Medicare Medical Policy

Serologic Testing and Therapeutic Monitoring for Inflammatory Bowel Disease

MEDICARE MEDICAL POLICY NUMBER: 344

Effective Date: 9/1/2024

Last Review Date: 8/2024

Next Annual Review: 8/2025

INSTRUCTIONS FOR USE: Company Medicare Medical Policies serve as guidance for the administration of plan benefits and do not constitute medical advice nor a guarantee of coverage. Company Medicare Medical Policies are reviewed annually to guide the coverage or non-coverage decision-making process for services or procedures in accordance with member benefit contracts (otherwise known as Evidence of Coverage or EOCs) and Centers of Medicare and Medicaid Services (CMS) policies, manuals, and other CMS rules and regulations. In the absence of a CMS coverage determination or specific regulation for a requested service, item or procedure, Company policy criteria or applicable utilization management vendor criteria may be applied. These are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

The Company reserves the right to determine the application of Medicare Medical Policies and make revisions to these policies at any time. Any conflict or variance between the EOC and Company Medical Policy will be resolved in favor of the EOC.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PRODUCT AND BENEFIT APPLICATION

☒ Medicare Only

MEDICARE COVERAGE CRITERIA

IMPORTANT NOTE: More than one Centers for Medicare and Medicaid Services (CMS) reference may apply to the same health care service, such as when more than one coverage policy is available (e.g., both an NCD and LCD exist). All references listed should be considered for coverage decision-making. The Company uses the most current version of a Medicare reference available at the time of publication; however, these websites are not maintained by the Company, so Medicare references and their corresponding hyperlinks may change at any time. If there is a conflict between the Company Medicare Medical Policy and CMS guidance, the CMS guidance will govern.

Service	Medicare Guidelines
Prometheus IBD sgi Diagnostic (California)	Local Coverage Determination (LCD): MolDX: Prometheus IBD sgi Diagnostic® Policy (L37299)
Thiopurine Methyltransferase (TPMT) and NUDT15 Genetic Testing	• **For testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, or WY:** Local Coverage Article (LCA): Billing and Coding: MolDX: Pharmacogenomics Testing (A57385) and LCD L38337 • **For testing performed in CA or NV:** LCA: Billing and Coding: MolDX: Pharmacogenomics Testing (A57384) and LCD L38335 **NOTES:** 1. **TPMT and NUDT15** testing may be medically necessary when treatment planning / medical management include consideration of the medication(s) associated with each gene specified in the above LCAs. Other uses of these gene tests would be considered not medically necessary otherwise. 2. The ***Prometheus® TPMT Genetics test*** (Prometheus Laboratories; California) **has** completed the technical assessment requirement to evaluate analytical validity, clinical validity, and clinical utility and may be **medically necessary** when the other requirements of the LCD/LCA are otherwise met. • **For testing performed in IL, MN, WI, CT, NY, ME, MA, NH, RI, or VT:** LCA: Billing and Coding: Molecular Pathology Procedures A56199 and LCD L35000. **NOTES:** 1. Apply the limited diagnosis code coverage detailed in the LCA A56199 for CPT **81335** (TPMT).

	2. According to LCA A56199, CPT **81306** (NUDT15) testing is subject to individual review. Since the LCA doesn't provide specific guidance for this gene testing, apply the Company medical policy criteria below. 3. Apply the same TPMT and NUDT15 criteria to the tests represented by PLA codes **0034U and 0169U**, since these "panels" are targeted to just two gene tests. According to LCD L35000, panels require medical necessity for each component, so the criteria for **both** genes must be met in order for these panels to be considered medically necessary. 4. For **0203U and 0286U**, according to LCD L35000, analytical validity and clinical utility must be documented, but with no guidance in the LCD, apply the Company medical policy criteria below.
NOD2/CARD15 Genetic Testing	The ***Prometheus® NOD2/CARD15 test*** (Prometheus Laboratories; California) is considered **not medically necessary** according to the DEX™ Diagnostics Exchange Registry, which holds MolDX coverage decisions for individual tests. I. Other NOD2/CARD15 tests not listed will require individual review.
Prometheus® Crohn's Prognostic test (Prometheus Laboratories; California)	As of the most recent review of this policy, this test is considered **not medically necessary** according to the DEX™ Diagnostics Exchange Registry, which holds MolDX coverage decisions for individual tests.

Medicare Coverage Criteria: "MA organizations may create publicly accessible internal coverage criteria… when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs." *(§ 422.101(b)(6) – see Policy Guidelines below*)

- **Medicare Coverage Manuals:** Medicare does not have criteria for the testing for serologic testing and therapeutic monitoring for the diagnosis and/or management of inflammatory bowel disease (IBD) in a coverage manual. **However, broad coverage requirements are provided by Medicare for diagnostic laboratory testing in general.** Specifically, Medicare requires diagnostic laboratory tests be ordered by a provider who is treating the member for a specific medical problem and who will promptly use the test results in the direct management of that specific medical problem.[1,2] These coverage criteria are considered "not fully established" under CFR § 422.101(6)(i)(A) as additional criteria are needed to interpret or supplement these general coverage provisions in order to determine medical necessity consistently.
- **National Coverage Determination (NCD):** Medicare does not have an NCD for testing used to diagnosis or manage IBD.
- **Local Coverage Determination (LCD)/Local Coverage Article (LCA):** According to Medicare guidelines, "Jurisdiction of payment requests for laboratory services furnished by an independent laboratory… lies with the A/B MAC (B) serving the area in which the laboratory test is performed."[3] Tests with available LCD or LCA guidance are identified above; however, the IBD tests identified below do **not** have an available LCD or LCA for their respective service areas.

- Therefore, in the absence of established Medicare coverage criteria in a manual, NCD, LCD, or other regulatory guidance for the service area in which the testing is being performed, Company criteria below are applied for medical necessity decision-making. Medicare statutes and regulation provide general coverage criteria for diagnostic testing, but additional criteria to interpret or supplement the Medicare criteria are being used in order to determine medical necessity consistently. These additional criteria provide clinical benefits that are highly likely to outweigh any clinical harms, including from delayed or decreased access to items or services **because the use of this additional criteria based on peer-reviewed evidence evaluates how testing is expected to improve IBD management or health outcomes, or change treatment decisions (e.g., obviate the need for colonoscopy in decision-making, etc.)**. Specifically, the literature review is used to evaluate whether or not each test has established clinical utility and/or analytic validity, and whether or not the sensitivity and specificity of each assay is effective for identifying the disease in question. Tests without proven clinical utility and/or analytical validity pose risk to patients by potentially resulting in inaccurate diagnosis, or delays in appropriate treatment.

Fecal Calprotectin Testing (CPT 83993) *Quantitative Polymerase Chain Reaction (PCR) Testing for the Diagnosis and/or Management of IBD (e.g., the PredictSURE IBD™ test, by KSL Diagnostics; [New York] [CPT 0203U])* *Thiopurine Therapeutic Drug Monitoring (Measurement of 6-thioguanine nucleotide [6-TGN] and 6-methylmercaptopurine nucleotide [6-MMPN] [e.g.,* ***Prometheus Thiopurine Metabolites]****)* *Testing for Serological Markers for Diagnosis and/or Management of IBD** *Other combination panel testing of serologic, genetic, and inflammatory markers for Diagnosis and/or Management of IBD, not otherwise addressed above.* ***Examples include:***	Company medical policy for Serologic Testing and Therapeutic Monitoring for Inflammatory Bowel Disease I. These services may be considered **medically necessary** for Medicare when the Company medical policy criteria are met. II. These services are considered **not medically necessary** for Medicare Plan members when the Company medical policy criteria are not met. See *Policy Guidelines below.* ***NOTE:*** *The summary of evidence, as well as the list of citations or references used in the development of the Company's internal coverage criteria, are publicly available and can be found using the Company medical policy link above [CFR § 422.101(6)(ii)(A) and (B)].*

• ***CNT [CEP72, TPMT and NUDT15] Genotyping Panel (RPRD Diagnostics; Wisconsin [0286U])***	

IMPORTANT NOTICE: While some services or items may appear medically indicated for an individual, they may also be a direct exclusion of Medicare or the member's benefit plan. Such excluded services or items by Medicare and member EOCs include, but are not limited to, services or procedures considered to be cosmetic, not medical in nature, or those considered not medically reasonable or necessary under *Title XVIII of the Social Security Act, §1862(a)(1)(A).* If there is uncertainty regarding coverage of a service or item, please review the member EOC or submit a pre-service organization determination request. Note that the Medicare Advance Beneficiary Notice of Noncoverage (ABN) form **cannot** be used for Medicare Advantage members. *(Medicare Advance Written Notices of Non-coverage. MLN006266 May 2021)*

POLICY CROSS REFERENCES

- Inflammatory Bowel Disease: Measurement of Antibodies to Immunosuppressive Therapies, MP345

The full Company portfolio of Medicare Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

GENERAL

***Serological Marker Testing for Diagnosis and/or Management of Inflammatory Bowel Disease**

Examples of these tests/panels include, but are not limited to, the following:

- Anti-Saccharomyces cerevisiae antibodies (ASCA)
- Anti-glycan-associated Saccharomyces cerevisiae antibodies (gASCA)
- Anti-neutrophilic cytoplasmic antibody (ANCA)
- Perinuclear antineutrophil cytoplasmic autoantibodies (pANCA)
- Anti-outer membrane porin protein C of Escherichia coli antibodies (anti-OmpC)
- Anti-chitobioside carbohydrate antibodies (ACCA)
- Anti-laminaribioside carbohydrate antibodies (ALCA)
- Anti-mannobioside carbohydrate antibodies (AMCA)

MEDICARE AND MEDICAL NECESSITY

Only medically reasonable and necessary services or items which treat illness or injury are eligible for Medicare coverage, as outlined in *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. MA organizations (MAOs) make medical necessity determinations based on coverage and benefit criteria, current standards of care, the member's unique personal medical history (e.g., diagnoses, conditions, functional status, co-morbidities, etc.), physician recommendations, and clinical notes, as well as involvement of a plan medical director, where appropriate. *(§ 422.101(c)(1))*

In addition:

> "MA organizations may create publicly accessible internal coverage criteria that are based on current evidence in widely used treatment guidelines or clinical literature when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs. Current, widely-used treatment guidelines are those developed by organizations representing clinical medical specialties, and refers to guidelines for the treatment of specific diseases or conditions. Acceptable clinical literature includes large, randomized controlled trials or prospective cohort studies with clear results, published in a peer-reviewed journal, and specifically designed to answer the relevant clinical question, or large systematic reviews or meta-analyses summarizing the literature of the specific clinical question." *(§ 422.101(b)(6) and Medicare Managed Care Manual, Ch. 4, §90.5)*

Medicare requires diagnostic laboratory tests be ordered by a provider who is treating the member for a specific medical problem **and** who will use the test results in the direct management of that specific medical problem.[1,2] Thus, diagnostic testing must have established clinical utility and analytic validity.

The Company policy for *PHA Medicare Medical Policy Development and Application* (MP50) provides details regarding Medicare's definition of medical necessity and the hierarchy of Medicare references and resources during the development of medical policies, as well as the Plan's use of evidence-based processes for policy development. For tests with no available NCD or LCD/LCA for the service area in which the testing is performed, Company policy criteria will be used to determine medical necessity in regard to clinical and analytical validity, as well as clinical utility, which are required to establish Medicare coverage.

REGULATORY STATUS

U.S. FOOD & DRUG ADMINISTRATION (FDA)

While clearance by the Food and Drug Administration (FDA) is a prerequisite for Medicare coverage, the 510(k) premarket clearance process does not in itself establish medical necessity. Medicare payment policy is determined by the interaction of numerous requirements, including but not limited to, the availability of a Medicare benefit category and other statutory requirements, coding and pricing guidelines, as well as national and local coverage determinations and clinical evidence.

BILLING GUIDELINES AND CODING

GENERAL

See the associated local coverage article (LCA) for related billing and coding guidance:

- LCA: Billing and Coding: MolDX: Prometheus IBD sgi Diagnostic Policy (A57516)

Only one genotypic (CPT code: 81401 or 84433) or phenotypic (CPT codes: 82542 and 82657) assay of TPMT is considered medically necessary, per individual, per lifetime.

CODING POLICY 30.0 LABORATORY PANEL BILLING

Testing panels must be billed using a single code. When no specific CPT or HCPCS code exists for the panel, the provider is required to bill the panel using an unlisted code. CPT guidelines state, "Do not select a CPT code that merely approximates the service provided. If no such specific code exists, then report the service using the appropriate unlisted procedure or service code."

Unbundling occurs when a laboratory bills separately for some or all tests analyzed as part of a panel. It is not appropriate for the provider to bill any of the tests in a panel separately as if they were performed individually. This is a misrepresentation of services performed.

Both the Prometheus IBD sgi Diagnostic and Prometheus Crohn's Prognostic tests are not medically necessary, regardless of what single code or code combination they are billed with.

CODES*		
CPT	0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) *(Used to report Thiopurine Methyltransferase [TPMT] and Nudix Hydrolase [NUDT15] Genotyping test, by Mayo Clinic; Minnesota)*
	0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants *(Used to report NT [NUDT15 and TPMT] Genotyping Panel test, by RPRD Diagnostics; Wisconsin)*
	0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness *(Used to report the PredictSURE IBD™ Test, by KSL Diagnostics; New York)*
	0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants *(Used to report CNT [CEP72, TPMT and NUDT15] genotyping panel, by RPRD Diagnostics; Wisconsin)*
	81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)
	81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81479	Unlisted molecular pathology procedure
	82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
	82657	Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen
	83993	Calprotectin, fecal

	84433	Thiopurine S-methyltransferase (TPMT)
	84999	Unlisted chemistry procedure
HCPCS	None	

***Coding Notes:**

- The code list above is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit. According to Medicare, "presence of a payment amount in the MPFS and the Medicare physician fee schedule database (MPFSDB) does not imply that CMS has determined that the service may be covered by Medicare." The issuance of a CPT or HCPCS code or the provision of a payment or fee amount by Medicare does **not** make a procedure medically reasonable or necessary or a covered benefit by Medicare. *(Medicare Claims Processing Manual, Chapter 23 - Fee Schedule Administration and Coding Requirements, §30 - Services Paid Under the Medicare Physician's Fee Schedule, A. Physician's Services)*
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. 42 CFR §410.32(a); Available at: https://www.govinfo.gov/content/pkg/CFR-2011-title42-vol2/pdf/CFR-2011-title42-vol2-sec410-32.pdf
2. Medicare Benefit Policy Manual, Ch. 15 – Covered Medical and Other Health Services, §80.1 - Clinical Laboratory Services; Available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
1/2023	Q1 2023 code updates (converted to new format 2/2023)
3/2023	Interim update (code configuration change only). Converted to new policy template.
11/2023	Annual review, no criteria changes but language revision due to policy changes from "Investigational" to "not medically necessary"
9/2024	Annual review, no change to criteria