
Policy # 00536
Original Effective Date: 11/16/2016
Current Effective Date: 01/09/2023

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: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is addressed separately in medical policy 00389.

Note: Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss is addressed separately in medical policy 00449.

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 chromosomal microarray analysis (CMA) as first-line testing to be eligible for coverage** in the initial evaluation of individuals with any of the following:

- Apparent nonsyndromic developmental delay/intellectual disability (DD/DI); or
- Autism spectrum disorder (ASD); or
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers panel testing using next-generation sequencing (NGS) in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability, autism spectrum disorder, or congenital anomalies to be investigational.*

Based on review of available data, the Company considers chromosomal microarray for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay to be investigational.*

Policy Guidelines
Use of CMA testing as outlined in this policy is not intended for use in the prenatal period.

A guidelines update from American College of Medical Genetics (Schaefer et al [2013]) stated that a stepwise (or tiered) approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and CMA testing.

Recommendations from the American College of Medical Genetics (Manning and Hudgins [2010]) on array-based technologies and their clinical utilization for detecting chromosomal abnormalities include the following: “Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH [fluorescent in situ hybridization] studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.”

In some cases of CMA analysis, the laboratory performing the test confirms all reported copy number variants with an alternative technology, such as fluorescent in situ hybridization analysis.

Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

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The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
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</table>

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.
Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview
Diagnostic Testing

Karyotyping and Fluorescent In Situ Hybridization
The goal of a cytogenetic evaluation is to identify chromosomal imbalances that cause a disorder. The most common imbalances are copy number variants (CNVs) or deletions and duplications of large segments of genomic material. CNVs are common in developmental delay/intellectual disability and autism spectrum disorder (ASD) but more often reflect the normal genetic variation. However, de novo CNVs are observed about 4 times more frequently in children with ASD than in normal individuals. Less frequently, other abnormalities such as balanced translocations (ie, exchanges of equally sized DNA loci between chromosomes) may be pathogenic. For many well-described syndromes, the type and location of the associated chromosomal abnormality have been established by studying large patient samples. For others, few patients with similar abnormalities may have been evaluated to establish genotype-phenotype correlation. Finally, in some patients, the cytogenetic analysis will discover chromosomal abnormalities that require study to determine their significance.

Prior to the advent of chromosomal microarray (CMAs), the initial step in the cytogenetic analysis was G-banded karyotyping, which evaluates all chromosomes. High-resolution G-banding can detect changes as small as 3 to 5 megabases in size, although standard G-banding evaluates more than 10 megabases changes. In children with developmental delay/intellectual disability, a review by Stankiewicz and Beaudet (2007) found G-banded karyotyping diagnostic in approximately 3%

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to 5% of cases. In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. Fluorescent in situ hybridization (FISH), a targeted approach, is used to identify specific chromosomal abnormalities associated with suspected diagnoses such as DiGeorge syndrome. Prior to CMAs, FISH was also used to screen the rearrangement-prone subtelomeric regions. Subtelomeric FISH was found to identify abnormalities in children with developmental delay and intellectual disability, and was diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.

**Chromosomal Microarrays**

Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNV) arrays. The aCGH approach uses DNA samples from a patient and normal control. Each is labeled with distinct fluorescent dyes (red or green). The labeled samples are then mixed and hybridized to thousands of cloned or synthesized reference (normal) DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions simultaneously. CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. If the patient sequence is missing part of the normal sequence (a deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication), the sequence imbalance is detected as a difference in fluorescence intensity (Korf and Rehm [2013] offers an illustrative graphic). For this reason, aCGH cannot detect balanced chromosomal translations (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base-pair order) because the fluorescence intensity would not change. A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that chromosomal rearrangements that appear balanced (and therefore not pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA testing.

Like aCGH, SNV arrays detect CNVs. In an SNV array, the 2 alleles for genes of interest are tagged with different fluorescent dyes. Comparative fluorescence intensity will be increased when there are...
duplications and diminished with deletions. The resolution provided by aCGH is higher than with SNV arrays. In addition, aCGH has better signal-to-background characteristics than SNV arrays. In contrast to aCGH, SNV arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy or consanguinity. Uniparental disomy occurs when a child inherits 2 copies of a chromosome from 1 parent and no copies from the other parent. Uniparental disomy can lead to syndromes such as Angelman and Prader-Willi.

Table 1 summarizes the cytogenetic tests used to evaluate children with developmental delay/intellectual disability and autism. The table emphasizes the large difference in resolution between karyotyping and CMA.

Table 1. Resolution and Analysis Comparison of FISH, Karyotyping, and CMA Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Resolution in Kilobases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotyping</td>
<td>3000-5000 kb</td>
<td>Genome-wide</td>
</tr>
<tr>
<td>CMA</td>
<td>≈50 kb</td>
<td>Genome-wide</td>
</tr>
<tr>
<td>FISH</td>
<td>≈500 to 1000 kb (depending on probe)</td>
<td>Targeted</td>
</tr>
</tbody>
</table>

CMA: chromosomal microarray; FISH: fluorescent in situ hybridization; kb: kilobases.

<sup>a</sup> 1 kb = 1000 bases, 1000 kb = 1 Mb.

Microarrays may be prepared by the laboratory using the technology or, more commonly, by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of laboratory-developed and commercially available platforms prompted the American College of Medical Genetics to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

**Next-Generation Sequencing**
Next-generation sequencing has been proposed to detect single-gene causes of autism and possibly identify a syndrome that involves autism in patients with normal array-based testing. Next-generation sequencing involves the sequencing of millions of fragments of genetic material in a massively parallel fashion. Next-generation sequencing can be performed on segments of the genetic
material of various sizes ¾ from the entire genome (whole-genome sequencing) to small subsets of genes (targeted sequencing). Next-generation sequencing allows the detection of SNVs, CNVs, insertions, and deletions. With higher resolution comes a higher likelihood of detection of variants of uncertain significance.

Genetic Associations With Developmental Delay/Intellectual Disability and Autism Spectrum Disorder

For common phenotypes and syndromes, the pathogenicity of CNVs may be supported by considerable evidence; for uncommon phenotypes and uncommon CNVs determining pathogenicity requires a systematic evaluation that includes parental studies, examining databases for reported associations, and considering the molecular consequences of the identified variant. Parental studies (eg, “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign. A variety of databases index the clinical implications of CNVs and their associations with a particular phenotype. CNVs are continuously cataloged and, with growth in CMA testing and improved resolution, databases have become increasingly extensive (eg, DECIPHER, ClinVar). For uncommon CNVs, in addition to reports of CNV-phenotype associations, the location and size of the CNV can offer clues to pathogenicity; larger CNVs are more often pathogenic and the role of affected genes in brain circuitry and effect of CNV on gene expression can implicate pathogenicity. Although uncommon, an observed phenotype can result from unmasking a mutated recessive allele on the unaffected (non-CNv) chromosome. Other considerations when determining pathogenicity include CNV dosage, X linkage, number of reports in the literature of an association between CNV and phenotype, and findings in “normal” individuals.

The American College of Medical Genetics has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles. The recommended categories of clinical significance for reporting are pathogenic, uncertain clinical significance (likely pathogenic, likely benign, or no subclassification), or benign. The International Standards for Cytogenomic Arrays Consortium more recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support the interpretation of clinically significant copy number variation.” The proposal defined levels of evidence that describe how well or how poorly detected variants or CNVs correlate with phenotype.
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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for CMA testing and next-generation sequencing are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In 2010, the FDA indicated that it would require microarray manufacturers to seek clearance to sell their products for use in clinical cytogenetics.

CMA Testing

CMA testing is commercially available through many laboratories and includes targeted and whole-genome arrays, with or without SNV microarray analysis.

In January 2014, the Affymetrix CytoScan®‡ Dx Assay (Thermo Fisher Scientific) was cleared by the FDA through the de novo 510(k) process. The FDA’s review of the CytoScan Dx Assay included an analytic evaluation of the test’s ability to detect accurately numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. The FDA found that the CytoScan Dx Assay could detect CNVs across the genome and adequately detect CNVs in regions of the genome associated with developmental delay/intellectual disability. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (generally recommended as the lower reporting limit). As of July 2017, Affymetrix™‡ contains 2.7 million markers for copy number, 750,000 SNVs, and 1.9 million non-polymorphic probes (Affymetrix was acquired by Thermo Fisher Scientific in 2016). FDA product code: PFX.

FirstStep™ PLUS®‡ (Lineagen) uses Lineagen’s custom-designed microarray platform manufactured by Affymetrix. As of July 2017, this microarray consists of a 2.8 million probe microarray for the detection of CNVs associated with neurodevelopmental disorders. The array

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includes probes that come standard on the Affymetrix CytoScan HD microarray, with an additional 88435 custom probes designed by Lineagen.

Ambry Genetics offers multiple tests (CMA and next-generation sequencing) designed for diagnosing ASD and neurodevelopmental disorders. As of July 2017, the CMA offered by Ambry Genetics includes over 2.6 million probes for copy number and 750,000 SNV probes. The expanded next-generation sequencing panel for neurodevelopmental disorders assesses 196 genes.

LabCorp offers the Reveal® SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, developmental delay/intellectual disability, and/or ASD. The Reveal microarray has 2695 million probes as of July 2017.

Next-Generation Sequencing
A variety of commercial and academic laboratories offer next-generation sequencing panels designed for the evaluation of ASD, developmental delay/intellectual disability, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Emory Genetics Laboratory offers a next-generation sequencing ASD panel of genes targeting genetic syndromes that include autism or autistic features. Greenwood Genetics Center offers a next-generation sequencing panel for syndromic autism that includes 83 genes. Fulgent Genetics offers a next-generation sequencing ASD panel that includes 121 genes.

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Chromosomal microarray (CMA) testing has been proposed for the detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability, autism spectrum disorder, and/or congenital anomalies. CMA testing increases the diagnostic yield over
karyotyping in children with the aforementioned characteristics, and CMA testing may impact clinical management decisions. Next-generation sequencing panel testing allows for the simultaneous analysis of a large number of genes and, in patients with normal CMA testing, the next-generation testing has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature.

Summary of Evidence
For individuals who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive CMA testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision-making, morbid events, and resource utilization. The available evidence supports test validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well-demonstrated. Direct evidence of improved outcomes with CMA compared with karyotyping is also lacking. However, for at least a subset of the disorders potentially diagnosed with CMA testing in this patient population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision-making as a result of positive test results. The information derived from CMA testing can accomplish the following: it could end a long diagnostic odyssey, or reduce morbidity for certain conditions by initiating surveillance/management of associated comorbidities, or it could impact future reproductive decision making for parents. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing panel testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision-making, morbid events, and resource utilization. The diagnostic yield associated with next-generation sequencing panel testing in this patient population is not well-characterized. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population; additionally, there are risks of uninterpretable and incidental results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Supplemental Information
Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics
In 2014, the American Academy of Pediatrics issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays or intellectual disability. Regarding chromosomal microarray (CMA) testing, this report stated:
“CMA now should be considered a first-tier diagnostic test in all children with [global developmental delay/intellectual disability] GDD/ID for whom the causal diagnosis is not known…. CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.”

American Academy of Child and Adolescent Psychiatry
In 2014, the American Academy of Child and Adolescent Psychiatry updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD). The Academy recommended that “all children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray.”

American Academy of Neurology and Child Neurology Society
In 2011, the American Academy of Neurology and the Child Neurology Society updated their guidelines on the evaluation of unexplained developmental delay and intellectual disability with information on genetic and metabolic (biochemical) testing to accommodate advances in the field. The guidelines concluded that CMA testing has the highest diagnostic yield in children with developmental delay/intellectual disability, that the “often complex results require confirmation and careful interpretation, often with the assistance of a medical geneticist,” and that CMA should be
considered the “first-line” test. The guidelines acknowledged that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”

**American College of Medical Genetics**
The American College of Medical Genetics (ACMG) (2010; reaffirmed 2020) published a clinical practice resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome
- Apparently nonsyndromic developmental delay/intellectual disability
- Autism spectrum disorder (ASD)

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software and for the interpretation and reporting of copy number variants, both intended for the postnatal setting. A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.

The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first tier including fragile X syndrome and CMA, and the second tier *MECP2* and *PTEN* testing. The guidelines stated that:

“this approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third-tier testing) will increase the diagnostic yield even more over the next few years.”

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

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Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in August 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

References
5. Moeschler JB. Medical genetics diagnostic evaluation of the child with global developmental delay or intellectual disability. Curr Opin Neurol. Apr 2008; 21(2): 117-22. PMID 18317267

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Policy History
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11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. New policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. The first policy statement was revised to remove the “postnatal” term; a second statement was added that chromosomal microarray analysis is investigational for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay.
11/08/2018 Medical Policy Committee review
11/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
11/07/2019 Medical Policy Committee review
11/13/2019 Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020 Medical Policy Committee review
11/11/2020 Medical Policy Implementation Committee approval. No change to coverage.
11/04/2021 Medical Policy Committee review
11/10/2021 Medical Policy Implementation Committee approval. No change to coverage.
12/01/2022 Medical Policy Committee review
12/14/2022 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 12/2023

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

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<tr>
<th>Code Type</th>
<th>Code</th>
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</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. Food and Drug Administration (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 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,

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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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.