Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 12/21/2016

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.

Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be met for whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of the following criteria are met:

- The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing.
- There is potential for a change in management and clinical outcome for the individual being tested.
- A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (e.g., chromosomal microarray analysis and/or targeted single-gene testing), OR when previous genetic testing has failed to yield a diagnosis and the affected individual is faced with invasive procedures or testing as the next diagnostic step (e.g., muscle biopsy).

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) for the diagnosis of genetic disorders in all other situations to be investigational.*

Based on review of available data, the Company considers whole genome sequencing (WGS) for the diagnosis of genetic disorders to be investigational.*
Based on review of available data, the Company considers whole exome sequencing (WES) and whole genome sequencing (WGS) for screening for genetic disorders to be investigational.*

**Background/Overview**

Whole exome sequencing sequences the portion of the genome that contains protein-coding DNA, while whole genome sequencing sequences both coding and noncoding regions of the genome. Whole exome sequencing and WGS have been proposed for use in patients presenting with disorders and anomalies that have not been explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

**CLINICAL CONTEXT AND TEST PURPOSE**

Whole exome sequencing is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while WGS uses next-generation sequencing (NGS) techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions. Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process. WES or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES 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 genome. It is believed that the exome contains about 85% of heritable disease-causing mutations. WES has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. WES shares some limitations with Sanger sequencing. For example, it will not identify: intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications; or rearrangements within genes, nucleotide repeats, or epigenetic changes. WGS uses techniques similar to WES, but includes noncoding regions. WGS has greater ability to detect large deletions or duplications in protein-coding regions compared to WES, but requires greater data analytics. Technical aspects of WES and WGS are evolving, including databases such as the National Institutes of Health’s ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) to catalog variants, 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. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.
In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to develop standard terminology for describing sequence variants.2 Guidelines developed by this workgroup, published in 2015, describe criteria for classifying pathogenic and benign sequence variants based on types of data into 5 categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

AVAILABLE WES AND WGS TESTING SERVICES
Several laboratories offer WES and WGS as a clinical service. Illumina 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). Ambry Genetics offers 2 WGS tests, the ExomeNext and ExomeNext-Rapid, which sequence both the nuclear and the mitochondrial genomes. GeneDx offers WES with its XomeDx™ test. Medical centers may also offer WES and WGS as a clinical service.

Examples of laboratories offering WES as a clinical service and their indications for testing are summarized in Table 1.

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

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indications for Testing</th>
</tr>
</thead>
<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>Illumina (San Diego, CA)</td>
<td>The TruGenome Undiagnosed Disease Test is indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene 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 management of patients with rare genetic disorders.”</td>
</tr>
<tr>
<td>Emory Genetics Laboratory (Atlanta, GA)</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, MO)</td>
<td>Provided as a service to families with children who have had an extensive negative workup for a genetic disease; also used to identify novel disease genes.</td>
</tr>
<tr>
<td>EdgeBio (Gaithersburg, MD)</td>
<td>“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”</td>
</tr>
</tbody>
</table>

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**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD).

**Rationale/Source**
This policy was created in 2013 based in part on a 2013 TEC Special Report on exome sequencing for patients with suspected genetic disorders, and has been updated periodically with literature reviews. The most recent literature update was conducted through August 22, 2016.

**Analytic Validity**

**Whole Exome Sequencing**
There is relatively little data specific to the analytic validity of WES. The NGS techniques used for WES are generally expected to have high accuracy for mutation detection, NGS platforms differ in terms of the depth of sequence coverage, methods for base calling and read alignment, and other factors. These factors contribute to potential variability across the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service. The American College of Medical Genetics (ACMG) has clinical laboratory standards for NGS, including WES. The guidelines outline the documentation of test performance measures that should be evaluated for NGS platforms, and note that typical definitions of analytic sensitivity and specificity do not apply for NGS.

Depending on the platform and variant call method used, WES may not accurately detect large insertions and deletions, large copy number variants (CNVs), and structural chromosome rearrangements due to the short sequence read lengths. WES may be less sensitive for the detection of CNVs than high-resolution microarray testing.

**Whole Genome Sequencing**
Whole genome sequencing is subject to the same considerations for potential variability in technical performance as WES. 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; range, 18%-21%) of genes associated with inherited disease and a median of 9%...
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(Illumina Inc.: range, 2%-27%) to 17% (Complete Genomics: range, 17%-19%) of 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 Validity and Clinical Utility
A number of studies have reported on the use of WES and, less frequently, WGS in clinical practice. Typically, the populations included in these studies have suspected rare genetic disorders, although the specific patient populations vary (see Tables 2 and 3).

Congenital Anomalies and Neurodevelopmental Disorders (Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Epileptic Encephalopathy)
Clinical Validity
Series have been reported with as many as 2000 patients. The largest reason for referral to a tertiary care center was an unexplained neurodevelopmental disorder. Patients had been through standard clinical workup and testing without identification of a genetic variant to explain their condition. Diagnostic yield in these studies, defined as the proportion of tested patients with clinically relevant genomic abnormalities, ranged from 25% to as many as 48%. When used as a first-line test in select infants with multiple congenital abnormalities and dysmorphic features, diagnostic yield rose to 58%. Testing parent-child trios has been reported to increase diagnostic yield, to identify an inherited variant from an unaffected parent and be considered benign, or to identify a de novo variant not present in an unaffected parent. Because there is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies, clinical confirmation may be the only method for determining false-positive and false-negative rates. No reports were identified of incorrect diagnoses, and how often they might occur is unclear.

Clinical Utility
Cohort studies following children from presentation to outcomes have not been reported. There are considerable challenges conducting studies of sufficient size given the underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes. Studies addressing clinical utility have reported mainly diagnostic yield and management changes. Thus, it is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to heterogeneity of disorders, rarity, and outcome importance that may differ according to identified pathogenic variants. Actionable items following testing in the reviewed studies (see Table 2) included family planning, change in management, change or avoidance of additional testing, surveillance for associated morbidities, prognosis, and ending the diagnostic odyssey.
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The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can: (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. When recurrence risk can be estimated for an identified variant (eg, by including parent testing), future reproductive decisions can be affected.

Table 2. Studies Reporting Diagnostic Yield for Congenital Anomalies or Neurodevelopmental Disorders

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2014)</td>
<td>Suspected genetic disorder (88% neurologic or developmental)</td>
<td>2000 (45% &lt;5 y; 42% 5-18 y; 12% adults)</td>
<td>Consecutive patients at single center</td>
<td>504 (25%)</td>
<td>Identification of novel variants. End of the diagnostic odyssey and change in management.</td>
</tr>
<tr>
<td>Yang et al (2013)</td>
<td>Suspected genetic disorder (80% neurologic)</td>
<td>250 (1% fetus; 50% &lt;5 y; 38% 5-18 y; 11% adults)</td>
<td>Consecutive patients at single center</td>
<td>62 (25%)</td>
<td>Identification of atypical phenotypes of known genetic diseases and blended phenotypes. 2 VUS for follow-up. 11 variants identified as de novo</td>
</tr>
<tr>
<td>Allen et al (2016)</td>
<td>Patients with unexplained early-onset epileptic encephalopathy</td>
<td>50 (95% &lt;1 y)</td>
<td>Single center</td>
<td>11 (22%)</td>
<td></td>
</tr>
<tr>
<td>Lee et al (2014)</td>
<td>Suspected rare Mendelian disorders (57% of children had developmental delay; 26% of adults had ataxia)</td>
<td>814 (49% &lt;5 y; 15% 5-18 y; 36% adults)</td>
<td>Consecutive patients at single center</td>
<td>213 (26%)</td>
<td>Trio (31% yield) vs proband only (22% yield)</td>
</tr>
<tr>
<td>Farwell et al (2015)</td>
<td>Unexplained neurologic disorders (65% pediatric)</td>
<td>500</td>
<td>WES laboratory</td>
<td>152 (30%)</td>
<td>Trio (37.5% yield) vs proband only (20.6% yield); 31 (7.5% de novo)</td>
</tr>
<tr>
<td>Soden et al (2014)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>119 (100 families)</td>
<td>Single-center database</td>
<td>53 (45%)</td>
<td>Change in clinical care or impression in 49% of families</td>
</tr>
<tr>
<td>Srivastava et al (2014)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>78</td>
<td>Pediatric neurogenetics clinic</td>
<td>32 (41%)</td>
<td>Changed medical management, prognostication, and family planning</td>
</tr>
<tr>
<td>Nolan and Carlson (2016)</td>
<td>Children with unexplained neurodevelopmental disorders</td>
<td>50</td>
<td>Pediatric neurology clinic</td>
<td>41 (48%)</td>
<td>Changed medication, systemic investigation, and family planning</td>
</tr>
<tr>
<td>Iglesias et al (2014)</td>
<td>Birth defects (24%); developmental delay (25%); seizures (32%)</td>
<td>115 (79% children)</td>
<td>Single-center tertiary clinic</td>
<td>37 (32%)</td>
<td>Discontinuation of planned testing, changed medical management, and family planning</td>
</tr>
<tr>
<td>Stark et al (2016)</td>
<td>Infants (&lt;2 y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features</td>
<td>80</td>
<td>Prospective comparative study at tertiary center</td>
<td>46 (58%)</td>
<td>First-line WES increased yield by 44%, changed clinical management and family planning</td>
</tr>
</tbody>
</table>

VUS: variants of uncertain significance; WES: whole exome sequencing.
Other Indications
Most of the literature on WES and WGS is on neurodevelopmental disorders in children, however, other potential indications for WES and WGS have been reported (see Table 3). These include limb-girdle muscular dystrophy (LGMD), inherited retinal disease, and other disorders including mitochondrial, endocrine, and immunologic disorders. The yield for unexplained LGMD and retinal disease is high, but a limited number of patients have been studied to date.

Table 3. Studies Reporting Diagnostic Yield for Other Conditions

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patient Population</th>
<th>N</th>
<th>Design</th>
<th>Yield, n (%)</th>
<th>Additional Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaoui et al (2015)</td>
<td>Unexplained limb-girdle muscular dystrophy</td>
<td>60 families</td>
<td>Prospective study of patients identified from a specimen bank</td>
<td>27 (60%)</td>
<td>Trio (60% yield) vs proband only (40% yield)</td>
</tr>
<tr>
<td>Ellingford et al (2016)</td>
<td>Unexplained inherited retinal disease</td>
<td>46</td>
<td>WGS in patients referred to a single center</td>
<td>24 (52%)</td>
<td>Estimated 29% increase in yield vs NGS</td>
</tr>
<tr>
<td>Taylor et al (2015)</td>
<td>Broad spectrum of suspected genetic disorders</td>
<td>217</td>
<td>Multicenter series</td>
<td>46 (21%)</td>
<td>34% yield in Mendelian disorders; 57% yield in trios</td>
</tr>
<tr>
<td>Posey et al (2016)</td>
<td>Adults (overlap of 272 patients reported by Yang et al, 2014), includes neurodevelopmental and other phenotypes</td>
<td>486 (53% 18-30 y; 47% &gt;30 y)</td>
<td>Review of lab findings of WES in adults</td>
<td>85 (18%)</td>
<td>Yield in patients 18-30 y (24%) vs those &gt;30 y (10.4%)</td>
</tr>
<tr>
<td>Valencia et al (2015)</td>
<td>Unexplained disorders: congenital anomalies (30%), neurologic (22%), mitochondrial (25%), endocrine (3%), immunodeficiencies (17%)</td>
<td>40 (&lt;17 y)</td>
<td>Consecutive patients in a single center</td>
<td>12 (30%)</td>
<td>Altered management including genetic counseling and ending diagnostic odyssey</td>
</tr>
<tr>
<td>Wortmann et al (2015)</td>
<td>Suspected mitochondrial disorder</td>
<td>109</td>
<td>WES in patients referred to a single center</td>
<td>42 (39%)</td>
<td>57% yield in patients with high suspicion of mitochondrial disorder</td>
</tr>
</tbody>
</table>

NGS: next-generation sequencing; WES: whole exome sequencing; WGS: whole genome sequencing.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>NCT02340871 Finding Genes With NGS Techniques in Whom Mutations Cause Neurological Diseases</td>
<td>75</td>
<td>Jul 2018</td>
</tr>
<tr>
<td></td>
<td>NCT 02418377 Whole-exome Sequencing to Identify Genetic Variants Associated With Severe Childhood Obesity, and Tracking the Changing Prevalence of Obesity Related Complications</td>
<td>1200</td>
<td>Aug 2018</td>
</tr>
</tbody>
</table>
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NCT02826694  North Carolina Newborn Exome Sequencing for Universal Screening  400  Aug 2018
NCT02077894  Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Cond  310  Sep 2018
NCT01087320  Whole Genome Medical Sequencing for Gene Discovery  400  No date
NCT01952275  Assessment of the Enrichment of Rare Coding Genetic Variants in Patients Affected by Neutrophil-Mediated Inflammatory Dermatoses  660  Jan 2020
NCT 02769975  Evaluation of Children With Endocrine and Metabolic-Related Conditions  15,000  Dec 2030

NCT: national clinical trial.

Summary
For individuals who have multiple unexplained congenital anomalies or a neurodevelopmental phenotype who receive WES, the evidence includes large case series and a within-subject comparison. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but the specific genetic alteration is unclear or unidentified by standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental phenotype who receive WES, the evidence includes small case series. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. There is 1 small series of patients with LGMD, and larger series of patients with a broad spectrum of suspected genetic disorders. The diagnostic yield for unexplained LGMD is high, but a limited number of patients have been studied to date. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a suspected genetic disorder who receive WGS, the evidence includes case series. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. No studies were identified that directly compared WGS with alternative testing strategies in terms of the testing yield for pathogenic variants associated with the phenotype being evaluated. One small series evaluated the yield of WGS in patients with inherited retinal disorders and found a genetic cause in about half of patients. The estimated increase in diagnostic yield was 29% compared to standard workup. However, positive results were obtained in only 24 patients, and additional
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study is needed to evaluate WGS for other disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History
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11/07/2013 Medical Policy Committee review
12/04/2014 Medical Policy Committee review
12/17/2014 Medical Policy Implementation Committee approval. Title changed from “Whole Exome Sequencing” to “Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders.” The policy investigational section was revised to clarify that the intent of the policy is limited to the diagnosis of genetic disorders.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. No change to coverage eligibility.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Added eligibility statement for WES with criteria and INV statement for WES and WGS in screening for genetic disorders.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/01/2017 Coding update
Next Scheduled Review Date: 12/2017

Coding
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CPT is a registered trademark of the American Medical Association.

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81415, 81416, 81417, 81425, 81426, 81427, 81479</td>
</tr>
<tr>
<td></td>
<td>New code eff 8/1/17: 0012U</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*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. 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.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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