Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions Using Cell-Free Fetal DNA

Policy # 00345
Original Effective Date: 12/20/2013
Current Effective Date: 04/13/2020

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 Are 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 concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 (T13) and/or trisomy 18 (T18) in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21 (T21) to be **eligible for coverage.****

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 nucleic acid sequencing-based testing of maternal plasma for T21 in women with high-risk singleton pregnancies undergoing screening for T21 to be **eligible for coverage.**** (Karyotyping would be necessary to exclude the possibility of a false positive nucleic acid sequencing–based test. Before testing, women should be counseled about the risk of a false positive test.)

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Patient Selection Criteria
Coverage eligibility will be met in high-risk singleton pregnancies, defined as women who meet at least ONE of the following high-risk criteria:

- Maternal age 35 years or older at delivery; OR
- Fetal ultrasonographic findings indicating increased risk of aneuploidy; OR
- History of previous pregnancy with a trisomy; OR
- Standard serum screening test positive for aneuploidy; OR
- Parental balanced Robertsonian translocation with increased risk of fetal T13 or T21.

When Services Are Considered Not Medically Necessary

The use of nucleic acid sequencing-based testing of maternal plasma for T13, T18, or T21 in women with average-risk (not meeting high-risk criteria) singleton pregnancies when patient selection criteria are not met is considered to be **not medically necessary.****

When 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 nucleic acid sequencing-based testing of maternal plasma for T21 in women with twin or multiple pregnancies to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing–based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified above, to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for microdeletions to be **investigational.***

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Policy Guidelines

Karyotyping would be necessary to exclude the possibility of a false-positive, nucleic acid sequencing–based test. Before testing, women should be counseled about the risk of a false-positive test. In Committee Opinion No. 640, the American College of Obstetricians and Gynecologists (2015) recommended that all patients receive information on the risks and benefits of various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing.

Studies published to date on noninvasive prenatal screening for fetal aneuploidies have reported rare but occasional false-positives. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. Diagnostic testing is necessary to confirm positive cell-free fetal DNA tests, and management decisions should not be based solely on the results of cell-free fetal DNA testing. The American College of Obstetricians and Gynecologists further recommended that patients with indeterminate or uninterpretable (ie, "no call") cell-free fetal DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because "no call" findings have been associated with an increased risk of aneuploidy.

Cell-free fetal DNA screening does not assess risk of neural tube defects. Patients should continue to be offered ultrasound or maternal serum -fetoprotein screening.

Background/Overview

Fetal Aneuploidy

Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. Most fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a trisomy 21 (T21; Down syndrome) affected birth is 1 in 1100 at age 25 to 29. The risk of a fetus with T21 (at 16 weeks of gestation) is about 1 in 250 at age 35 and 1 in 75 at age 40.

T21 is the most common chromosomal aneuploidy and provides the impetus for current maternal serum screening programs. Other trisomy syndromes include T18 (Edwards syndrome) and T13

(Patau syndrome), which are the next most common forms of fetal aneuploidy, although the percentage of cases surviving to birth is low and survival beyond birth is limited. Detection of T18 and T13 early in pregnancy can facilitate preparation for fetal loss or early intervention.

Fetal Aneuploidy Screening

Standard aneuploidy screening involves combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of noninvasive testing ranges from 60% to 96% when the false-positive rate is set at 5%. When tests indicate a high risk of a trisomy syndrome, direct karyotyping of fetal tissue obtained by amniocentesis or chorionic villous sampling (CVS) is required to confirm that T21 or another trisomy is present. Both amniocentesis and CVS are invasive procedures and have procedure-associated risks of fetal injury, fetal loss, and infection. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures or increases detection of T21, T18, and T13 could improve outcomes. Confirmation of positive noninvasive screening tests with amniocentesis or CVS is recommended; with more accurate tests, fewer women would receive positive screening results.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes is now available. The testing technology involves detection of cell-free fetal DNA fragments present in the plasma of pregnant women. As early as 8 to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total cell-free fetal DNA in a maternal plasma sample. The tests are unable to provide a result if the fetal fraction is too low (ie, <4%). The fetal fraction can be affected by maternal and fetal characteristics. For example, the fetal fraction was found to be lower at higher maternal weights and higher with increasing fetal crown-rump length.

Cell-Free Fetal DNA Analysis Methods

Sequencing-based tests use 1 of 2 general approaches to analyzing cell-free fetal DNA. The first category of tests uses quantitative or counting methods. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation sequencing). DNA fragments are amplified by polymerase chain reaction; during the sequencing process, the amplified fragments are spatially segregated and sequenced simultaneously in a massively parallel fashion. Sequenced fragments can be mapped to the reference human genome to obtain numbers of fragment counts per chromosome. The sequencing-derived percent of fragments from the chromosome of interest reflects the chromosomal representation of the maternal and fetal DNA fragments in the original maternal

plasma sample. Another technique is direct DNA analysis, which analyzes specific cell-free fetal DNA fragments across samples and requires approximately a tenth the number of cell-free DNA fragments as MPS. The digital analysis of selected regions (DANSR™‡) is an assay that uses direct DNA analysis.

The second general approach is single nucleotide variant based methods. They use targeted amplification and analysis of approximately 20,000 single nucleotide variants on selected chromosomes (eg, 21, 18, 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome. At least some of the commercially available cell-free fetal DNA prenatal tests also test for other abnormalities including sex chromosome abnormalities and selected microdeletions.

Copy Number Variants and Clinical Disorders
Microdeletions (also known as submicroscopic deletions) are chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. They can be as small as 1 and 3 megabases long. Along with microduplications, microdeletions are collectively known as copy number variants. Copy number variants can lead to disease when the change in copy number of a dose-sensitive gene or genes disrupts the ability of the gene(s) to function and affects the amount of protein produced. A number of genomic disorders associated with microdeletion have been identified, which may be associated with serious clinical features, such as cardiac anomalies, immune deficiency, palatal defects, and developmental delay as in DiGeorge syndrome. Some of the syndromes (eg, DiGeorge) have complete penetrance yet marked variability in clinical expressivity. A contributing factor is that the breakpoints of the microdeletions may vary, and there may be a correlation between the number of haplo-insufficient genes and phenotypic severity.

A proportion of microdeletions are inherited and some are de novo. Accurate estimates of the prevalence of microdeletion syndromes during pregnancy or at birth are not available. The risk of a fetus with a microdeletion syndrome is independent of maternal age. There are few population-based data and most studies published to date have based estimates on phenotypic presentation. The 22q11.2 (DiGeorge) microdeletion is the most common associated with a clinical syndrome. Table 1 provides prevalence estimates for the most common microdeletion syndromes. These numbers likely underestimate the prevalence of these syndromes in the prenatal population because the population of variant carriers includes phenotypically normal or very mildly affected individuals.

Table 1. Recurrent Microdeletion Syndromes

	Syndrome	Location	Estimated Prevalence
1	DiGeorge	22q11.2	1/2000
2	1p36 deletion	1p36-	1/5000
3	Prader-Willi and Angelman	Del 15q11.2	1/20,000
4	Wolf-Hirschhorn	4p-	1/50,000 to 1/20,000
5	Cri du chat	5p-	1/50,000
6	Miller-Dieker	Del 17p13.3	1 /100,000

Adapted from Chitty et al (2018).

Routine prenatal screening for microdeletion syndromes is not recommended by national organizations. Current practice is to offer invasive prenatal diagnostic testing in select cases to women when a prenatal ultrasound indicates anomalies (eg, heart defects, cleft palate) that could be associated with a particular microdeletion syndrome. Samples are analyzed using fluorescence in situ hybridization, chromosomal microarray analysis, or karyotyping. Additionally, families at risk (eg, those known to have the deletion or with a previously affected child) generally receive genetic counseling and those who conceive naturally may choose prenatal diagnostic testing. Most affected individuals, though, are identified postnatally based on clinical presentation and may be confirmed by genetic testing. Using 22q11.2 deletion syndrome as an example, although clinical characteristics vary, palatal abnormalities (eg, cleft palate) occur in approximately 69% of individuals, congenital heart disease in 74%, and characteristic facial features are present in a majority of individuals of northern European heritage.

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 Act. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of noninvasive prenatal screening tests using cell-free fetal DNA.

Commercially available tests include but are not limited to the following:

- The VisibiliT™‡ (Sequenom Laboratories, now LabCorp) tests for T21 and T18, and tests for sex.
- MaterniT21™‡ PLUS (Sequenom Laboratories, now LabCorp) core test includes T21, T18, T13, and fetal sex aneuploidies. The enhanced sequencing series includes testing for T16, T22, and 7 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q (Prader-Willi and Angelman syndromes), 1p36 deletion syndrome, 4p (Wolf-Hirschhorn syndrome), 8q (Langer-Giedion syndrome), and 11q (Jacobsen syndrome). The test uses MPS and reports results as positive or negative. The enhanced sequencing series is offered on an opt-out basis.
- Harmony™‡ (Ariosa Diagnostics, now Roche) tests for T21, T18, and T13. The test uses directed DNA analysis and results are reported as a risk score.
- Panorama™‡ (Natera) is a prenatal test for detecting T21, T18, and T13, as well as select sex chromosome abnormalities. It uses single nucleotide variant technology; results are reported as a risk score. An extended panel tests for 5 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q11-13 (Prader-Willi and Angelman syndromes), and 1p36 deletion syndrome. Screening for 22q11.2 will be included in the panel unless the opt-out option is selected; screening for the remaining 4 microdeletions is offered on an opt-in basis.
- Verifi®‡ (Verinata Health, now Illumina) is a prenatal test for T21, T18, and T13. The test uses MPS and calculates a normalized chromosomal value, reporting results as 1 of 3 categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.
- InformaSeqSM (Integrated Genetics, now LabCorp) is a prenatal test for detecting T21, T18, and T13, with optional testing for select sex chromosome abnormalities. It uses the Illumina platform and reports results in a similar manner.
- QNatal Advanced™‡ (Quest Diagnostics) tests for T21, T18, and T13.

Rationale/Source

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies, an abnormal number of chromosomes. Trisomy syndromes are aneuploidies involving three copies of one chromosome. Trisomies 21 (T21), 18 (T18), and 13 (T13) are the most common forms of fetal aneuploidy. Fetuses with T18 and T13

generally do not survive to birth. There are numerous limitations to standard screening for these disorders using the maternal serum and fetal ultrasound. Noninvasive prenatal screening (NIPS) analyzing cell-free fetal DNA in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using cell-free fetal DNA has also been proposed to screen for microdeletions.

For individuals who have a singleton pregnancy who receive NIPS for T21, T18, and T13 using cell-free fetal DNA, the evidence includes observational studies and systematic reviews. The relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Published studies on available tests and meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only women at high-risk of T21 but several studies have reported similar levels of diagnostic accuracy in average-risk women. Compared with standard serum screening, both the sensitivity and specificity of cell-free fetal DNA screening are considerably higher. As a result, screening with cell-free fetal DNA for T21 will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. Screening for T18 and T13 along with T21 may allow for preparation for fetal demise or termination of the pregnancy prior to fetal loss. The evidence is sufficient to determine qualitatively that that the technology results in a meaningful improvement in the net health outcome, particularly in high-risk women.

For individuals who have a singleton pregnancy who receive NIPS for sex chromosome aneuploidies using cell-free fetal DNA, the evidence includes observational studies, mainly in high-risk pregnancies, and systematic reviews. The relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Meta-analyses of available data have suggested high sensitivities and specificities but the small number of cases makes definitive conclusions difficult. In addition, the clinical utility of identifying sex chromosome aneuploidies during pregnancy is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a twin or multiple pregnancy who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes observational studies and a systematic review. The relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The total number of cases of aneuploidy identified in these studies is small and is

insufficient to draw conclusions about clinical validity. There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be conducted due to the paucity of evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pregnancy(ies) who receive NIPS for microdeletions using cell-free fetal DNA, the evidence includes several observational studies. The relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations (eg, missing data on confirmatory testing, false-negatives), and the added benefit of NIPS compared with current approaches is unclear. Moreover, the clinical utility of NIPS for microdeletions remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

ACOG Practice Bulletin number 163 reaffirmed 2018:

Summary:
"All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders regardless of maternal age. The choice of screening test is affected by many factors, including a desire for information before delivery, prior obstetric history, family history, and the number of fetuses."

"No one test is superior for all test characteristics and not every test is available at all centers. Each test has advantages and disadvantages that should be discussed with each patient, with the appropriate test offered based on her concerns, needs, and values."

"The sensitivity and specificity in the general obstetric population are now available. The sensitivity and specificity in the general obstetric population are similar to the levels previously published for the high-risk population. However, cell-free DNA screening cannot have the same accuracy in low-risk pregnancies (eg in young women) because the positive predictive value is affected by the prevalence of the disorder in the population. The positive predictive value is lower in the general obstetric population because of the lower prevalence of aneuploidy in this population."

The following recommendations cell-free DNA are based on "good and consistent" scientific evidence:

- "Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result."
- "Because cell-free DNA is a screening test with the potential for false-positive and false-negative results, such testing should not be used as a substitute for diagnostic testing."
- "All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken."
- "Women who's cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy."

The following recommendations are based on "limited or inconsistent" scientific evidence:

- "Cell-free DNA screening tests for microdeletions have not been validated clinically and are not recommended at this time."
- "No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher-order multifetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies."

The following recommendations are based primarily on based "primarily on consensus and expert opinion":

- "Some women who receive a positive test result from traditional screening may prefer to have cell-free DNA screening rather than undergo definitive testing."
- "This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy."
- "Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost effective and should not be performed."

Statement from Society for Maternal-Fetal Medicine

"The likelihood that a patient with a positive cfDNA has an affected fetus-the positive predictive value-is lower if her background risk is low. For low risk women for rare disorders, a positive test

is more likely to be a false positive. cfDNA testing is therefore not recommended for low-risk women."

Centers for Medicare and Medicaid Services (CMS)
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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions Using Cell-Free Fetal DNA", 4.01.21, September 2019.
2. Committee Opinion No. 640: Cell-free DNA Screening for Fetal Aneuploidy. Obstet Gynecol. Jun 29 2015. PMID 26114726
3. American College of Obstetricians and Gynecologists (ACOG). Commitee Opinion: Noninvasive Prenatal Testing for Fetal Aneuploidy. 2012; http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Genetics/Noninvasive_Prenatal_Testing_for_Fetal_Aneuploidy.
4. Society for Maternal-Fetal Medicine Publications Committee. Electronic address eso. SMFM Statement: clarification of recommendations regarding cell-free DNA aneuploidy screening. Am J Obstet Gynecol. Dec 2015;213(6):753-754. PMID 26458766
5. Practice Bulletin No. 163 Summary: Screening for Fetal Aneuploidy. Obstet Gynecol. May 2016 (Reaffirmed 2018);127(5):979-981. PMID 27101120

Policy History

Original Effective Date: 12/20/2013
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02/20/2013	Medical Policy Implementation Committee approval. New policy.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015	Coding Update
02/05/2015	Medical Policy Committee review

02/18/2015	Medical Policy Implementation Committee approval. Title changed from "Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA" to "Noninvasive Prenatal Testing for Fetal Aneuploidies Using Cell-Free Fetal DNA". Removed the statement from the coverage section that stated to deny as investigational if criteria are not met for clarification. Statement added that concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18 may be considered medically necessary in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21. In addition, 2 investigational statements were added, 1 for nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified in the medically necessary statement and the other for fetal sex chromosome aneuploidies.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Title change. Testing for microdeletions added to the policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2017	Coding update
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy Guidelines section added to the policy.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Added a statement for when nucleic acid sequencing–based testing of maternal plasma for trisomy 13 and/or 18 is investigational.
09/09/2019	Coding update
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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06/10/2020 Coding update
Next Scheduled Review Date: 03/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from current Current Procedural Terminology (CPT®)‡, copyright 2019 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.

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

Code Type	Code
CPT	81420, 81422, 81479, 81507, 81599 Code deleted eff 1/1/2020: 0009M Code deleted eff 7/1/2020: 0126U Code added eff 4/1/2020: 0168U

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HCPCS	No codes
ICD-10 Diagnosis	O09.511, O09.512, O09.513, O09.519, Z31.5, Z36.0-Z36.9

*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 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.

‡ 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.