Next-Generation Sequencing for the Assessment of Measurable Residual Disease

Policy # 00656
Original Effective Date: 12/19/2018
Current Effective Date: 04/01/2024

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.

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 next-generation sequencing (e.g., clonoSEQ) to detect measurable residual disease (MRD) following treatment as an alternative to standard testing (e.g., flow cytometry or polymerase chain reaction) in individuals with acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or multiple myeloma to be **eligible for coverage.****

Note:
For individuals with CLL, based on the NCCN guidelines, MRD testing will be approved only once, after end of treatment.

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 next-generation sequencing to detect MRD in all other situations, including in individuals with diffuse large B-cell lymphoma and mantle cell lymphoma, to be **investigational.***

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Background/Overview

Disease

There are 3 main types of hematologic malignancies: lymphomas, leukemias, and myelomas. Lymphoma begins in lymph cells of the immune system, which originate in the bone marrow and collect in lymph nodes and other tissues. Leukemia is caused by the overproduction of abnormal white blood cells in the bone marrow, which leads to a decrease in the production of red blood cells and plasma cells. The most common forms of leukemia are acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. Multiple myeloma (MM), also called plasma myeloma, is a malignancy of plasma cells in the bone marrow. The present evidence review will address B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, diffuse large B-cell lymphoma, and mantle cell lymphoma. As B-Cell acute lymphoblastic leukemia and B-Cell lymphoblastic lymphoma are generally considered clinically indistinct, reference to B-Cell acute lymphoblastic leukemia is intended to encompass both entities.

Treatment

Treatment depends on the type of malignancy and may include surgery, radiotherapy, chemotherapy, targeted therapy, plasmapheresis, biologic therapy, or hematopoietic cell transplant. Treatment of acute leukemias can lead to complete remission. Multiple myeloma and the chronic leukemias are treatable but generally incurable. Outcomes of lymphoma vary by subtype, and some forms are curable.

Measurable Residual Disease

Relapse is believed to be due to residual clonal cells that remain following "complete response" after induction therapy but are below the limits of detection using conventional morphologic assessment. Residual clonal cells that can be detected in the bone marrow or blood are referred to as measurable residual disease (MRD), also known as minimal residual disease. MRD assessment is typically performed by flow cytometry or polymerase chain reaction (PCR) with primers for common variants. Flow cytometry or next generation flow cytometry evaluates blasts based on the expression of characteristic antigens, while PCR assesses specific chimeric fusion gene transcripts, gene variants, and overexpressed genes. PCR is sensitive for specific targets, but clonal evolution may occur between diagnosis, treatment, remission, and relapse that can affect the detection of MRD. Next-generation sequencing (NGS) has 10- to 100-fold greater sensitivity for detecting clonal cells, depending on the amount of DNA in the sample (see Table 1) and does not require patient-specific

primers. For both PCR and NGS a baseline sample at the time of high disease load is needed to identify tumor-specific sequences. MRD with NGS is frequently used as a surrogate measure of treatment efficacy in drug development.

It is proposed that by using a highly sensitive and sequential MRD surveillance strategy, one could expect better outcomes when therapy is guided by molecular markers rather than hematologic relapse. However, some individuals may have hematologic relapse despite no MRD, while others do not relapse despite residual mutation-bearing cells. Age-related clonal hematopoiesis, characterized by somatic variants in leukemia-associated genes with no associated hematologic disease, further complicates the assessment of MRD. One available test (clonoSEQ) uses both PCR and NGS to detect clonal DNA in blood and bone marrow. ClonoSEQ Clonality (ID) PCR assessment is performed when there is a high disease load (eg, initial diagnosis or relapse) to identify dominant or "trackable" sequences associated with the malignant clone. NGS is then used to monitor the presence and level of the associated sequences in follow-up samples. As shown in Table 1, NGS can detect clonal cells with greater sensitivity than either flow cytometry or PCR, although next-generation flow techniques have reached a detection limit of 1 in 10^{-5} cells, which is equal to PCR and approaches the limit of detection of NGS (see Table 1).

Table 1. Sensitivity of Methods for Detecting Measurable Residual Disease

Technique	Sensitivity	Detection limit of blasts per 100,000 Nucleated Cells
Microscopy (complete response)		50,000
Multiparameter flow cytometry	10^{-4}	10
Next-generation flow cytometry	10^{-5}	1.0
Polymerase chain reaction	10^{-5}	1.0
Quantitative next-generation sequencing	10^{-5}	1.0
Next-generation sequencing	10^{-6}	0.1

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The clonoSEQ®‡ Minimal Residual Disease Test is offered by Adaptive Biotechnologies. clonoSEQ®‡ was previously marketed as clonoSIGHT™‡ (Sequenta), which was acquired by Adaptive Biotechnologies in 2015. clonoSIGHT™‡ was a commercialized version of the LymphoSIGHT platform by Sequenta for clinical use in MRD detection in lymphoid cancers. In September 2018, clonoSEQ received marketing clearance from the U.S. Food and Drug Administration (FDA) through the de novo classification process to detect MRD in individuals with acute lymphoblastic leukemia or multiple myeloma. In 2020, clonoSEQ received marketing clearance from the FDA to detect MRD in individuals with chronic lymphocytic leukemia. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological features.

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.

Measurable residual disease (MRD), also known as minimal residual disease, refers to residual clonal cells in blood or bone marrow following treatment for hematologic malignancies. MRD is typically assessed by flow cytometry (FC) or polymerase chain reaction, which can detect 1 clonal cell in 100,000 cells. It is proposed that next-generation sequencing (NGS), which can detect 1 residual clonal sequence out of 1,000,000 cells, will improve health outcomes in individuals who have been treated for hematologic malignancies such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL).

Review of Evidence - Intro

For individuals with B-cell ALL (B-ALL) who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of 10^{-4}, the evidence includes retrospective comparisons of data from trials Relevant outcomes are overall survival (OS), disease-specific

survival, test validity, change in disease status, quality of life (QOL), and treatment-related morbidity. Comparison of NGS and the established standard of FC showed good concordance when the same threshold (10^{-4}) was used for both NGS and FC. OS in pediatric individuals with MRD positivity was significantly lower than in pediatric individuals who were MRD negative at this threshold. The relatively small subset of individuals who were discordant for FC and NGS results had outcomes that were midway between individuals who were concordant as MRD positive or MRD negative for both tests. As the vast majority of individuals had concordant results for NGS and FC at a threshold of 10^{-4}, NGS can be considered an alternative to FC for monitoring MRD in individuals with B-ALL. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with B-ALL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of less than 10^{-4}, the evidence includes retrospective analysis of prognosis from trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. NGS can be more sensitive than FC to detect the presence of residual leukemic cells, but specificity may be decreased at the more sensitive thresholds resulting in potential harm from overtreatment. Further study is needed to clarify whether MRD at levels lower than 1 in 10,000 cells represents clinically significant disease and if the more sensitive test can be used to risk-stratify individuals with B-ALL. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with CLL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of 10^{-4}, the evidence includes analysis of samples from clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. These studies evaluated the association between the level of MRD detected by NGS in bone marrow or blood and progression-free survival (PFS) in completed phase 2 and 3 trials. Two studies demonstrated an association between the level of MRD and PFS with lower risk of progression in individuals who exhibit MRD negativity below 10^{-4} compared to individuals who have detectable residual disease. In one study of participants treated with ibrutinib+venetoclax, PFS at one year was high regardless of MRD status using threshold of 10-4 at the end of treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with CLL who are being monitored for residual disease following treatment who receive NGS for MRD at a threshold of less than 10^{-4}, the evidence includes analysis of samples from clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. NGS can be more sensitive than FC to detect the presence of residual leukemic cells, but it is not clear if prognosis is improved at the lower thresholds. Currently, no additional treatment is offered to eradicate low-level MRD ($<10^{-4}$) after first-line treatment of CLL. Further study is needed to clarify whether MRD at levels lower than 1 in 10,000 cells represents clinically significant disease and if the more sensitive test can be used for prognosis in individuals with CLL. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MM who have achieved a complete response (CR) following treatment who receive NGS for MRD at a threshold of 10^{-5}, the evidence includes retrospective comparisons of NGS and FC data from MM treatment trials and from a clinical series. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. Concordance has been demonstrated between NGS and the established standard of FC at 10^{-4} as well as with next generation flow cytometry (NGF) at a threshold of 10^{-5}. PFS in individuals with MRD positivity is significantly shorter than in individuals who are MRD negative at these thresholds. The relatively small subset of individuals who were discordant for FC and NGS results had outcomes that were, on average, midway between individuals who were concordant as MRD positive or MRD negative for both tests. Retrospective studies also indicate improved PFS when MRD is less than 10^{-5} compared to individuals who have MRD greater than 10^{-5}. This threshold is consistent with current guideline-based care for prognostication using either NGF or NGS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MM who have achieved a CR following treatment who receive NGS for MRD at a threshold of less than 10^{-5}, the evidence includes retrospective studies on prognosis. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. There is some evidence that MRD may be a prognostic marker, but there is insufficient evidence on the number of false positives in individuals with CR at the more sensitive threshold provided by NGS for prognostication or to guide therapy. A chain of evidence regarding management changes based on the assessment of MRD with NGS to detect 1 malignant clonal sequence out of 1,000,000 cells cannot be completed. Direct evidence from randomized

controlled trials is needed to evaluate whether patient outcomes are improved by changes in postinduction care (eg, continuing or discontinuing therapy, avoiding unnecessary adverse events) following NGS assessment of residual disease at a threshold lower than 10^{-5}. Trials that will test the effectiveness of NGS to guide therapy in MM are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with DLBCL who are being monitored for residual disease following treatment who receive NGS for MRD, the evidence includes an analysis from a single-center, prospective trial. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. Although both PFS and OS are correlated with MRD positivity, the trial is limited by its small sample-size and inclusion of only individuals eligible for HSCT from a single center. Guideline support for using MRD with any method or threshold to make management decisions is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with MCL who are being monitored for residual disease the evidence includes retrospective analyses of NGS testing during therapeutic clinical trials. Relevant outcomes are OS, disease-specific survival, test validity, change in disease status, QOL, and treatment-related morbidity. A retrospective analysis of a "research version" of an NGS test has demonstrated concordance between NGS and FC at 10^{-4} during induction therapy. MRD positivity as determined by either the "research version" of NGS or FC was associated with worse PFS. An exploratory analysis found improved survival in individuals who were MRD negative after 2 cycles of induction; however, this is based on a small number of samples with an undefined threshold for NGS testing. Overall, the literature is limited, and guidelines for NGS testing to detect MRD in individuals with MCL are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

International Myeloma Working Group
The International Myeloma Working Group published consensus criteria in 2016 for response and minimal residual disease (MRD) assessment in multiple myeloma (Table 2).

Table 2. IMWG Criteria

Standard Response Criteria	
Complete response	"Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates"
Stringent complete response	"Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ individuals, respectively, after counting ≥100 plasma cells)"
MRD Response Criteria (requires a complete response)	
Sequencing MRD-negative	Absence of clonal plasma cells by NGS using the LymphoSIGHT platform (or validated equivalent) with a minimum sensitivity of 1 in 10^5 nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus imaging criteria
Sustained MRD-negative	MRD negativity by NGF or NGS, and by imaging, at a minimum of 1 year apart.

FLC: free light chain; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NGF: next-generation flow; NGS: next-generation sequencing.

International Workshop on Chronic Lymphocytic Leukemia
The 2018 guidelines from the International Workshop on Chronic Lymphocytic Leukemia (CLL) have the following recommendations regarding the assessment of MRD:

"The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR [polymerase chain reaction], or next generation sequencing can detect MRD in many individuals who achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become well standardized. Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of 1 CLL cell in 10,000 leukocytes. Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81). As such, individuals will be defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with,1 CLL cell per 10,000 leukocytes."

The National Comprehensive Cancer Network
The National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 3).

Table 3. Recommendations on Assessing Measurable Residual Disease

Guideline	Version	Recommendation
Acute lymphoblastic leukemia	3.2023	MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping

Guideline	Version	Recommendation
		. The most frequently employed methods for MRD assessment include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays specifically designed to detect MRD immunophenotypes at low frequency, real-time quantitative polymerase chain reaction (RQ-PCR) assays (eg, clonally rearranged Ig, TCR genes), and reverse transcriptase quantitative PCR (RT-qPCR) assays (eg, BCR/ABL1)

Guideline	Version	Recommendation
		High sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1x10-4 (0.01%) bone marrow mononuclear cells (MNCs). NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of 1x10-6 (0.0001%) MNCs. If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity.
Chronic lymphocytic leukemia/small lymphocytic lymphoma https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf	3.2023	Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end

Guideline	Version	Recommendation
		of treatment is an important predictor of treatment efficacy. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method.
Multiple myeloma	1.2024	Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS. Surveillance for smoldering disease: Bone marrow aspirate and biopsy with FISH, SNP array, NGS, or multiparameter flow

Guideline	Version	Recommendation
		cytometry may be used as clinically indicated. Consider MRD testing as indicated for prognostication after shared decision with patient. International Myeloma Working Group (IMWG) response criteria: Flow MRD-negative: Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in

Guideline	Version	Recommendation
		105 nucleated cells or higher. Sequencing MRD-negative: Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 105 nucleated cells or higher.
B-cell lymphomas	6.2023	MRD surveillance is not included in the current guidelines.

ALL: acute lymphoblastic leukemia, CR: complete response; ERIC: European Research Initiative on CLL; FC: flow cytometry; FISH: fluorescence in situ hybridization; MRD: measurable residual disease; NGF: next generation flow; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

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

Medicare National Coverage
Molecular Diagnostic Services Program has determined that clonoSEQ Assay testing is reasonable and necessary when performed on bone marrow specimens in individuals with B-Cell acute lymphoblastic leukemia (ALL), CLL, multiple myeloma, or diffuse large B-cell lymphoma. Medicare will pay for a single episode of testing using clonoSEQ for a patient with ALL, CLL or multiple myeloma when clonoSEQ is being used according to its U.S. Food and Drug Administration cleared indications and clinical guidelines. An episode of testing will typically require a baseline assay and 3 follow-up assays.

Local Coverage Determination
According to LCD L38835 (Minimal Residual Disease Testing for Cancer), although many CLL patients have prolonged survival or cure after treatment with fludarabine, cyclophosphamide, and rituximab, the risk of relapse remains. Flow cytometry is an accepted method for risk stratification of patients and assessment for CR after treatment to assess residual disease; however, NGS-based MRD was demonstrated to be more sensitive and a better predictor of patient outcomes, possibly because other methods are not sensitive enough to accurately predict CR.

For patients with cancer, the unit of service for this type of test (i.e., ClonoSeq) is 1. Billing should occur at the start of the episode of testing. Regarding the use of NGS-based MRD tests (i.e., ClonoSeq®)‡ in patients with cancer, the service may be performed once per patient per cancer diagnosis, unless there is clinical evidence of *a priori* change in genetic content.

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

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT04545333[a]	Real World Observational Study Using clonoSEQ®‡ Next Generation Sequencing in Hematologic Malignancies: The 'Watch' Registry	528	Dec 2024
NCT05625971	Non-Invasive Minimal Residual Disease (MRD) Assessment in Multiple Myeloma Via Functional Imaging and Liquid Biopsy	88	Sep 2024
NCT03509961	A Phase II Pilot Trial to Estimate Survival After a Non-total Body Irradiation (TBI) Based Conditioning Regimen in Patients Diagnosed With Acute Lymphoblastic Leukemia (ALL) Who Are Pre-allogeneic Hematopoietic Cell Transplantation (HCT) Next-generation-sequence (NGS) Minimal Residual Disease (MRD) Negative (ENRAD)	95	Jul 2026
NCT05255354	Optimizing ctDNA-based MRD Assessment in DLBCL, MCL, and FL Patients Undergoing CAR Therapy	300	Mar 2027

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

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Current Effective Date: 04/01/2024

12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. New policy.
12/05/2019 Medical Policy Committee review
12/11/2019 Medical Policy Implementation Committee approval. No change to coverage.
12/03/2020 Medical Policy Committee review
12/09/2020 Medical Policy Implementation Committee approval. No change to coverage.
02/04/2021 Medical Policy Committee review
02/10/2021 Medical Policy Implementation Committee approval.
03/04/2021 Medical Policy Committee review
03/10/2021 Medical Policy Implementation Committee approval. Coverage statement went from Investigational to "Based on review of available data, the Company may consider next-generation sequencing (eg clonoSEQ) to detect measurable residual disease (MRD) as an alternative to standard testing (e.g., flow cytometry or polymerase chain reaction) in patients with acute lymphoblastic leukemia (ALL),

	chronic lymphocytic leukemia (CLL), or multiple myeloma to be eligible for coverage." and "Based on review of available data, the Company considers next-generation sequencing to detect MRD in all other situations to be investigational."
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Senate bill review. Added the words "following treatment" in the coverage criteria statement.
03/19/2023	Coding Update
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Diffuse large B-cell lymphoma and mantle cell lymphoma added to investigational statement. Body of policy updated.
01/04/2024	Medical Policy Committee review
01/10/2024	Medical Policy Implementation Committee approval. FDA section updated. Added local coverage determination. Note added. Body of the policy and references updated.

Next Scheduled Review Date: 01/2025

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 2023 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	0171U, 0306U, 0307U, 0364U, 81479, 81599
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****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, 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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.