Pharmacogenomics Testing

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➲ Instructions for Use

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Related Medicare Advantage Medical Policies

- Clinical Diagnostic Laboratory Services
- Molecular Pathology/Molecular Diagnostics/Genetic Testing
- Molecular Pathology/Genetic Testing Reported with Unlisted Codes
- Tier 2 Molecular Pathology Procedures

Related Medicare Advantage Reimbursement Policies

- Clinical Laboratory Improvement Amendments (CLIA) ID Requirement Policy, Professional
- Laboratory Services Policy, Professional
- Molecular Pathology Policy, Professional and Facility

Coverage Rationale

Overview

Genetic testing holds the potential to provide great value in improving health outcomes for all individuals. The scope of this policy includes testing to determine how Genes affect the body's response to certain medicines, known as pharmacogenetic, or pharmacogenomic testing.

A person's genetic code can influence various steps in drug response. Examples of these steps where genetic variation may influence response include drug receptor type and number, increased or decreased drug uptake, and increased or decreased drug metabolism. Depending on the specific situation, these interactions can result in increased or decreased drug effectiveness as well as adverse drug reactions.

Single Gene, Multi-Gene Panels, and combinatorial tests aimed at determining an individual's drug response are addressed.

CMS National Coverage Determinations (NCDs)

Medicare has an NCD 90.1 Pharmacogenomics Testing for Warfarin Response. Medicare does not have an NCD for Pharmacogenomics Testing addressed in this policy.

CMS Local Coverage Determinations (LCDs) and Articles

Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) exist and compliance with these policies is required where applicable. For specific LCDs/LCAs, refer to the table for Pharmacogenomics Testing.

For coverage guidelines for states/territories with no LCDs/LCAs or when the LCDs/LCAs are silent on coverage criteria, refer to the coverage rationale below.

Covered Indications

Pharmacogenetics testing will be considered reasonable and necessary if:

- The patient has a condition where clinical evaluation has determined the need for a medication that has a known Gene-drug interaction(s) for which the test results would directly impact the drug management of the patient's condition; and
- The test meets evidence standards for genetic testing as evaluated by a scientific, transparent, peer-reviewed process and determined to demonstrate actionability in clinical decision making by Clinical Pharmacogenetics Implementation Consortium (CPIC®) guideline level A or B; or is listed in the U.S. Food and Drug Administration (FDA) table of known Gene-drug interactions where data support therapeutic recommendations or a potential impact on safety or response or the FDA label; https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling; https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations.

TPMT (Thiopurine S-Methyltransferase)

Based on the results of *TPMT* genotype testing, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend adjusting starting doses of Thiopurines (class): mercaptopurine, azathioprine, thioguanine (CPIC level A: testing recommended). *TPMT* is included in the Table of Pharmacogenomic Associations from the FDA for which the data support therapeutic recommendations or a potential impact on safety or response.

Non-Covered Indications

Genetic testing where either Analytical Validity, Clinical Validity, or Clinical Utility has not been established is considered not reasonable and necessary.

CYP1A2 (Cytochrome P450 Family 1, Subfamily A, Member 2)

CYP1A2 genotype polymorphisms do not have a clinically meaningful effect on the pharmacokinetics of rucaparib.

CYP3A4 (Cytochrome P450 Family 3, Subfamily A Member 4)

No recommendations are provided for dosing statins due to insufficient evidence to support clinical implementation [Clinical Pharmacogenetics Implementation Consortium (CPIC) level C: no recommendation].

COMT (Catechol-O-Methyltransferase)

There are no therapeutic recommendations for dosing opioids based on *COMT* genotype [Clinical Pharmacogenetics Implementation Consortium (CPIC) level C: no recommendation].

Foundation PI

Urinary biomarker laboratory tests for chronic pain are not reasonable and necessary.

Psych HealthPGx Panel and Genomind Professional PGx Express CORE

These panels are not reasonable and necessary for pharmacogenomic testing due to insufficient evidence of efficacy.

TYMS (Thymidylate Synthetase)

No recommendations are provided for capecitabine and fluorouracil [Clinical Pharmacogenetics Implementation Consortium (CPIC) Provisional Level D: no recommendation].

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service; however, language may be included in the listing below to indicate if a code is non-covered. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
Non-Covered	
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)

CPT Code	Description
Non-Covered	
0032U	COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G > A (rs4680) variant
0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T > C], HTR2C rs3813929 [c.-759C > T] and rs1414334 [c.551-3008C > G]) (Deleted 12/31/2025)
0117U	Pain management, analysis of 11 endogenous analytes (methylmalonic acid, xanthurenic acid, homocysteine, pyroglutamic acid, vanilmandelate, 5-hydroxyindoleacetic acid, hydroxymethylglutarate, ethylmalonate, 3-hydroxypropyl mercapturic acid (3-HPMA), quinolinic acid, kynurenic acid), LC-MS/MS, urine, algorithm reported as a pain-index score with likelihood of atypical biochemical function associated with pain (Foundation PI℠)
0173U	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes (Psych HealthPGx Panel)
0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes (Genomind® Professional PGx Express™ CORE)
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
81346	TYMS (thymidylate synthetase) (e.g., 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (e.g., tandem repeat variant)
Provisional Coverage	
81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)

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Diagnosis Code	Description
For CPT Code 81335	
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission (Effective 01/01/2024) (Deleted 07/12/2025)
C91.11	Chronic lymphocytic leukemia of B-cell type in remission (Effective 01/01/2024) (Deleted 07/12/2025)
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse (Deleted 07/12/2025)
C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission (Deleted 07/12/2025)
C91.40	Hairy cell leukemia not having achieved remission
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.60	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.A0	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.Z0	Other lymphoid leukemia not having achieved remission
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse
K50.00	Crohn's disease of small intestine without complications
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.8A	Other specified rheumatoid arthritis, other specified site
Z94.0	Kidney transplant status
Z94.84	Stem cells transplant status

Definitions

Actionable Use: A test is considered to have an Actionable Use when the genotype information may lead to selection of or avoidance of a specific therapy or modification of dosage of a therapy. The selection, avoidance, or dose change must be based on the FDA-label for the drug, an FDA warning or safety concern, or a CPIC level A or B Gene-drug interaction. An intended change in therapy based on the result of a genotyping test that is not supported by one of these sources is not considered an Actionable Use.

Analytical Validity (AV): A process intended to determine if a test, tool, or instrument has acceptable technical performance (sensitivity, specificity, accuracy, precision, etc.). Analytical validation is an assessment of the test's technical performance (the test measures what it was designed to measure), not its usefulness or clinical significance. Analytical Validity includes the ability of the test to accurately and reliably detect the mutation and/or variant.

Clinical Utility (CU): The ability of a test to provide information related to the patient's care and management, and thus, its ability to inform treatment decisions. Centers for Medicare and Medicaid Services (CMS) is most focused on assessing Clinical Utility in the context of whether or not a test is used to guide patient management and whether or not use of the test results leads to treatment that improves health outcomes.

Clinical Validity (CV): The ability of a test to classify a patient's specific circumstance into a diagnostic, prognostic, or predictive functional category. It should be noted that Clinical Validity is not a fixed value. Clinical Validity includes the ability of the test to accurately and reliably detect the disease of interest in the defined population.

Combinatorial PGx Test: A type of Multi-Gene Panel that requires a proprietary algorithm to evaluate pharmacokinetic or pharmacodynamic relationships resulting in drug recommendations or warnings.

Gene: The term "Gene" in this document will be used as a term to encapsulate all of the following: Gene, pseudogene, and genetic locus.

Multi-Gene Panel: A laboratory test to detect genetic variants of at least two Genes, wherein the clinician does not individually order Genes, but orders a panel with a specified list of Genes.

Provisional CPIC Level Status: The levels (A, B, C, and D) assigned are subject to change and are initially given a "provisional" CPIC level status; only those Gene/drug pairs that have been the subject of guidelines have had sufficient in-depth review of evidence to provide definitive CPIC level assignments ("final" CPIC level status) (CPIC Genes-Drugs, 2025).

Single-Gene Test: A laboratory test to detect relevant genetic variants (alleles) of one Gene. If two or more different single Genes are ordered individually but simultaneously, this is not a panel but rather a couple of or multiple Single-Gene Tests.

Centers for Medicare and Medicaid Services (CMS) Related Documents

After checking the table below and searching the Medicare Coverage Database, if no NCD, LCD, or LCA is found, refer to the criteria as noted in the Coverage Rationale section above.

NCD	LCD	LCA	Contractor Type	Contractor Name
Pharmacogenomics Testing				
N/A	L39073 Pharmacogenomics Testing	A58812 Billing and Coding: Pharmacogenomics Testing	Part A and B MAC	First Coast
N/A	L39063 Pharmacogenomics Testing	A58801 Billing and Coding: Pharmacogenomics Testing	Part A and B MAC	Novitas**

NCD	LCD	LCA	Contractor Type	Contractor Name
Pharmacogenomics Testing				
N/A	L39995 Pharmacogenomic Testing	A59915 Billing and Coding: Pharmacogenomic Testing	Part A and B MAC	NGS
N/A	L39616 Urinary Biomarkers for Chronic Pain Management	A59423 Billing and Coding: Urinary Biomarkers for Chronic Pain Management	A and B MAC	CGS

Medicare Administrative Contractor (MAC) With Corresponding States/Territories	
MAC Name (Abbreviation)	**States/Territories**
CGS Administrators, LLC (CGS)	KY, OH
First Coast Service Options, Inc. (First Coast)	FL, PR, VI
National Government Services, Inc. (NGS)	CT, IL, ME, MA, MN, NH, NY, RI, VT, WI
Noridian Healthcare Solutions, LLC (Noridian)	AS, AK, AZ, CA, GU, HI, ID, MT, NV, ND, Northern Mariana Islands, OR, SD, UT, WA, WY
Novitas Solutions, Inc. (Novitas)	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX, VA**
Palmetto GBA (Palmetto)	AL, GA, NC, SC, TN, VA**, WV
Wisconsin Physicians Service Insurance Corporation (WPS)*	IA, IN, KS, MI, MO, NE
Notes	
*Wisconsin Physicians Service Insurance Corporation: Contract Number 05901 applies only to WPS Legacy Mutual of Omaha MAC A Providers. **For the state of Virginia: Part B services for the city of Alexandria and the counties of Arlington and Fairfax are excluded for the Palmetto GBA jurisdiction and included within the Novitas Solutions, Inc. jurisdiction.	

CMS Benefit Policy Manual

Chapter 15; § 80.1 – 80.1.3 Clinical Laboratory Services.

CMS Claims Processing Manual

Chapter 12; § 60 Payment for Pathology Services.
Chapter 16, § 10.2 General Explanation of Payment; § 20 Calculation of Payment Rates - Clinical Laboratory Test Fee Schedules; § 40 Billing for Clinical Laboratory Tests

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Others

CMS Clinical Laboratory Fee Schedule, CMS Website.
Palmetto GBA MolDx Website.
Palmetto GBA MolDx Manual, Palmetto GBA MolDx Website.
L36021 MolDX: Molecular Diagnostic Tests (MDT)
A56973 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L35160 MolDX: Molecular Diagnostic Tests (MDT)
A57526 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L36256 MolDX: Molecular Diagnostic Tests (MDT)
A57527 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L35025 MolDX: Molecular Diagnostic Tests (MDT)
A56853 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L36807 MolDX: Molecular Diagnostic Tests (MDT)
A57772 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L34519 Molecular Pathology Procedures
A58918 Billing and Coding: Molecular Pathology and Genetic Testing
L35062 Biomarkers Overview

A58917 Billing and Coding: Molecular Pathology and Genetic Testing
L38288 MolDX: Repeat Germline Testing
A57141 Billing and Coding: MolDX: Repeat Germline Testing
L38351 MolDX: Repeat Germline Testing
A57331 Billing and Coding: MolDX: Repeat Germline Testing
L38353 MolDX: Repeat Germline Testing
A57332 Billing and Coding: MolDX: Repeat Germline Testing
L38274 MolDX: Repeat Germline Testing
A58017 Billing and Coding: MolDX: Repeat Germline Testing
L38429 MolDX: Repeat Germline Testing
A57100 Billing and Coding: MolDX: Repeat Germline Testing
L38394 MolDX: Pharmacogenomics Testing
A58324 Billing and Coding: MolDX: Pharmacogenomics Testing
L38335 MolDX: Pharmacogenomics Testing
A57384 Billing and Coding: MolDX: Pharmacogenomics Testing
L38337 MolDX: Pharmacogenomics Testing
A57385 Billing and Coding: MolDX: Pharmacogenomics Testing
L38294 MolDX: Pharmacogenomics Testing
A58318 Billing and Coding: MolDX: Pharmacogenomics Testing
L38435 MolDX: Pharmacogenomics Testing
A58395 Billing and Coding: MolDX: Pharmacogenomics Testing
L39365 Genetic Testing in Oncology: Specific Tests

Clinical Evidence

Clinical Pharmacogenetics Implementation Consortium (CPIC)

The focus of this evidence review is on genetic testing used to guide drug therapies, and whether the evidence is adequate to draw conclusions about improved health outcomes for the Medicare population. In general, improved health outcomes of interest include patient mortality and morbidity, as well as patient quality of life and function. Standardized evaluation of analytical validity, clinical validity, and clinical utility should be fully elucidated, and reflect the level of confidence that the performance of this test will directly benefit patients. Tests with analytic and clinical validity, with demonstrated clinical utility that provide confidence to accurately enhance clinician decision-making, have the potential to alter clinical management leading to improved patient outcomes. Ideal patient outcomes demonstrate reduced mortality and morbidity, improved patient quality of life and function.

Pharmacogenomic testing endeavors to improve patient outcomes to optimize medication choice, thereby reducing ineffective medication use and reducing adverse events. Outcomes of interest remain the patient-centered outcomes noted above.

The U.S. sources of pharmacogenomic (PGx) test recommendations available to provide guidance to clinicians as to how available genetic test results should be interpreted for drug therapy improvement include the U.S. Food and Drug Administration (FDA) drug labels, FDA Table of Pharmacogenetic Associations, and the CPIC.

The CPIC is an international organization with membership including clinicians, scientists, laboratorians, and other pharmacogenomic (PGx) experts with the purpose of facilitating the use of PGx test results for patient care. CPIC's goal is to address the barrier caused by difficulty translating genetic laboratory test results into actionable prescribing decisions for applicable drugs by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug clinical practice guidelines. CPIC started as a shared project between the Pharmacogenetics Research Network (PGRN) and the Pharmacogenomics Knowledge Base (PharmGKB) in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by the American Society of Health-System Pharmacists (ASHP) and the American Society for Clinical Pharmacology and Therapeutics (ASCPT), and are referenced in ClinGen and PharmGKB (CPIC, 2025).

Tibben et al. (2025) outline the standardized processes and framework used by CPIC to assign allele clinical functional status through the work of Pharmacogene Curation Expert Panels (PCEPs). These panels, comprised of multidisciplinary experts, systematically review and evaluate evidence to assign functional status to pharmacogenetic haplotypes. The process includes rigorous evidence review, use of standardized terminology, and consensus-driven functional assignments. The resulting allele functionality tables and phenotype mapping tables are crucial for standardized

interpretation of pharmacogenetic test results and the development of CPIC guidelines. The authors conclude that the adherence to the standards and procedures promotes the global adoption of CPIC guidelines in clinical practice. CPIC's standardized terminology is supported by respected professional organizations, including the College of American Pathologists, the Association for Molecular Pathology, the American Society of Health-System Pharmacists, and the American Society for Clinical Pharmacology and Therapeutics emphasizing the importance of consistent language in pharmacogenomics. The authors acknowledge limitations in the process in that it is resource-intensive and relies greatly on expert interpretation. Also, the need for ongoing updates can be challenging.

Morris et al. (2022) performed a systematic review and analyzed 108 studies evaluating the cost-effectiveness of pharmacogenomic (PGx) testing for drugs with CPIC guidelines. The review found that 71% of these studies demonstrated PGx-guided treatment to be either cost-effective (44%) or cost-saving (27%), with the majority of these studies (87%) being of high quality as indicated by a Quality of Health Economic Studies (QHES) score of 75 or higher. Specifically, the drugs clopidogrel and warfarin were the most studied, with 96% of clopidogrel-related studies showing cost-effectiveness or cost-saving outcomes. In contrast, only 44% of warfarin studies showed cost-effectiveness, with none reporting cost savings. Moreover, the review highlighted that the majority of studies (69%) were based on hypothetical populations, and most were conducted in North America (47%) and Europe (24%). The findings underscore that while PGx testing is generally considered cost-effective or cost-saving, there are significant variations depending on the drug, gene, and study design. Additionally, studies from Asia were more likely to report PGx testing as not cost-effective (36%), suggesting geographical and methodological factors may influence cost-effectiveness outcomes. This variability emphasizes the need for region-specific evaluations when considering the adoption of PGx testing in clinical practice. Study limitations reported by the authors included that some drug-gene pairs had a limited number of studies.

Relling et al. (2020) discuss CPIC's progress over the past 10 years. CPIC has become widely recognized as the gold standard resource for the clinical implementation of pharmacogenetics and guidelines are internationally used. Interactions with other databases, resources, websites and genomic communities have grown including National Institutes of Health (NIH)-funded resources such as PharmVar/ClinGen/ClinVar, the Genetic Testing Registry, Logical Observation Identifiers Names and Codes (LOINC), the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT), eMERGE, IGNITE, Dutch Pharmacogentics Working Group, European Pharmocogenetics Implementation Consortium, and other key stakeholders, including PharmCAT, the U.S. Food and Drug Administration (FDA), and other partners. CPIC guidelines are widely used and a trusted source of unbiased information.

CPIC Level Definitions for Genes and Drugs (CPIC, 2025)

CPIC Level	Clinical Context	Level of Evidence	Strength of Recommendation
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended

CPIC Level	Clinical Context	Level of Evidence	Strength of Recommendation
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended

Clinical Practice Guidelines

Clinical Pharmacogenetics Implementation Consortium (CPIC)

In a CPIC guideline, Cooper-DeHoff et al. (2022) conducted a systematic review of the literature, focusing on associations of statin-related clinical endpoints (toxicity and efficacy) with gene variants of *SLCO1B1*, *ABCG2*, *CYP2C9*, *CYP3A4*, *CYP3A5*, and *HMGCR*. The authors concluded there was insufficient evidence to support clinical implementation, no recommendations are provided for *HMGCR*, *CYP3A4*, or *CYP3A5*. Therefore, the guideline only focuses on *SLCO1B1*, *ABCG2*, and *CYP2C9* genetic variations. In a 2025 supplement to this guideline, the authors note that while *CYP3A4**1B and *CYP3A5**3 are in strong linkage disequilibrium (D' > 0.8), the *CYP3A5**3 allele is thought to be the causal variant driving the association between this locus and creatine kinase (CK) elevation during atorvastatin therapy. Since this variant only predicts the severity of how high the CK may go, it does not predict who will develop statin-associated muscle symptoms (SAMS). Therefore, the association may not be clinically actionable. Additional published studies exist but the overall strength of evidence was rated as weak for *CYP3A4/5* and statin response. The authors concluded that at this time, the current guideline does not make any recommendations regarding *CYP3A4/5* genotype.

In a CPIC guideline, Crews et al. (2021) summarized the evidence regarding *CYP2D6*, *OPRM1,* and *COMT* and their impact on opioid analgesia as well as adverse events and provided therapeutic recommendations for *CYP2D6* genotype result usage related to prescription of codeine and tramadol. There is substantial evidence that has linked *CYP2D6* to variations in effect and toxicity of codeine and tramadol, but insufficient evidence to support use of this genotyping for prescribing hydrocodone, oxycodone, or methadone. *OPRM1* variants have inconsistently been shown to alter dose requirements for postoperative pain in some opioids, but there is insufficient evidence to clearly demonstrate altered analgesic response to these variants. The most highly studied *COMT* variant is rs4680, but there is no evidence to support association of this variant with adverse effects of opioids and there is mixed evidence for association between *COMT* rs4680 genotype and dosing requirements. For all other variants of *COMT*, there is mixed evidence regarding association between *COMT* and analgesia, opioid dosing, and adverse events. Overall, there is limited or weak data for use of *CYP2D6* genotyping for hydrocodone, oxycodone, and methadone and for *OPRM1* and *COMT* in clinical use. In a supplement to this guideline, the authors note there is insufficient evidence for an association between *COMT* genotype, analgesia, opioid dose requirements. No recommendations are provided.

In a CPIC guideline, Relling et al. (2019) summarized the evidence regarding *TPMT* genotype and its impact on starting doses of thiopurines. Based on *TPMT* results, they recommend adjusting starting doses of azathioprine, mercaptopurine, and thioguanine. General use of mercaptopurine and azathioprine are for nonmalignant immunologic disorders, mercaptopurine for lymphoid malignancies, and thioguanine for myeloid leukemias. There is substantial evidence that has linked *TPMT* genotype with phenotypic variability. Pre-emptive dose adjustments based on *TPMT* genotype were shown to reduce thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects. In a 2024 update, the recommendation for a *TPMT* intermediate metabolizer/*NUDT15* intermediate metabolizer was updated for all thiopurines recommending a starting dose at 20%-50% of normal dosages, depending on the starting dose.

Biomarkers for Chronic Pain

There is insufficient evidence to support biomarkers for chronic pain. Well-designed, randomized controlled trials with large sample sizes and long-term follow-up are needed to establish the impact on health outcomes.

Binvignat et al. (2023) conducted a prospective cohort study that investigated serum tryptophan metabolite levels, metabolite-ratios, and metabolism pathway activation in patients with erosive and non-erosive hand osteoarthritis (HOA). The conclude tryptophan metabolites disturbance is associated with erosive HOA and pain and emphasize the role of low-grade inflammation and gut dysbiosis in HOA. While this study did show variations in these levels there was no comparison to patients without HOA or other types of pain. The authors postulate significant alterations in metabolites indicate potential involvement of gut dysbiosis and intestinal permeability in patients with HOA, but this was not measured directly by stool sample. The authors conclude this provides a "new hypothesis for the hand osteoarthritis pathophysiology and potential new biomarkers." Limitations of this study reported by the authors included its cross-sectional design, lack of

a non-HOA group, lack of stool sample utilization, exclusion of complementary measures of intestinal biomarkers, confounding as a result of intake of patients with previously gut microbiome alterations, and lack of measures of different pain types.

Üstün Özek (2022) conducted a cross-sectional retrospective study on the correlation between pain frequency and severity and vitamin B12 levels in episodic and chronic migraine. Enrollees included 127 patients who were diagnosed as having migraine according to the International Classification of Headache Disorders (ICHDIII) and 45 healthy controls. Visual analogue scale (VAS) scores were used to evaluate pain. Serum Vitamin B12 levels were obtained and considered low if below 300 ng/L. "Vitamin B12 levels were found to be significantly lower in migraineurs compared to the control group (227.30 ±104.72 ng/L vs 278.44 ±149.83 ng/L; p = 0.047). Chronic migraine (CM) patients had lower levels of vitamin B12 compared to patients with less frequent migraines (197.50 ±69.16 ng/L vs 278.56 ±147.91 ng/L; p = 0.019). Ratios of vitamin B12 levels of 300 ng/L and above in patients with CM was lower than that of patients with episodic migraine ($p < 0.05$)." The author concluded the patients with chronic migraine had lower vitamin B12 levels and a more holistic approach to care may be warranted. They note the need for more robust studies to support their findings. The author reports that this study was limited by its study design, moderate sample size, and a lack of measurement of folic acid, homocysteine and methylmalonic acid levels.

Hagedorn et al. (2021) conducted a narrative review to assess the literature regarding the use of laboratory biomarkers in chronic pain. A total of 304 manuscripts were produced from PubMed, Science Direct, and Google Scholar databases. Ultimately 75 manuscripts were included. Authors concluded that biomarkers, including urinary, serum, cerebrospinal fluid, and salivary, may be helpful in identifying patients at risk of developing disease and may help predict disease progression and assist with plan of treatment. They go further to state "additional research is necessary before specific recommendations can be made, and current clinical decision-making is modified". This study was limited in that it was a narrative review of the literature. Also, two out of three authors of this paper have conflicts of interest due to relationships with Ethos Laboratories.

Groven et al. (2021) conducted a prospective cohort study evaluating blood plasma analyzed for the following metabolites involved in the kynurenine pathway: tryptophan, kynurenine, kynurenic acid (KA), 3-hydroxykykynurenine (HK), anthranilic acid, xanthurenic acid (XA), 3-hydroxyanthranilic acid, quinolinic acid (QA) and picolinic acid in female patients aged 18 to 60 with chronic fatigue syndrome, fibromyalgia, and healthy controls. They conclude there is an association between kynurenine metabolism and chronic fatigue syndrome and fibromyalgia as well as characteristic symptoms like fatigue and pain. The study's strengths included a control group and control for age, BMI and symptoms of anxiety and depression however it was not a randomized controlled trial introducing the potential risk of selection bias. Limitations include cross sectional design and causality cannot be established, self-report bias, and lack of dietary restricts for blood samples. The study was limited to female patients out of the Medicare age range, and inclusion of university and hospital staff for control group so not representative of general population.

Aroke et al. (2020) performed a systematic review on the metabolomics of chronic pain conditions reviewed published studies that used various metabolomic approaches to investigate chronic pain conditions among subjects of all ages. A total of 586 articles were identified and 18 included in the review that included fibromyalgia (n = 5), osteoarthritis (n = 4), migraine (n = 3), musculoskeletal pain (n = 2), and other chronic pain conditions (n = 1). The authors looked at several metabolites including amino acids (e.g., glutamine, serine, and phenylalanine) and intermediate products (e.g., succinate, citrate, acetylcarnitine, and Nacetylornithine) of pathways that metabolize various macromolecules. The authors conclude that despite the increase in research few metabolites have been validated as biomarkers for pain management. Preliminary evidence supports that there may be a role for these markers, and they call for a need for further investigation as this could be a potentially useful pathway to help in management of these conditions. They conclude "Alterations in the intermediate metabolites of carbohydrates, proteins, and other macromolecules are associated with chronic pain conditions such as fibromyalgia, osteoarthritis, and migraine. Unfortunately, many studies in the present review did not quantify the amount of pain experienced by participants. Further investigations are warranted to identify complete metabolomic profiles of various chronic pain conditions. Also, studies are needed to examine whether multiple metabolomic profiles correlate with pain outcomes such as pain severity and quality of life. These studies may lead to the identification of biomarkers and individualized strategies for the prevention, diagnosis, and management of chronic pain. Nurse scientists and other investigators should consider using standardized measurements to phenotype pain to facilitate comparisons across pain conditions and patient populations." Study limitations reported by the authors include that the studies did not utilize the same metabolomic approach and that different articles from the same sample were counted as individual papers, possibly inflating the number of papers included in the review.

Staats Pires et al. (2020) conducted an observational, case-control study measuring serum samples from 21 patients with definite clinical diagnosis of type 1 diabetes mellitus with neuropathic pain for 14 cytokines. They reported increases in two inflammatory biomarkers: neopterin and the kynurenine (KYN) and tetrahydrobiopterin (BH4) ratio, a marker of

indoleamine 2,3-dioxygenase activity. They conclude the results suggest that inflammatory activation through elevated pro inflammatory cytokines neopterin and upregulation of the kynurenine pathway might be associated with neuropathic pain in type 1 diabetes mellitus and encourage future studies. Study limitations reported by the authors were small sample size and that the subjects were not fasted prior to obtaining blood samples.

Lifestyle Modification and Nutritional and Supplemental Treatments for Pain and Inflammation

The basis of the Foundation Pain Index (FPI) test is mechanistic insight into the underlying biochemical and nociceptive sources of pain so providers can design treatment approaches that target these pathologies at their core such as nutritional deficiencies, metabolic abnormalities, and oxidative stress that can be treated by dietary modifications or supplementation. The concept of lifestyle and nutrition in pain has been explored. Several complementary medicine options ranging from non-pharmaceutical, dietary supplements and other modalities have been explored but the mechanism of these pathways are not clear, and interventions are not supported by high-quality evidence.

Frediani et al. (2024) performed a systematic review on the role of diet and non-pharmacologic supplements in the treatment of chronic neuropathic pain. The final review following Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines included 40 studies. Primary outcomes were patient or clinician reported pain outcomes using many different measurements of pain score to evaluate mean change or percent change from baseline. The results were categorized by type of pain. The chemotherapy-induced peripheral neuropathy (CIPN) studies utilized various interventions such as goshajinkigan, guilongtonluofang, ninjin'yoeito, vitamin B12, vitamin E, glutamine, N-acetyl-cysteine, acetyl-l-carnitine, alpha-lipoic acid, l-carnosine, magnesium and calcium, crocin, and antioxidants. Some studies used multiple interventions. All CIPN studies involved different cancers and/or chemotherapies, advising caution for generalizability of results. Interventions for diabetic peripheral neuropathy (DPN) included alpha-lipoic acid, acetyl-l-carnitine, vitamin B12, vitamin D, vitamin E, and a low-fat plant-based diet. Vitamin C was studied for the treatment of complex regional pain syndrome (CRPS-I). For other or mixed neuropathologies, St. John's wort and magnesium were studied. Results showed that acetyl-l-carnitine was likely to be ineffective or harmful. Alpha-lipoic acid was not found to be effective. Goshajinkigan, vitamin E, vitamin B12, and glutamine had conflicting results regarding efficacy, with one study finding it harmful. Ninjin'yoeito, guilongtonluofang, and antioxidants displayed various degrees of potential effectiveness. The authors concluded that no recommendation can be made for any supplement for managing CIPN. The review supports acetyl-l-carnitine, alpha-lipoic acid, and vitamin D for DPN. Early use of vitamin C prophylaxis for the development of CRPS-I appears to be promising. The authors note further research is needed to confirm their findings. Study limitations reported by the authors included the lack of high-quality studies, small sample size in many of the studies, and the heterogeneity of neuropathic pain scales used.

The Agency of Healthcare Research and Quality, McDonagh et al. (2020), conducted a systematic review which included 185 randomized controlled trials (RCTs) in 221 publications and five systematic reviews on nonopioid pharmacologic agents in patients with chronic pain. Meta-analyses were conducted where data allowed. The authors concluded small improvements in pain and/or function with serotonin-norepinephrine reuptake inhibitor antidepressants for neuropathic pain, fibromyalgia, osteoarthritis, and low back pain; pregabalin/gabapentin for neuropathic pain and fibromyalgia; oxcarbazepine for neuropathic pain; and nonsteroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis and inflammatory arthritis. Other drugs studied, including acetaminophen (osteoarthritis), capsaicin (neuropathic pain), cannabis (neuropathic pain), amitriptyline (fibromyalgia, neuropathic pain), and cyclobenzaprine (fibromyalgia) had no clear effects. While supplements were not included in this report, this demonstrates they are not considered as part of the standard management for chronic pain conditions at this time. Study limitations reported by the authors were limited ability to evaluate publication bias (small sample size bias), due to most of their meta-analyses included fewer than 10 studies and that they restricted inclusion to RCTs, limited to monotherapy, and limited the trials to those with at least 12 weeks of treatment.

Brain et al. (2019) performed a systematic review and meta-analysis to explore the impact of nutritional interventions on participants reported pain severity and intensity in a population with chronic pain. They included studies that explored overall diet (such as vegan, vegetarian, reduced fat diet), altered specific nutrition, supplementation and fasting. The meta-analysis concludes that nutritional interventions had a significant effect on pain reduction with the studies tested reporting an altered overall diet or just one nutrient having the greatest effect. In the supplementation analysis 11 studies reported statistically significant differences between groups in pain while the remaining 22 did not. The overall results were mixed and there was a lack of clear pattern of nutritional intervention to explain results. The meta-analysis included all types of nutritional interventions and the high heterogeneity between the included studies make the results unreliable. The authors conclude, “The included studies are of limited quality and explore a range of nutrition interventions in those with chronic pain. This highlights the need for more rigorous nutrition intervention studies where chronic pain is the primary outcome. High-quality studies testing nutrition advice and support in populations with chronic pain and where pain is the primary outcome would be of benefit to researchers and clinicians.” Additional study limitations reported by the

authors were the age of the studies and that only 13% of studies assessed the impact of the intervention on pain outcomes at any follow-up beyond the completion of the intervention.

Crawford et al. (2019) conducted a systematic review and meta-analysis of the evidence based recommendations for dietary ingredients as alternative approach for mitigation of pain using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Nineteen eligible dietary ingredients were assessed for quality, efficacy, and safety. The panel concludes, “Currently the scientific evidence is insufficiently robust to establish definitive clinical practice guidelines, but processes could be established to track the impact of these ingredients. Until then, providers have the evidence needed to make informed decisions about the safe use of these dietary ingredients, and future research can address existing gaps.” Study limitations reported by the authors include that no studies involved military populations acknowledging that musculoskeletal conditions are very prevalent in this population and that analyses showed inconsistencies in the details of reported dietary ingredient interventions making it challenging to develop evidence-based decisions around the delivery methods

Literature investigating the role of nutritional and dietary supplements for the management of a variety of underlying conditions including pain were reviewed. Additional investigation is needed to understand the role of these complementary and alternative therapies on the long-term outcome of the disease course or pain which is under investigation. Several studies demonstrate improvement in pain when Vitamin B12 deficiencies are present.

Foundation Pain Index (FPI)

Pope et al. (2021) conducted a retrospective observational study at a single center site to validate the Foundation Pain Index (FPI) by evaluating associations between deranged and biochemical function and PROMIS-29 domains. The study included 298 patients with chronic pain (defined as symptoms persisting longer than three months). Relationships between deranged biochemical function and quality of life outcomes were evaluated. Patients provided a urine sample and completed a PROMIS-29 survey 15 days of the initial encounter for pain biomarker testing. FPI domains including physical function, impact score, fatigue, pain interference, and depression were significantly associated with PROMIS-29 domains ($p < 0.05$). FPI analytes significantly correlated with PROMIS-29 domains ($p < 0.05$). These included 5-hydroxyindolacetic acid (pain interference, physical function, and pain impact scores), hydroxymethylglutarate (physical function), homocysteine (pain impact scores), kynurenic acid (pain interference and physical function), and quinolinic acid (physical function). Authors conclude there is a strong association between FPI scores and clinical assessments in patients with chronic pain. Limitations to this study include the retrospective observational design and reporting bias, and risk of bias associated with the study being conducted by Ethos.

Gunn et al. (2020) conducted a retrospective observational study to determine and evaluate the prevalence of abnormal biomarker findings in a population of patients with chronic pain reports on data collected at a single industry site (Ethos Research & Development, Newport, KY) from clinical samples collected and analyzed from July to December 2018. 17,834 unique patient samples were analyzed and abnormal was defined as being outside of the 95% confidence interval reference range established using healthy population of donors who had no history of chronic pain or opioid use. The authors reported that at least one abnormal biomarker was exhibited in 77% (n = 13,765) of patients with chronic pain. The authors conclude that this novel biomarker assay reveals high prevalence of atypical biochemistry in the chronic pain population and can play a role in personalized pain management. Limitations to this study include the retrospective observational design, confounding due to medications and/or conditions other than those associated with chronic pain were not evaluated as potential causes of abnormal biomarker findings and risk of bias as the study was funded by Ethos. The authors conclude this panel can indicate novel, safe, and cost-effective pain treatments, but the treatment of pain and outcomes were beyond the scope of this retrospective review. Additionally, the role of the individual biomarkers in chronic pain is not clearly established and there are not specific biomarkers for chronic pain.

Amirdelfan et al. (2020) conducted a cross-sectional observational study to validate the Foundation Pain Index (FPI) as an indicator of abnormal biochemical function in a chronic pain population. This report, developed by Ethos research team, sought to determine the discriminant validity by comparing FPI scores of chronic pain subjects to age- and sex-matched pain-free controls. Urine samples from153 patients with chronic pain and 334 sex-matched, pain-free controls were measured for levels of 11 urinary pain biomarkers and tabulated using a proprietary algorithm. FPI scores were compared to the 36-Item Short Form Health Survey (SF-36) scores among chronic pain subjects. The authors report FPI scores were significantly correlated with the 36-Item Short Form Health Survey (SF-36) scores among chronic pain subjects ($p < 0.015$) and specific components of SF-36, including emotional well-being, limitations due to emotional problems, and general health ($p < 0.05$). Area under the receiver operating characteristics analysis (AUROC) revealed FPI to accurately distinguish biomarker profiles between pain-free and chronic pain cohorts (AUROC: 0.7490, $p < 0.0001$) as well as the SF-36 scores between chronic pain subjects with low vs high FPI scores (AUROC: 0.7715, $p < 0.01$). Authors concluded these study findings establish the validity and discriminatory power of a novel multi-biomarker test that evaluates the role of biochemistry in chronic pain and correlates with clinical assessments. They go further to state the test provides

reproducible, objective data which may pave the way for non-opioid therapeutic strategies to treat chronic pain. Biomarkers and FPI scores were assessed by a single point, cross-sectional analysis, and longitudinal monitoring through repeat FPI testing is necessary to establish the efficacy of modulating therapies. Limitations include observational design, risk of bias, lack of validation of the individual biomarkers used in the analysis and their role in pain management and confounding due to medication use and/or underlying medical conditions that were not evaluated. The authors also conclude these tools will likely improve compliance and motivate patients to adhere to the metabolic correction protocol, but this conclusion is beyond the scope the study and no data to support this conclusion was investigated.

Peabody et al. (2020) conducted a randomized controlled trial (RCT) to examine the clinical utility of urine-based pain biomarker panel. Primary care physicians were randomized into the test group and compared to controls. Participants were randomly assigned to either intervention or control group in a 1:1 ratio using a coin flip methodology. Their ability to make the diagnosis and treat a total of nine standardized patients was measured, with common cases of chronic pain, over two rounds of data collection in a pre–post design. Intervention doctors received educational materials on a novel pain biomarker panel after the baseline round and had access to biomarker test results. The provider responses were measured against an evidence-based criteria developed by the investigators. They report that at baseline providers provided "similar poor care for three different primary pain pathways: (1.2% control versus 0% intervention treated, p = 0.152)". They report that after receiving the results of the Foundation Pain Index (FPI) biomarker test, physicians in the intervention group were "41.5% more likely to make the diagnosis of a micronutrient deficiency, 29.4% more likely to identify a treatable metabolic abnormality and 26.1% more likely to identify an oxidative stressor". The authors report diagnostic and treatment improvements ranging from a relative + 54% (p = 0.004) for chronic neuropathic pain to + 35% (p = 0.007) in chronic pain from other causes to + 38% (p = 0.002) in chronic pain with associated mental health issues. They state that the intervention doctors were more likely (75.1%) to provide a non-opioid treatment to patients on chronic opioids [OR (odds ratio) 1.8, 95% CI (confidence interval) 0.8-3.7], 62% less likely to order unnecessary imaging for their patients with low back pain (OR 0.38, 95% CI 0.15-0.97) and 66% less likely to order an unnecessary pain referral (OR 0.34, 95% CI 0.13-0.90). The standard of practice that was used to establish this change was Measurement Using Clinical Performance and Value (CPV®) vignettes. The paper acknowledges the limitations include "practice impact opportunities for the provider and patient satisfaction was not considered, only considered three pain pathways, and multidisciplinary non-pharmacologic therapies for chronic pain, were not considered nor if they should be integrated with biomarker testing". Authors concluded the study showed significant clinical utility of a validated pain biomarker panel that resulted in change of practice for chronic pain treatment. Limitations of this study are the CPV were designed to look for primary contributing diagnosis that are not established as cause of the primary diagnosis. For instance, lumbar spinal stenosis is caused by narrowing of the spinal foramen and the CPV states it is caused by Vitamin B12 deficiency and low serotonin syndrome which is not an established etiology of this pain condition. While this was the intent, as the authors postulate these alternative pathways may be associated with the underlying pain condition, it bypasses the standard of care for these conditions and lacks evidence to support a role for these pathways in management of the underlying conditions. It would not be expected the providers would identify and treat that condition based on the author's criteria making the measurement for practice change invalid. The paper does not consider how chronic pain, underlying co-morbidities, mental health concerns may impact the test results and does not cite the source of the CPV and education used.

Grading Quality of Evidence and Strength Using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Pro Software was Conducted for the Single RCT

Summary of Findings

Urinary biomarker test for chronic pain compared to standard of care for impact treatment decisions by Primary Care Physicians (PCPs) for patients with chronic pain.

Patient or Population: Impact treatment decisions by Primary Care Physicians (PCPs) for patients with chronic pain
Intervention: Urinary biomarker test for chronic pain
Comparison: Standard of care

Outcomes	Anticipated absolute effects* (95% CI): Risk with standard of care	Anticipated absolute effects* (95% CI): Risk with urinary biomarker test for chronic pain	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
Change in treatment assessed with: CPV scores	0 per 1,000	0 per 1,000 (0 to 0)	Not estimable	151 (1 RCT)	Very low[2,a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence Interval.
GRADE Working Group grades of evidence:

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

- a. Lack of blinding, randomization, COI.
- b. Lack of diagnostic criteria for chronic pain, no quantification of pain.

Professional Society Input

The following professional society guidelines were reviewed and there was no mention of urinary biomarkers as part of management pathways for chronic pain. There were also no treatment pathways that include specific nutritional or dietary interventions are part of standard of care treatment for chronic pain.

- Practice Guidelines for Chronic Pain Management developed by the American Society of Anesthesiologist (ASA, 2010).
- The American Academy of Pain Medicine guidelines includes an evidence based document for use of clinical laboratory testing for monitoring drug therapy and pain management patients (Jannetto and Langman, 2018) and consensus recommendations for urine drug monitoring in patients receiving opioids for chronic pain (Argoff et al., 2018).
- National Institute for Health and Care Excellence (NICE) Guidelines: Chronic pain in over 16s: assessment of all chronic pain and management of chronic primary pain (Carville et al., 2021).
- Institute for Clinical Systems Improvement (ICSI) guidelines for assessment of chronic in adults. The guidelines state “there is no diagnostic test for chronic pain” (Lambert, 2010).
- Patients Experience Evidence Research (PEER) simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care (Korownyk et al., 2022).
- Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians (Qaseem et al., 2017).
- The Health and Human Services (HHS) pain management best practice Inter-Agency Task force report calls for patient-centered and individualized care (Cheng et al., 2020).

Genetic Test Assessment

A Genetic Test Assessment was conducted by ECRI concluding the evidence is inconclusive based on too little data on outcomes of interest (ECRI, 2023). This report utilized clinical literature from January 1, 2018 to May 18, 2023 which included a full text case control study (Amirdelfan et al., 2020) and a cohort study (Pope et al., 2021). The report expresses concerns about the very low quality evidence and reporting on too few patients to establish clinical validity of the Foundation Pain Index (FPI) test. The report names the following limitation: the studies pooled patients included different chronic pain etiology limiting the ability to interpret results, and high risk of bias due to small sample size, single centered focus and retrospective design. The report states that clinical validity outcomes have not established for this test and health outcomes of patients whose management was guided based on the FPI tests are needed to establish clinical utility. The single study that randomized physician to online patient stimulations (Peabody et al., 2020) was not included in the analysis because it did not report on outcomes of interest.

CYP1A2 (Cytochrome P450 Family 1, Subfamily A, Member 2)

PharmGKB has evolved to ClinPGx, a comprehensive clinical pharmacogenomic (PGx) resource created to support and expand PGx knowledge, implementation and education. It integrates the PharmGKB, CPIC and PharmCAT projects, with additional features and content to come. Summary annotations assigns *CYP1A2* level 3 (low level of evidence) and 4 (unsupported) for various drugs. Drug label annotations assigns *CYP1A2* PGx level as No Clinical PGx per the FDA label for rucaparib. The label states that particular gene/protein/chromosomal variants or metabolizer phenotypes do not impact a drug’s efficacy, metabolism, dosage, or toxicity. Or, the label states that particular variants or phenotypes affect a drug’s

efficacy, metabolism, dosage or toxicity, but the effect is not clinically significant. The label notes that rucaparib concentrations did not differ significantly based on *CYP2D6* or *CYP1A2* genotypes (ClinPGx, 2026).

Green et al. (2022) developed a population pharmacokinetics (PPK) model for rucaparib, an oral poly(ADP-ribose) polymerase inhibitor. The PPK analysis used PK data from patients in Study 1014 (NCT01009190, n = 35), Study 10 (NCT01482715, n = 123), and ARIEL2 (NCT01891344, n = 300), which included intensive intravenous data (12–40 mg), intensive and sparse oral data [12–360 mg single-dose, 40–500 mg once daily, and 240–840 mg twice daily (BID)], and intensive single-dose oral data under fasted conditions and after a meal high in fat (40, 300, and 600 mg). Rucaparib PK was well described by a two-compartment model with sequential zero-order release and first-order absorption and first-order elimination. A meal high in fat slightly increased bioavailability at 600 mg but not at lower doses; which is not considered clinically significant, and rucaparib can be taken with or without food. Covariate effects of baseline creatinine clearance and albumin on rucaparib clearance were detected. Although there were numerical elevations in exposure with renal impairment, dose adjustment is not recommended for patients with mild or moderate renal impairment. There were no statistically significant relationships detected for demographics, hepatic function (normal versus mild impairment), *CYP1A2* and *CYP2D6* phenotypes, or strong *CYP1A2* or *CYP2D6* inhibitors. Concomitant proton pump inhibitors displayed no clinically significant effect on absorption. External validation of the model with data from ARIEL3 (NCT01968213) and TRITON2 (NCT02952534) studies displayed no clinically meaningful PK differences across indications or sex. The authors concluded that the PPK model adequately described rucaparib PK, and none of the covariates analyzed had a clinically relevant effect. Study limitations included that attempts to include more mechanistic or nonlinear absorption models were unsuccessful due to over-parameterization and insufficient data. Therefore, the model may not have fully captured variability in absorption under different conditions.

Pharmacogenetic Panel Testing (Psychiatry)

Up to 42% of variance in therapy response for major depressive disorders (MDD) may be explained by genetic variation (Tansey et al., 2013), which has led to the development of pharmacogenetic (PGx) tests to inform the use of certain psychiatric medications. Currently, multiple combinatorial PGx tests (panels) are commercially available; however, the existing published evidence does not support the use of combinatorial PGx tools for psychiatric indications. Additional high quality studies utilizing fully blinded designs along with focus on the design of effective, evidence-based tools that assess both likelihood for adverse drug effects as well as efficacy are required.

Zhang et al. (2025) published a systematic review and meta-analysis comparing the effectiveness of pharmacogenomic (PGx)-guided antidepressant treatment vs treatment as usual (TAU) in individuals with major depressive disorder (MDD). Using data from 13 randomized controlled trials (RCTs) conducted between 2013 and 2024, the authors evaluated response and remission rates at 8 and 12 weeks, while also conducting subgroup and cumulative meta-analyses to assess the influence of ethnicity, disease severity, and gene panel size. The findings revealed that PGx-guided treatment appeared to significantly improve response rates at both 8 weeks [relative risk (RR), 1.23; 95% CI, 1.05-1.43] and 12 weeks (RR, 1.29; 95% CI, 1.17-1.43) and remission rates at 8 weeks (RR, 1.37; 95% CI, 1.19-1.57). However, remission at 12 weeks did not reach statistical significance (RR, 1.56; 95% CI, 0.93-2.61). Subgroup analyses suggested stronger benefits in Asian populations and in those with difficult-to-treat MDD, but the researchers indicated that these findings require further validation. Cumulative analyses showed that larger PGx panels yielded diminishing clinical returns, suggesting that targeted panels may be more cost-effective. Despite its strengths, the study has notable limitations. PGx panel composition varied in size and content across the trials, as did trial designs and participant populations, which may affect generalizability. Ethnic differences in drug metabolism were noted but not fully explored, and long-term outcomes, adverse events, and cost-effectiveness were not addressed. The authors highlight the need for optimization of multigene panel design and note the lack of comparative trials that assess the impact of large genetic panel use compared with that of smaller, targeted panels. Lastly, the researchers recommend performance of additional high-quality trials that include larger sample sizes and are focused on outcomes such as adverse effects, long-term remission, and efficacy across more clearly identified levels of disease severity. They further suggest that refining gene panel selection and limiting the use of PGx to difficult-to-treat cases may increase clinical utility.

In a Clinical Utility Evaluation (2025b), Hayes assessed the use of pharmacogenomic (PGx) testing in individuals with major depressive disorder (MDD) and found uncertain clinical value of PGx when used to guide medication selection/dosage, with the goal of superior clinical outcomes for affected individuals. In total, six publications were included in the evidence review. Although low-quality evidence from some studies demonstrated that PGx may be related to improved short-term outcomes, Hayes determined that significant uncertainty regarding the benefits of PGx compared with treatment as usual (TAU) persists due to overall inconsistent results among studies. In addition, adequately powered trials addressing medication effectiveness/potential side effects, with longer-term follow up, are lacking.

Hayes appraised the value of pharmacogenomic (PGx) for improving clinical outcomes when used to guide medication selection and dosage in individuals with schizophrenia in an additional 2025 Clinical Utility Evaluation (Hayes, 2025c). A

total of four studies met the inclusion criteria for the evaluation and were analyzed in the report. Hayes determined that there is significant uncertainty regarding the clinical utility of PGx in individuals with schizophrenia, citing a low-quality, small body of evidence that demonstrated inconsistent results in terms of the clinical impact of therapy informed by PGx vs treatment as usual (TAU).

Xu et al. (2024) conducted a randomized controlled trial evaluating the impact of pharmacogenomic (PGx) on treatment outcomes in participants with major depressive disorder (MDD) over a 12-week period. The study objective was to determine whether the selection of antidepressant medications based on PGx test results would lead to better response and remission rates as well as fewer adverse drug effects than treatment as usual (TAU). The trial enrolled 665 adults diagnosed with MDD who were either initiating or switching antidepressant therapy. The PGx testing group (n = 333) underwent PGx testing (including a range of genes), after which clinicians customized a treatment plan specific to PGx test results. The control group (n = 332) received TAU based on clinical experience and knowledge of the treating provider. The primary outcome was the proportion of cases with remission/response assessed via the Hamilton Depression Rating Scale; secondary outcomes included variations in Hamilton Depression Rating Scale scores over time as well as frequency of reported adverse drug reactions (ADRs). The study results indicated that the PGx-guided group achieved higher response rates at week 8 (39.3% vs 25.7%) and week 12 (48.7% vs 37.3%), higher rates of remission at week 8 (24.0% vs 15.1%) and week 12 (31.0% vs 20.0%), and fewer ADRs overall. The authors concluded that PGx testing allows clinicians to provide more personalized medication regimens for individuals with MDD, which ultimately improves treatment outcomes. However, the study had several significant limitations reported by the authors: (1) neither the clinicians providing clinical treatment nor the participants were blinded, which may have introduced bias; (2) the study was conducted at a single center, with a relatively homogeneous sample, limiting the generalizability of the trial's results; and (3) the study included only 12 weeks of follow-up, which is insufficient to fully evaluate the potential treatment benefits of PGx. Additional high-quality randomized controlled trials, with longer-term follow-up, are required.

Milosavljević et al. (2024) evaluated the clinical utility of pharmacogenomic (PGx) testing in guiding antidepressant therapy in a recent systematic review and meta-analysis. Leveraging data from 15 randomized controlled trials (RCTs) and focusing on both dichotomous and continuous outcomes, the researchers measured antidepressant efficacy via assessment of relative and absolute changes in severity of symptoms after eight weeks of treatment as well as by response/remission rates; tolerability was estimated by the rate of study discontinuation for any reason. The evaluation revealed that PGx-guided treatment appeared to improve antidepressant efficacy and tolerability compared with treatment as usual (TAU), with individuals having higher rates of remission and response after eight weeks; the PGx group had a 3.4% greater [95% confidence interval (CI), 1.6%-5.2%] reduction in symptom severity than the TAU group. No significant differences in rate of treatment discontinuation for any reason were detected between the PGx and TAU groups at eight weeks. However, the authors acknowledge several limitations. The heterogeneity among included trials, such as differences in PGx testing panels, antidepressant regimens, and outcome measures, may affect the generalizability of the findings. Additionally, some trials lacked blinding or had small sample sizes, which could introduce bias. Variability in interpretation and application of PGx results in clinical decision-making also limits the consistency of outcomes. Importantly, the authors point out that some currently marketed PGx tools include variants for which relevance to antidepressant treatments are not well established or clearly understood. Despite these challenges, the authors acknowledge the potential of PGx-guided prescribing to personalize depression treatment and improve outcomes in individuals, while emphasizing the need for standardized protocols and further large-scale studies.

Tesfamicael et al. (2024) performed an umbrella review and meta-analysis by synthesizing the existing evidence addressing the clinical utility and safety of pharmacogenomic (PGx) testing when used to guide antidepressant therapy. After a systematic search and screening, six meta-analyses and four systematic reviews, comprising data from a total of greater than 17,000 adults with depression, were included in the umbrella review. Five additional studies, all published after 2020, were evaluated via meta-analyses. Pooled effect sizes of randomized controlled trials were documented as risk ratios for noncontinuous data and mean differences for continuous data. Overall, the authors observed that PGx-guided prescribing of antidepressants was associated with improved clinical outcomes in individuals with depression after 8 weeks of treatment; those receiving PGx-guided therapy were 20% to 49% more likely to respond to antidepressants and 41% to 78% more likely to achieve remission than those receiving treatment as usual (TAU). Although these results appear promising, the publication also highlights several important study limitations. The heterogeneity of PGx testing/panels, differences in study designs, and variability in clinical implementation likely contributed to inconsistent findings across trials. Some of the included studies reported no significant benefit with PGx, underscoring the need for standardized testing protocols and clearer clinical guidelines. In addition, several primary studies were included across the various reviews, creating a high proportion of overlap. The majority of studies excluded individuals with comorbid psychiatric conditions, limiting generalizability to broader populations of individuals. Further research is needed to optimize panel design, validate findings across diverse populations, and assess long-term outcomes.

Baum et al. (2024) published an update to the 2018 report of the American Psychiatric Association (APA) Council of Research Workgroup on Biomarkers and Novel Treatments on the use of pharmacogenetic (PGx) tests in treatment selection for individuals with depression. The workgroup reviewed evidence newly published since the prior report (eleven clinical trials and five meta-analyses), all of which had primary outcomes focused on speed and/or efficacy of response to therapy. Only three trials (using three distinct PGx tests) demonstrated efficacy with statistical significance on the primary outcome measure; two of the studies showing efficacy were small, single-blind trials and one was open-label. Only one of the trials reviewed addressed adverse effects as a primary outcome. All studies examined had significant limitations, such as lack of full blinding. The workgroup concluded that recent published data does not support the use of currently marketed multigene panels for guiding selection of therapies for major depressive disorder (MDD). They recommend further investigation using fully blinded studies and including the evaluation of promising variants that are not included in currently marketed pharmacogenomic tests. Studies focused on additional purposes of pharmacogenomic testing, such as evaluation of likelihood of adverse drug effects, are also advised.

Saadullah Khani et al. (2024) published a systematic review assessing the influence of pharmacogenomic (PGx) testing on individuals undergoing antipsychotic treatment. A total of 13 studies were included in the analysis. The authors determined that while the existing evidence shows either no difference or positive clinical outcomes with PGx-guided prescribing, the studies identified had methodological limitations. Several of the studies were not blinded or randomized and all studies had fewer than 300 participants. The reviewers indicate that confounding factors such as selection bias were underestimated as well. With these limitations, the researchers recommend interpreting the results with caution. High quality studies are needed to evaluate the specific benefits of PGx testing for mental health conditions.

Skokou et al. (2024) reported on the findings specific to psychiatric-related pharmacogenomic (PGx) testing from the PREemptive Pharmacogenomic testing for preventing Adverse drug REactions (PREPARE) study. PREPARE was a multicenter, open-label, prospective study of the clinical utility of pharmacogenomic (PGx)-guided treatment which employed a 12-gene PGx panel and investigated the occurrence of adverse drug reactions (ADRs). In this publication, outcomes focused specifically on 1,076 individuals affected with schizophrenia, major depressive disorders (MDD), or bipolar disorder are described. The primary goal of this investigation was to evaluate the impact of PGx-guided therapy on incidence of adverse drug reactions in individuals affected with the above noted psychiatric indications. Although each sample was genotyped for 12 genes, only *CYP2C19* and/or *CYP2D6* were considered as part of this analysis, as these are the two pharmacogenes related to metabolism of psychiatric medications. The researchers found that individuals with an actionable phenotype in the PGx-guided arm of the study (n = 25) showed 34.1% fewer adverse drug reactions when compared to those in the control arm (n = 36). In addition, there were 41.2% fewer hospitalizations and less polypharmacy in the PGx-guided arm (n = 124 individuals prescribed at least 4 psychiatric drugs in the PGx-guided arm vs n = 143 in the control arm). Nine deaths were reported in the control arm compared to only one death in the PGx-guided arm. The authors determined that PGx-guided therapy may have a helpful impact on individuals with psychiatric diagnoses. However, the proportion of individuals with an actionable genotype in this study was small (~25%), which impacted statistical significance. This study focused only on occurrence of adverse drug reactions; drug efficacy was not evaluated. As such, additional study focused on drug efficacy as well as occurrence of adverse drug reactions is recommended. In addition, the study focused only on the impact of *CYP2C19* and *CYP2D6* and did not incorporate findings from other pharmacogenes that may be included in larger PGx panels.

Kang et al. (2023) investigated the effectiveness of multigenetic pharmacogenomics-guided treatment (MPGT) compared with that of treatment as usual (TAU) in a randomized controlled trial comprising hospitalized Han Chinese men with schizophrenia. Conducted across two hospitals from 2020 to 2022, the study enrolled 210 male participants aged 18 to 60 years with a clinical diagnosis of schizophrenia. Participants were randomized to receive either MPGT or TAU over a 12-week period, with the primary outcome being the percentage change in Positive and Negative Syndrome Scale scores at week six. Secondary outcomes included response and symptomatic remission rates. The researchers found that participants in the MPGT group experienced significantly greater symptom improvement, with a 74.2% reduction in Positive and Negative Syndrome Scale scores compared with 64.9% in the TAU group [95% confidence interval (CI), 4.4-14.1 percentage points; $p < 0.001$]. Additionally, the MPGT group had higher response rates (82.3% vs 64.9%) and remission rates at week 12 (62.8% vs 45.4%). Notably, the pharmacogenomic (PGx)-guided group achieved these outcomes with relatively lower medication doses. While the study included both first episode and relapsed participants, subgroup analyses were exploratory and did not detect statistically significant differences between the groups. No serious adverse events were reported during this trial. The study had several limitations reported by the authors. It focused exclusively on hospitalized male participants of Han Chinese ethnicity, which may limit generalizability to other populations. The trial did not assess long-term outcomes of PGx-guided treatment; this is an area that warrants future investigation in well-designed trials with larger samples sizes. Additionally, prescribing physicians were not blinded to the study groups, which may have created bias. The authors caution that while the findings are promising, further research is needed to design appropriate PGx testing panels for diverse populations and validate MPGT in broader clinical settings and populations.

Bunka et al. (2023) conducted a meta analysis and rapid review focused on appraising the impact of pharmacogenomic (PGx) testing on clinical outcomes compared to treatment as usual for individuals with major depressive disorders (MDD). The analysis incorporated results from ten randomized controlled trials (RCTs). All PGx decision-support tools used for depression included *CYP2C19* and *CYP2D6* pharmacogenes, but no specific test or panel was evaluated by this review; rather, the review focused on PGx testing in general. Based on this analysis, the authors determined that PGx-guided care for MDD more often resulted in remission and response than treatment as usual. Despite this finding, there are notable limitations reported by the authors, including high risk of bias and inconsistencies between the various trials; additional high-quality research is needed. Further studies should incorporate diverse populations and address the lack of evidence focused on adverse effects as well as the measurement of long-term efficacy, including rates of recurrence.

Wang et al. (2023) performed a systematic review and meta analysis of randomized controlled trials investigating the impact of using pharmacogenomic (PGx) testing to guide treatment on clinical outcomes of individuals with major depressive disorders (MDD). A total of eleven studies including 5,347 participants were included in the evaluation. Various marketed tests with differing numbers of genes were used in the studies. The authors note that most of the studies were considered to have a high risk of bias as they were funded by the industry. The group of individuals whose treatment was guided by pharmacogenomic testing was associated with increased response rate at week eight [OR (odds ratio) 1.32, 95% CI (confidence interval) 1.15–1.53, eight studies, 4,328 participants] and week 12 (OR 1.36, 95%CI 1.15–1.62, four studies, 2,814 participants) when compared with the usual treatment group. In addition, the group with pharmacogenomically guided treatment had an association with increased remission rates at week eight (OR 1.58, 95% CI 1.31–1.92, eight studies, 3,971 participants) and week 12 (OR 2.23, 95%CI 1.23–4.04, five studies, 2,664 participants). However, no significant differences in either response rate or remission rate were found between the two groups at week four or week 24. The meta-analysis also found that medication congruence in 30 days showed a significant reduction in the pharmacogenomic testing group versus the usual care group (OR 2.07, 95%CI 1.69–2.54, three studies, 2,862 participants). Subgroup analysis revealed a significant difference between the Asian subgroup and the Caucasian subgroup, possibly due to the sub-genotype of allele frequencies of gene variants. The authors concluded that in all, the results of this analysis indicate that pharmacogenomically guided treatment led to faster clinical remission or response in individuals with MDD but resulted in no difference in final response or remission at the end of the pharmacogenomically guided treatment. These results differ from those of previous meta-analyses, which showed overall higher response/remission rates in individuals with MDD who underwent pharmacogenomically guided treatment compared to those who underwent usual treatment. The researchers speculate that the lack of significant changes at week four may be due to the long onset time of anti-depressants and the lack of significant changes at week 24 may be due to the pharmacogenomic testing showing an accelerated process of excluding unsuitable anti-depressants for individuals with MDD. Ongoing, high-quality studies are recommended to continue assessment of the benefits of pharmacogenomic testing, especially across differing populations and ethnic groups. Study limitations reported by the authors included that the study was based on data in per-protocol analysis rather than intention -to-treat analysis. This may have led to overestimating the outcomes of pharmacogenomic testing guided treatment on MDD medications.

Brown et al. (2022) performed a systematic review and meta-analysis of 13 clinical trials comprising 4,767 individuals with MDD. Prescribing recommendations for individuals who were in the pharmacogenomic (PGx)-guided treatment group were based on their *CYP2C19* and *CYP2D6* genotypes, while treatment recommendations for those in the treatment as usual (TAU) group were based on current Australian guidelines for the prescribing of antidepressant medications. Study findings revealed that the application of PGx test results for treatment guidance in individuals with MDD resulted in a modest but significant increase in the remission of depressive symptoms. Across all trials, individuals receiving PGx-guided treatment for MDD were 41% [95% confidence interval (CI), 15%-74%] more likely to reach remission than those whose treatment was not guided by PGx. However, the authors highlighted that the trials included in this systematic review and meta-analysis used tests that assessed variants in genes beyond *CYP2C19* and *CYP2D6* (e.g., *SLC6A4, HTR2A*) since this additional testing is often included in panels marketed by various commercial laboratories, even though no dosing guidelines for these genes are available. In addition, many of the test panels used in these trials included proprietary algorithms that could result in conflicting recommendations, highlighting the need for standardization and regulation of PGx testing in the context of MDD treatment.

Regarding the use of PGx testing to assist with medication or dose selection for individuals diagnosed with attention deficit hyperactivity disorder (ADHD), a Hayes Clinical Utility Evaluation (2022, updated 2025a) found insufficient evidence to support clinical utility/improved clinical outcomes. The authors suggested that future studies to evaluate pharmacogenomic (PGx) testing assessing effects on ADHD symptoms, medication side effects and other clinical outcomes are needed.

An Ontario Health Technology Assessment (2021), which included a systematic review of the literature, evaluated the safety, effectiveness, and cost-effectiveness of multi-gene pharmacogenomic tests designed with decision-support tools to aid in treatment of individuals with major depressive disorders (MDD). Fourteen studies, including evaluation of six

multi-gene pharmacogenomic tests (GeneSight, NeuroIDgenetix, CNSdose, Neuropharmagen, Genecept and one unspecified test), were reviewed. Heterogeneity of available multi-gene pharmacogenomic tests as well as study design, populations included and outcomes reported were noted. Effectiveness of the six tests evaluated was inconsistent; clinical utility of one test may not apply to the others. Little to no differences were found in score changes on the HAMD-17 in individuals who underwent pharmacogenomic testing compared to those who were treated with usual care; however some of the tests showed promising results in terms of response to treatment or remission from their symptoms. The authors noted that the review was limited in that it did not assess the clinical or analytical validity of pharmacogenomic testing.

Aboelbaha et al. (2021) performed a systematic review to summarize and assess the state of evidence regarding the use of pharmacogenomic (PGx) testing in individuals with depression. The researchers queried scientific databases from inception through June 30, 2020, for randomized controlled trials (RCTs) and systematic reviews which assessed clinical utility of PGx testing for treatment of depression. A total of six systematic reviews and three RCTs ultimately met criteria for inclusion in this study. The results provided evidence on efficacy of PGx testing, with newer RCTs of better quality showing clinical promise regarding efficacy outcomes, especially in participants with gene-drug interactions. The researchers state that PGx testing before initiation of treatment or during therapy may improve efficacy outcome and recommend further studies to assess impact of PGx testing on safety outcomes. Study limitations noted by the authors include that a meta analysis was hard to conduct due to the high heterogeneity of the included studies, different study designs, different reported safety and efficacy outcomes, different population characteristics and sample size, and different reported interventions.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA Table of Pharmacogenetic Associations lists pharmacogenetic associations for which the data support therapeutic management recommendations. TPMT is identified in this table. Refer to the following website for more information: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. (Accessed January 14, 2026)

The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling identifies *CYP1A2* with rucaparib. Refer to the following website for more information: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. (Accessed January 14, 2026)

CYP1A2 genotype polymorphisms did not have a clinically meaningful effect on the pharmacokinetics of rucaparib in patients age 20-86 years old, race (White, Black, and Asian), sex, body weight (41 to 171 kg), mild to moderate renal impairment, and mild hepatic impairment. Refer to the following website for more information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209115s014s015lbl.pdf. (Accessed January 14, 2026)

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Policy History/Revision Information

Date	Summary of Changes
03/01/2026	**Coverage Rationale** • Removed content/language addressing HTR2A (5-Hydroxytryptamine Receptor 2A) and HTR2C (5-Hydroxytryptamine Receptor 2C) **Applicable Codes** • Added notation to indicate CPT code 0033U was "deleted Dec. 31, 2025" **Supporting Information** • Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version MMP391.15

Instructions for Use

The Medicare Advantage Policy documents are generally used to support UnitedHealthcare coverage decisions. It is expected providers retain or have access to appropriate documentation when requested to support coverage. This document may be used as a guide to help determine applicable:

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- Medicare coding or billing requirements.

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UnitedHealthcare follows Medicare coverage guidelines found in statutes, regulations, NCDs, and LCDs to determine coverage. The clinical coverage criteria governing certain items or services referenced in this Medical Policy have not been fully established in applicable Medicare guidelines because there is an absence of any applicable Medicare statutes, regulations, NCDs, or LCDs setting forth coverage criteria and/or the applicable NCDs or LCDs include flexibility that explicitly allows for coverage in circumstances beyond the specific indications that are listed in an NCD or LCD. As a result, in these circumstances, UnitedHealthcare applies internal coverage criteria as referenced in this Medical Policy. The internal coverage criteria in this Medical Policy was developed through an evaluation of the current relevant clinical evidence in acceptable clinical literature and/or widely used treatment guidelines. UnitedHealthcare evaluated the evidence to determine whether it was of sufficient quality to support a finding that the items or services discussed in the

policy might, under certain circumstances, be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Providers are responsible for submission of accurate claims. Medicare Advantage Policies are intended to ensure that coverage decisions are made accurately. UnitedHealthcare Medicare Advantage Policies use Current Procedural Terminology (CPT®), Centers for Medicare and Medicaid Services (CMS), or other coding guidelines. References to CPT® or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee claims payment.

For members in UnitedHealthcare Medicare Advantage plans where a delegate manages utilization management and prior authorization requirements, the delegate's requirements need to be followed.