MEDICAL POLICY

POLICY TITLE	**PHARMACOGENOMIC AND METABOLITE MARKERS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH THIOPURINES**
POLICY NUMBER	**MP 2.218**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**7/1/2024**

I. POLICY

Genotypic or phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) may be considered **medically necessary** in patients initiating 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.

Analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-MMP and 6-TG, may be considered **medically necessary** for optimizing the therapeutic response to 6-MP (azathioprine, Imuran®) if the therapeutic response is not reached with standard dosing.

Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease may be considered **medically necessary** for the following indications:

- To measure blood levels in individuals suspected of having toxic responses to AZA and/or 6-MP (e.g., hepatotoxicity or myelotoxicity);
- To measure drug levels in individuals who have not responded to therapy (e.g., persistent fever, further weight loss, and bloody diarrhea).

Genotypic and/or phenotypic analysis of the enzyme TPMT and NUDT15 is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

Thiopurine methyltransferase (TPMT) and/or nudix hydrolase (NUDT15) testing cannot substitute for complete blood count monitoring in patients receiving thiopurines. TPMT phenotype or genotype testing is suggested but not required by the US Food and Drug Administration (FDA) prior to thiopurine use. Early drug discontinuation 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.

II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND TOP

Thiopurines

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* genes affect drug hydrolysis and hence, increase susceptibility to drug-induced toxicity. Mercaptopurine and thioguanine are directly metabolized by the 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.

Thiopurines or purine analogues are immunomodulators. They include azathioprine (AZA; Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and inflammatory bowel disease (IBD), and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of IBD, particularly in patients with corticosteroid-resistant disease. However, use of thiopurines is limited by both its long onset of action (3-4 months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions. Pretreatment determination of *TPMT* genotype to guide dosing has been shown to be effective at reducing the risk of thiopurine-related bone marrow suppression.

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 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 level of TPMT (in categories) along with clinical interpretation. Two commercial tests are illustrated below as examples: 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

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.

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,

TPMT 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
NUDT15 Allele	**cDNA Nucleotide Change**	**Amino Acid Change**	**Effect on Enzyme Metabolism**
1	None (wild type)	None (wild type)	Normal activity
***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.

Regulatory Status

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 Laboratories (TPMT DNA); Specialty Laboratories (TPMT GenoTypR™); 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. Therefore, evidence for these indications is not reviewed in the Rationale section.

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

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.

IV. RATIONALE

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Summary of Evidence

For individuals who are treated with thiopurines who receive TPMT genotype analysis or TPMT phenotype analysis, the evidence includes studies of diagnostic performance, systematic reviews, and randomized controlled trials. Relevant outcomes are symptoms, morbid events, and change in disease status. A large number of studies have assessed the diagnostic performance of TMPT genotyping and phenotyping tests. A meta-analysis found a pooled sensitivity of about 80% and specificity near 100% for identifying patients with subnormal enzymatic activity. Three randomized controlled trials (total N=1145 patients) compared TPMT genotype/phenotype testing with no testing and empirical weight-based thiopurine dosing. There was no significant difference in the incidence of hematologic adverse events, treatment discontinuation rates, or clinical remission. However, secondary analysis of a small number of individuals who had intermediate enzymatic activity/heterozygous genotype or homozygous genotype/low enzymatic activity showed that TPMT testing to guide dosing was associated with statistically significant risk reduction in hematologic adverse events with a wide margin of error. In summary, 200 patients would have to be genotyped to avoid 1 episode of a hematologic adverse drug reaction (7. vs 7. i.e., 0. risk difference). The number needed to treat to avoid 1 episode of a hematologic adverse drug reaction would be 5 for at-risk individuals (risk difference in patients with a genetic variant, 20. 2. vs 22. In addition, a small, inadequately powered randomized controlled trial that assessed phenotype TPMT testing found no difference in treatment discontinuation rates due to adverse drug reactions between the 2 arms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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V. DEFINITIONS

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CROHN'S DISEASE is a chronic inflammatory bowel disease of unknown origin, usually affecting the ileum, the colon, or another part of the gastrointestinal tract.

IMMUNOSUPPRESSIVE refers to any treatment used to block abnormal or excessive immune responses.

METABOLITE refers to any product of metabolism.

NEOPLASIA is the development of neoplasms that are new and abnormal formations of tissue such as tumors or growths.

CROHN'S DISEASE is a chronic inflammatory bowel disease of unknown origin, usually affecting the ileum, the colon, or another part of the gastrointestinal tract.

PHARMACOGENOMIC refers to the study of the effects of genetic differences among people and the impact these differences have on the uptake, effectiveness, toxicity, and metabolism of drugs.

THIOPURINE METHYLTRANSFERASE ENZYME (TPMT) is an enzyme that is active in the metabolism of azathioprine in the body.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes							
80299	81335	82542	82657	84433	0034U	0169U	0286U
0461U							

ICD-10-CM Diagnosis Code	Description
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn’s disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn’s disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess

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ICD-10-CM Diagnosis Code	Description
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn’s disease, unspecified, without complications
K50.911	Crohn's disease, unspecified with rectal bleeding
K50.912	Crohn's disease, unspecified with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.40	Inflammatory polyps of colon without complications

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ICD-10-CM Diagnosis Code	Description
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.90	Ulcerative colitis, unspecified without complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified, with intestinal obstruction
K51.913	Ulcerative colitis, unspecified, with fistula
K51.914	Ulcerative colitis, unspecified, with abscess
K51.918	Ulcerative colitis, unspecified, with other complication
K51.919	Ulcerative colitis, unspecified, unspecific complications

IX. REFERENCES

TOP

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POLICY TITLE	**PHARMACOGENOMIC AND METABOLITE MARKERS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH THIOPURINES**
POLICY NUMBER	**MP 2.218**

X. POLICY HISTORY

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MP 2.218	**06/03/2019 Consensus Review**. Policy statement unchanged. References updated**.**
	05/12/2020 Consensus Review. Policy Statement unchanged. References checked and updated. Coding checked with no changes.
	06/16/2021 Minor Review. Addition of NUDT15 as MN. Updated coding, background, references, and rationale.
	12/01/2021 Administrative Update. Added 0286U
	12/01/2022 Administrative Update. Added 84433
	12/14/2022 Consensus Review. Minor editorial updates, no change to intent. Updated background and references. Missing ICD10 codes added.
	06/11/2024 Administrative Update. New code 0461U, effective 7/1/24.

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