was substantially lower among genetic variants that were candidates for inherited disease risk (median, 33%; range, 10%-75%).

Clinical Utility

The clinical utility of WES and WGS 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.

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

WES/WGS 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/WGS include facilitating the accurate diagnosis of people 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.6

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

As cited in a 2013 TEC Special Report on exome sequencing for patients with suspected genetic disorders, 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. 7 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 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.

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. A sample of such studies is shown in Table 2. However, evidence related to the use of WES test results in changes in medical management or reproductive decision making is limited.

### Table 2: Studies Evaluating WES/WGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Condition</th>
<th>No. of Subjects for WES/WGS</th>
<th>Summary of Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenway</td>
<td>Familial atrial septal defect</td>
<td>2 family members</td>
<td>• Identification of alpha-cardiac actin (ACTC1) as the candidate disease-causing gene</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td>with atrial septal defect</td>
<td></td>
</tr>
<tr>
<td>Jiang</td>
<td>ASD</td>
<td>32 patients with ASD</td>
<td>• Identification of deleterious de novo mutations in 6 families (19%) and X-linked or</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td>autosomal inherited alterations in 10 families (31%)</td>
</tr>
<tr>
<td>Kim</td>
<td>Autosomal dominant nonsyndromic hearing loss</td>
<td>21 family members</td>
<td>• Variants were found in 4 unrecognized, 9 known, and 8 candidate ASD risk genes</td>
</tr>
<tr>
<td>(2013)</td>
<td>diLQTS</td>
<td>with AD-NSHL</td>
<td></td>
</tr>
<tr>
<td>Weeke</td>
<td>diLQTS</td>
<td>65 diLQTS patients</td>
<td>• Identification of rare variants in KCNE1 and ACN9 as risk factors for diLQTS</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td>and 148 drug-exposed control</td>
<td></td>
</tr>
<tr>
<td>Zhou</td>
<td>Syndrome of intermittent fevers, early-onset lacunar</td>
<td>3 unrelated subjects with</td>
<td>• Identification of mutations in CECR1 (cat eye syndrome chromosome region, candidate 1), encoding adenosine deaminase 2 as candidate gene</td>
</tr>
<tr>
<td>(2014)</td>
<td>strokes, and other neurovascular manifestations,</td>
<td>syndrome and unaffected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hepatosplenomegaly, and systemic vasculopathy</td>
<td>parents</td>
<td></td>
</tr>
</tbody>
</table>

AD-NSHL: autosomal dominant nonsyndromic hearing loss; ASD: autism spectrum disorder; diLQTS: drug-induced long-QT syndrome.

One study was identified that addressed the use of either WES or WGS in clinical practice. Yang et al reported results from the first 250 patients who underwent WES at a single institution. Most patients (80%) were children presenting with phenotypes consistent with a neurologic disorder. Sixty-two patients were identified to have 86 mutated alleles that satisfied criteria for a molecular diagnosis for an overall rate of a positive molecular diagnosis of 25%. Thirty-nine of the patients with a molecular diagnosis had rare genetic diagnoses. In addition to diagnostic findings, 30 patients had medically actionable incidental findings in a total of 16 genes, and 13 had carrier-status mutations in genes from the ACMG-recommended population-screening panel. This study suggests
that WES can have a high diagnostic yield in an appropriately-selected population. However, rates of incidental findings were also high, and the impact on clinical outcomes is unknown.

**Ongoing and Unpublished Clinical Trials**

An online search of ClinicalTrials.gov on August 6, 2014, identified a number of studies related to the use of WES, most of which were studies designed to identify new mutations associated with a range of clinical conditions, including juvenile idiopathic arthritis (NCT02067962), severe early onset epilepsies (NCT01858285), nonsyndromic congenital diaphragmatic hernia (NCT02175264), neutrophil-mediated skin disorders (NCT01952275), and inherited and congenital eye conditions (using WES and WGS; NCT02077894). Similarly, several studies of WGS were identified that were designed to identify new mutations associated with several clinical conditions, including multiple congenital anomaly syndromes (NCT01087320) and hereditary nonsyndromic oral clefts (NCT00340626).

Studies using WES or WGS in clinical decision making include:

- **Worm Study: Identification of Modifier Genes in a Unique Founder Population With Sudden Cardiac Death (NCT02014961)** – This is a prospective case-control study to compare differences in genetic profiles on WES for subjects who are carriers for mutations associated with long-QT syndrome and Brugada syndrome expressing different phenotypes and nonmutation carriers. Enrollment is planned for 400 subjects; the estimated study completion date is July 2024.

- **NCGENES: North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing (NCT01969370)** – This is a randomized, single-blind study to compare outcomes for patients who have the option to receive nonactionable incidental genetic information with a control group among patients who are considered to have a significant chance of having a genetic disorder. The primary outcome is the extent of test-specific distress 2 weeks after return of results. Enrollment is planned for 750 subjects; the estimated study completion date is December 2015.

**Summary of Evidence**

Whole exome sequencing (WES) and whole genome sequencing (WGS) using next-generation sequencing have been recently introduced as a laboratory-developed diagnostic clinical laboratory test. A potential major indication for their 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 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 diagnosis, may return a likely pathogenic variant.

However, at this time, there are many technical limitations to WES and WGS that prohibit their 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. WGS has also been used on a limited basis on a population level; additionally, 1 study demonstrated poor concordance between WGS testing platforms and with other forms of sequencing. Therefore, the use of WES and WGS is considered investigational for all indications.
Supplemental Information

Practice Guidelines and Position Statements

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:

a. 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.

b. 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.

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

d. 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


**Documentation Required for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
The following services are considered investigational and therefore not covered for any indication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81415</td>
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<td></td>
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<td>Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)</td>
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<td>81426</td>
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</tr>
<tr>
<td></td>
<td>81427</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81460</td>
<td>Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

Unlisted molecular pathology procedure
This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>1/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements**

This service (or procedure) is considered medically necessary in certain instances and investigational in others (refer to policy for details).

For instances when the indication is medically necessary, clinical evidence is required to determine medical necessity.

For instances when the indication is investigational, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.