



Louisiana

Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 03/08/2021

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 a one-time genotypic or phenotypic analysis of thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) OR in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be **eligible for coverage.****

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 genotypic and/or phenotypic analysis of the thiopurine methyltransferase (TPMT) and NUDT15 in all other situations to be **investigational.***

Based on review of available data, the Company considers analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN) to be **investigational.***

Policy Guidelines

Thiopurine methyltransferase (TPMT) and/or nudix hydrolase (NUDT15) testing cannot substitute for complete blood count monitoring in patients receiving thiopurines. Early drug discontinuation

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may be considered in patients with abnormal complete blood count results. Dosage reduction is recommended in patients with reduced TPMT/NUDT15 activity. Alternative therapies may need to be considered for patients who have low or absent TPMT/NUDT15 activity (homozygous for nonfunctional alleles). Accurate phenotyping results are not possible in patients who have received recent blood transfusions. TPMT/NUDT15 genotyping and phenotyping would only need to be performed once.

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

Thiopurines

Thiopurines or purine analogues are immunomodulators. They include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and inflammatory bowel disease, and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of inflammatory bowel disease, particularly in patients with corticosteroid-resistant disease. However, the use of thiopurines is limited by both long onset of action (3-4 months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions.

Thiopurines are metabolized by a complex pathway to several metabolites including 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). Thiopurine methyltransferase (TPMT) is one of the key enzymes in thiopurine metabolism. Patients with low or absent TPMT enzyme activity can develop bone marrow toxicity with thiopurine therapy due to excess production of 6-TG metabolites, while elevated 6-MMP levels have been associated with hepatotoxicity. In population studies, the

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activity of the TPMT enzyme has been shown to be trimodal, with 90% of subjects having high activity, 10% intermediate activity, and 0.3% with low or no activity. Variants in another metabolizing enzyme, NUDT15 (nudix hydrolase, NUDIX 15), have been identified that strongly influence thiopurine tolerance in patients with IBD. Homozygous carriers of NUDT15 variants are intolerant of thiopurine compounds because of risk of bone marrow suppression. Individuals with this variant are sensitive to 6-MP and have tolerated only 8 percent of the standard dose. Several variant alleles have been identified with varying prevalence among different populations and varying degrees of functional effects. NUDT deficiency is most common among East Asians (22.6%), followed by South Asians (13.6%), and Native American populations (12.5%-21.2%). Studies in other populations are ongoing.

Phenotype Testing for Thiopurine Methyltransferase Activity

The testing involves incubation of RBC lysate in a multisubstrate cocktail. The enzymatically generated thiomethylated products are measured by liquid chromatography tandem mass spectrometry to produce an activity profile for thiopurine methyltransferase. Multiple assays are available and use different reference standards. Results are based on the quantitative activity level of TPMT (in categories) along with clinical interpretation. Two commercial tests are illustrated below as examples:

ARUP Labs:

- Normal TPMT activity levels: Individuals are predicted to be at low risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine therapy; no dose adjustment is recommended.
- Intermediate TPMT activity levels: Individuals are predicted to be at intermediate risk of bone marrow toxicity (myelosuppression), as a consequence of standard thiopurine therapy; a dose reduction and therapeutic drug management is recommended.
- Low TPMT activity: Individuals are predicted to be at high risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine dosing. It is recommended to avoid the use of thiopurine drugs.
- High TPMT activity: Individuals are not predicted to be at risk for bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine dosing, but may be at risk for therapeutic failure due to excessive inactivation of thiopurine drugs. Individuals may require higher than the normal standard dose. Therapeutic drug management is recommended.

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Lab Corp

- Normal: 15.1 to 26.4 units/ml RBC
- Heterozygous for low TPMT variant: 6.3 to 15.0 units/ml RBC
- Homozygous for low TPMT variant: <6.3 to units/ml RBC

Genotype Testing for Thiopurine Methyltransferase Activity/Nudix Hydrolase (*NUDT15*) Gene Polymorphism

The genotypic analysis of the *TPMT/NUDT15* gene is based on polymerase chain reaction technology to detect distinct variants. These are listed in Table 1.

Table 1. Identified Genetic Variants for *TPMT/NUDT15* Testing

<i>TPMT</i> Allele	cDNA Nucleotide Change	Amino Acid Change	Effect on Enzyme Metabolism
*1	None (wild type)	None (wild type)	Normal function
*2	c.238G>C	p.Ala80Pro (p.A80P)	No activity
*3A	c.460G>A and c.719A>G	p.Ala154Thr (p.A154T) and p.Tyr240Cys (p.Y240C)	No activity
*3B	c.460G>A	p.Ala154Thr (p.A154T)	No activity
*3C	c.719A>G	p.Tyr240Cys (p.Y240C)	No activity
*4	c.626-1G>A	Not applicable, splice site	No activity
*5	c.146T>C	p.Leu49Ser (p.L49S)	No activity
*8	c.644G>A	p.Arg215His (p.R215H)	Reduced activity
*12	c.374C>T	p.Ser125Leu (p.S125L)	Reduced activity
<i>NUDT15</i> Allele	cDNA Nucleotide Change	Amino Acid Change	Effect on Enzyme Metabolism
1	None (wild type)	None (wild type)	Normal activity

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*2 or *3	c.415C>T	p.Arg139Cys (p.R139C)	No activity
*4	c.416G>A	p.Arg139His (p.R139H)	No activity
*5	c.52G>A	p.Val18Ile (p.V18I)	No activity

Metabolite Markers

The therapeutic effect of thiopurines has been associated with the level of active 6-TGN metabolites, and hepatotoxicity has been associated with higher levels of the inactive metabolites 6-MMP and 6-methylmercaptopurine ribonucleotides. Therefore, it has been proposed that therapeutic monitoring of these metabolites may improve patient outcomes by identifying the reason for a non-response or sub-optimal response. Conversely by measuring 6-MMP levels, a subgroup of patients can be identified who preferentially convert 6-MP to 6-MMP (toxic metabolite) and often do not achieve sufficient 6-TGN levels. This group of patients, often described as “shunters,” may be susceptible to hepatotoxicity because thiopurine dose escalation leads to 6-MMP accumulation.

Therapeutic monitoring of thiopurine metabolite levels is typically performed in patients with IBD as 1) reactive strategy in response to either lack of clinical improvement or observed treatment-related toxicity 2) routine proactive clinical care in patients with quiescent disease.

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. Several thiopurine genotypes, phenotype, and metabolite tests are available under the auspices of the 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.

Prometheus, a commercial laboratory, offers thiopurine genotype, phenotype, and metabolite testing for those on thiopurine therapy. The tests are referred to as Prometheus^{®‡} TPMT Genetics, Prometheus^{®‡} TPMT enzyme, and Prometheus^{®‡} thiopurine metabolites, respectively. Other laboratories that offer *TPMT* genotyping include: Quest Diagnostics (TPMT Genotype); ARUP

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Laboratories (TPMT DNA); Specialty Laboratories (TPMT GenoTypR^{TM†}); PreventionGenetics (TPMT Deficiency via the TPMT Gene); Genelex (TPMT); Fulgent Genetics (TPMT); and LabCorp (TPMT enzyme activity and genotyping).

FDA Labeling on Pharmacogenomic Test for Thiopurines

The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, the FDA has given clear and specific directives on use of pharmacogenomic testing for azathioprine (a prodrug for mercaptopurine), mercaptopurine, and thioguanine.

Mercaptopurine

- Consider testing for TPMT and NUDT15 deficiency in patients who experience severe myelosuppression or repeated episodes of myelosuppression Homozygous Deficiency in either TPMT or NUDT15: Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.
- Heterozygous Deficiency in TPMT and/or NUDT15: Reduce the dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended dosage, but some require dose reduction based on adverse reactions. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dose reductions.

Azathioprine

- Patients with TPMT and/or NUDT15 Deficiency: Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction
- Homozygous deficiency in either TPMT or NUDT15: Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency
- Heterozygous deficiency in TPMT and/or NUDT15: Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterozygous

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deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions.

Thioguanine

- Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression.
- Evaluate patients with repeated severe myelosuppression for TPMT or NUDT15 deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions.

Rationale/Source

The thiopurine class of drugs, which include azathioprine (a pro-drug for mercaptopurine), mercaptopurine, and thioguanine, are used to treat a variety of diseases; however, it is recommended the use of thiopurines be limited due to a high rate of drug toxicity. The *TPMT* and *NUDT15* genes encode for the enzymes thiopurine S-methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) respectively. These enzymes are involved in the metabolism of thiopurines. Genetic variants in *TPMT* and *NUDT15* gene affects drug hydrolysis and hence, increases susceptibility to drug-induced toxicity. Mercaptopurine and thioguanine are directly metabolized by the thiopurine S-methyltransferase (TPMT) enzyme. Susceptibility to drug toxicity is linked to the level of TPMT activity. The variation in TPMT activity has been related to 3 distinct TPMT variants. TPMT can be assessed through genetic analysis for polymorphisms in leukocyte DNA (genotype) or by measurement of the enzyme activity in circulating red blood cells (RBCs; phenotype). NUDT15 is measured by genetic analysis only (genotype). Pharmacogenomic analysis of TPMT/NUDT15 status is proposed to identify patients at risk of thiopurine drug toxicity and adjustment of medication doses accordingly. Measurement of metabolite markers has also been proposed.

For individuals who receive thiopurines metabolite monitoring to guide treatment changes, the evidence includes 2 RCTs. Relevant outcomes are change in disease status, treatment-related mortality and treatment-related morbidity. The evidence for the use of reactive thiopurine metabolite monitoring to guide treatment changes in patients being treated with thiopurines includes only retrospective studies that were not included in this review. The evidence for the use of routine thiopurine drug monitoring to guide treatment changes in patients being treated with thiopurines

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includes 2 small, randomized studies. Both studies were terminated early due to slow recruitment and failure to meet prespecified enrollment targets. Additionally, there was high attrition rate in both trials (33% to 46%). The pooled analysis of both trials reported in the systematic review did not show statistical significant difference in clinical remission in patients who underwent routine TDM-guided dose adaptation compared with standard weight-based dosing. The rate of serious adverse events (requiring discontinuation of therapy) was also comparable between the 2 arms. Based on 2 small RCTs at high risk of bias, there is uncertainty whether reactive or routine thiopurine metabolite monitoring to guide treatment changes are superior to empirical clinical-based or standard weight-based dosing changes. The evidence is insufficient to determine the effects of technology on net health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.1.2020) guidelines on adult and adolescent/young adult acute lymphoblastic leukemia state:

- “For patients receiving 6-MP [mercaptopurine] consider testing for TPMT [thiopurine methyltransferase] gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.”

National Comprehensive Cancer Network (v.1.2021) guidelines for pediatric acute lymphoblastic leukemia state:

- Genetic testing for no function alleles of TPMT and NUDT-15 should be considered prior to the initiation of thiopurine therapy, or if excessive toxicity is encountered following treatment with thiopurines.
- Dosing recommendation for patients who are heterozygous or homozygous for TPMT no function allele are summarized in Table 2.
- For patients homozygous for normal function TPMT and NUDT15, who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte TPMT activity. Genetic testing may fail to identify rare or previously undiscovered no function alleles.

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Table 2. Dosing Guidelines for Thiopurines on TPMT Phenotype

Genotype/Phenotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Homozygous for normal function alleles (eg *1/*1); normal metabolizer	Starting dose should be based on treatment protocol (typically 75 mg/m ² /day). Allow 2 weeks to achieve steady state prior to making dosing adjustments	Starting dose should be based on treatment protocol (typically 60 mg/m ² /day). Allow 2 weeks to achieve steady state prior to making dosing adjustments
Heterozygous for no function alleles (eg *1/*2, 3A, 3B, 3C or 4); intermediate metabolizer	Starting dose at 30 to 80% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2 to 4 weeks to achieve steady state prior to making dosing adjustments.	Reduce starting dose by 30 to 80%. ^a Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2 to 4 weeks to achieve steady state prior to making dosing adjustments.
Homozygous for no function alleles (eg *2/*3A, *3/*4); poor metabolizer	Starting dose at approx 10% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4 to 6 weeks to achieve steady state prior to making dosing adjustments.	Starting dose at approx 10% of full dose as dictated by protocol. Allow 4 to 6 weeks to achieve steady state prior to making dosing adjustments.

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^aFor patients already receiving reduced starting dose of thiopurines (<75 mg/m²/day of 6-MP or <40 mg/m²/day of 6-TG) further dose reduction may not be needed.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (2013) on inflammatory bowel disease (IBD) published consensus recommendations on the role of the TPMT enzyme and thiopurine metabolite testing in pediatric IBD. Recommendations (high and moderate) included:

1. “TPMT testing is recommended before initiation of TPs [thiopurines] to identify individuals who are homozygous recessive or have extremely low TPMT activity....
2. Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leucopenia.
3.All individuals on TPs should have routine monitoring of CBC [complete blood cell] and WBC [white blood cell] counts to evaluate for leucopenia regardless of TPMT testing results.
4. Metabolite testing can be used to determine adherence to TP therapy.
5. Metabolite testing can be used to guide dosing increases or modifications in patients with active disease....
6. Routine and repeat metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP.”

American Gastroenterological Association Institute

Recommendations from the American Gastroenterological Association Institute (2017) guidelines on therapeutic drug monitoring in IBD are summarized in Table 3.

Table 3. Summary of Findings of American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of IBD

Key Question	Conclusion	QOE
In patients with IBD being started on thiopurines, is routine TPMT measurement (to guide dosing) superior to no TPMT measurement (with empiric weight-based dosing of thiopurines)?	Benefit is uncertain but may avoid serious harm in a small fraction of patients	Low

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In patients with active IBD treated with thiopurines or with side effects thought to be due to thiopurine toxicity, is reactive therapeutic drug monitoring to guide treatment changes superior to no therapeutic drug monitoring with empiric treatment changes?	May be a benefit	Very low
In patients with IBD treated with thiopurines, is routine therapeutic drug monitoring to guide thiopurine dosing superior to empiric weight-based dosing?	Benefit is uncertain	Very low

AGA: American Gastroenterological Association; IBD: inflammatory bowel disease; QOE: quality of evidence; *TPMT*: thiopurine methyltransferase.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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

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
<i>Unpublished</i>			
NCT02929706	Effectiveness of Thiopurine Dose Optimization by NUDT15 R139C on Reducing Thiopurine-Induced Leucopenia in Inflammatory Bowel Disease	400	Aug 2018 (ongoing; last updated May 2018)

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NCT03093818	PREemptive Pharmacogenomic Testing for Preventing Adverse Drug REactions (PREPARE)	6892	Dec 2019
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NCT: national clinical trial.

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Policy History

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|------------|---|
| 05/07/2009 | Medical Director review |
| 05/20/2009 | Medical Policy Committee approval. New policy. |
| 06/03/2010 | Medical Policy Committee approval |
| 06/16/2010 | Medical Policy Implementation Committee approval. Policy title changed by taking out azathioprine (6-MP) and replacing it with “Thiopurines”. Policy statement changed to “a one-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT) gene in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be eligible for coverage.” |
| 06/02/2011 | Medical Policy Committee review |
| 06/15/2011 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/14/2012 | Medical Policy Committee review |
| 06/20/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/11/2013 | Codes updated. |
| 06/06/2013 | Medical Policy Committee review |

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Louisiana

Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 03/08/2021

06/25/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/05/2014 Medical Policy Committee review

06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

09/03/2015 Medical Policy Committee review

09/23/2015 Medical Policy Implementation Committee approval. Statement added that genotypic and/or phenotypic analysis of the enzyme TPMT is considered investigational in all other situations.

11/03/2016 Medical Policy Committee review

11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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. Coverage eligibility unchanged.

04/01/2018 Coding update

11/08/2018 Medical Policy Committee review

11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/07/2019 Medical Policy Committee review

11/13/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

03/09/2020 Coding update

09/14/2020 Coding update

11/05/2020 Medical Policy Committee review

11/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/04/2021 Medical Policy Committee review

02/10/2021 Medical Policy Implementation Committee approval. NUDT15 gene was added to eligible for coverage and investigational statements.

Next Scheduled Review Date: 02/2022

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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 2020 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	0034U, 0169U, 81335, 81401
HCPCS	No codes
ICD-10 Diagnosis	K50.00-K50.919, K50.90-K50.919, K51.00-K51.919, M05.00-M05.9, M06.00-M06.9, M08.00-M08.99, M12.00-M12.09 Added codes eff 10/1/2020: M05.7A, M05.8A, M06.0A, M06.8A, M08.0A, M08.2A, M08.4A, M08.9A

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***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.

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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.

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