Pharmacogenomics Testing

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➲ Instructions for Use

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Related Medicare Advantage Reimbursement Policies

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- 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, 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 CPIC guideline level A or B1; or is listed in the 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.

Some panel/combinatorial tests may include content that has demonstrated actionability and some may include content that has not. In these circumstances, the components of the tests that have demonstrated actionability as noted in the second bullet above will be considered reasonable and necessary.

TPMT (Thiopurine S-Methyltransferase)

Based on the results of *TPMT* genotype testing, 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 (CPIC level C: no recommendation).

COMT (Catechol-O-Methyltransferase)

There are no therapeutic recommendations for dosing opioids based on *COMT* genotype (CPIC level C: no recommendation).

Foundation PI℠

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

HTR2A (5-Hydroxytryptamine Receptor 2A) and HTR2C (5-Hydroxytryptamine Receptor 2C)

Clinical recommendations are not provided for serotonin reuptake inhibitor antidepressants based on *HTR2A* genotype because the evidence supporting an association is mixed and/or insufficient to support clinical validity and utility (CPIC level C: no recommendation). No recommendations are provided for *HTR2C* (CPIC Provisional Level C: no recommendation).

Psych HealthPGx Panel and Genomind® Professional PGx Express™ CORE

These panels include content that have demonstrated actionability and some that have not. In these circumstances, the components of the tests that have demonstrated actionability will be considered reasonable and necessary. If a treating clinician orders a Single-Gene Test or a test for a particular allele(s), but as a matter of operational practicality, the laboratory tests that Single Gene or allele on a platform that looks for variants in other Genes/alleles as well, that particular test done in that particular instance is considered a Single Gene/allele test for coverage purposes. In this scenario the provider may bill for the component of the test that was reasonable and necessary (in this example, the Single-Gene Test).

TYMS (Thymidylate Synthetase)

No recommendations are provided for capecitabine and fluorouracil (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)
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])
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
0173U	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
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)
C91.11	Chronic lymphocytic leukemia of B-cell type in remission (Effective 01/01/2024)
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission
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

Diagnosis Code	Description
For CPT Code 81335	
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.

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 2 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, 2024)

Single-Gene Test: A laboratory test to detect relevant genetic variants (alleles) of 1 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**
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	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

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

Clinical Evidence

Introduction

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.

Internal Technology Assessment

The U.S. sources of 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. FDA drug labels, FDA Table of Pharmacogenetic Associations, and the CPIC.

The CPIC publishes open-source genotype-based drug guidelines to help clinicians understand how available genetic test results could be used to optimize drug therapy. Caudle et. al (2014) describes the CPIC guideline development process for incorporation of PGx testing into clinical practice and compares the process to the Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines. The CPIC is a shared project between the Pharmacogenomics Knowledgebase and the Pharmacogenomics Research Network, established to address the need for practice guidelines for the translation of genetic laboratory test results into actionable decision making for specific drugs. The guidelines are developed using standardized methods. As the authors state, "Therefore, CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered."

A table is provided comparing the IOM standard to the CPIC Guideline development standard, listed as a point-by-point comparison. All CPIC guidelines adhere to each standard with some exceptions. One exception is IOM standard 4, the clinical practice guideline-systematic review intersection. Here, CPIC meets some but not all these standards. The explanation being that because of the nature of PGx test studies, the CPIC guideline development process often relies on published results that can vary with respect to methodological rigor and outcomes. Management of conflict of interest also does not exactly match the IOM standard. Divestiture of interests and ensuring those with conflict of interest are in the minority is not required, however the author notes in most cases, the majority of guideline authors declare no conflicts of interest. In addition, the guidelines focus on how to use the information as opposed to whether or not to order the test. Another area of deviation is IOM standard 3.2 and 3.3. While all guidelines are posted in draft form on the website for comment by CPIC members prior to publication, there is no mechanism for public representation or public comment.

Caudle et. al (2016) describes the state of PGx test evidence and evidence-based resources that facilitate the uptake of PGx testing into clinical practice. The authors state the threshold for evidence needed for clinical implementation of PGx testing is controversial and good quality randomized controlled trials (RCTs) are rarely available. A standardized approach to evaluate the literature and provide guidance to clinicians is essential in facilitating the implementation of PGx testing

into routine practice. The CPIC believes there is a critical need to provide classification of gene/drug groupings based on being actionable in clinical decision making based on reliable standardized criteria. A prioritization algorithm for considerations for new gene/drug groups is provided for review. CPIC levels of evidence for genes and drugs, Table 2:

CPIC Level Definitions for Genes and Drugs

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
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®)

CPIC® is an international organization with membership including clinicians, scientists, laboratorians, and other 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.

In an updated guideline (Bousman et al., 2023) CPIC expanded on their existing guideline for *CYP2D6* and *CYP2CD19* genotypes and selective serotonin reuptake inhibitor (SSRI) antidepressant dosing and summarizes the effect of *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4* and *HTR2A* genotypes on the dosing, efficacy, and tolerability of antidepressant medications. They state that *CYP2D6*, *CYP2C19*, and/or *CYP2B6* genotype results can be beneficial for detecting individuals who are at a higher risk either adverse drug reactions or inadequate response to SSRI therapy. Risks, including the potential to miss the identification of rare or new variations that are usually not tested on current platforms, have been identified. In such cases, the actual phenotype may be different from the predicted phenotype. Other factors, such as age, diet, comorbidities, smoking, pregnancy, concomitant medications, and epigenetic variation may also apply. CPIC did not provide recommendations for *HTR2A* and *SLC6A4* because the evidence supporting an association between these genotypes and SSRI antidepressants is mixed/insufficient to support clinical validity and utility at this time (CPIC level C: no recommendation).

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 focused on *SLCO1B1*, *ABCG2*, and *CYP2C9* genetic variations.

In a recent 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 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.

Biomarkers for Chronic Pain

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 HOA patients, 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 included 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 (2022) conducted a cross-sectional retrospective study on the correlation between pain frequency and severity and vitamin B12 levels in episodic and chronic migraine. 127 patients who were diagnosed as having migraine according to the International Classification of Headache Disorders (ICHDIII) were enrolled and 45 healthy controls. 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 ($p < 0.05$).” Authors concluded the chronic migraine patients 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. This study was limited by 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”. Two out of three authors of this paper have conflicts of interest due to relationship 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.”

Staats Pires et al. (2020) measured 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 is limited by study design and small sample size.

Park et al. (2017) conducted a cross-sectional study on 43 consecutive patients with Parkinson’s disease and 15 patients with peripheral neuropathy. Serum vitamin B12, methylmalonic acid (MMA), and homocysteine levels were obtained, and they found no correlation in the patients with peripheral neuropathy. MMA levels showed a positive correlation to neuropathy pain scales in the Parkinson’s disease patients with peripheral neuropathy, while Vitamin B12 and homocysteine showed no statistically significant correlation. They conclude serum MMA is a more sensitive marker than vitamin B12 in reflecting the severity of neuropathic pain in patients with IPD. Limitations include cross-sectional study design so causality cannot be established, and small sample size in Asian population so lacks generalizability.

Lifestyle Modification and Nutritional and Supplemental Treatments for Pain and Inflammation

The basis of the 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.

The Agency of Healthcare Research and Quality, McDonagh et al. (2020), conducted a systematic review which included 185 RCTs in 221 publications and 5 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 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.

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."

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 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."

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.

Foundational 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 3 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 chronic pain patients. 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 chronic pain patients. 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 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. 153 chronic pain patients and 334 sex-matched, pain-free controls urine samples 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 value < 0.015) and specific

components of SF-36, including emotional well-being, limitations due to emotional problems, and general health (P value < 0.05). Area under ROC analysis (AUROC) revealed FPI to accurately distinguish biomarker profiles between pain-free and chronic pain cohorts (AUROC: 0.7490, P value < 0.0001) as well as the SF-36 scores between chronic pain subjects with low vs. high FPI scores (AUROC: 0.7715, P value < 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 (O.R. 1.8, 95% C.I. 0.8-3.7), 62% less likely to order unnecessary imaging for their patients with low back pain (O.R. 0.38, 95% C.I. 0.15-0.97) and 66% less likely to order an unnecessary pain referral (O.R. 0.34, 95% C.I. 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 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 chronic pain patients.

Patient or Population: Impact treatment decisions by Primary Care Physicians (PCPs) for chronic pain patients
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:
- Lack of blinding, randomization, COI.
- Lack of diagnostic criteria for chronic pain, no quantification of pain.

Societal Input

The following Societal 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.
- 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 and consensus recommendations for urine drug monitoring in patients receiving opioids for chronic pain.
- NICE Guidelines: Chronic pain in over 16s: assessment of all chronic pain and management of chronic primary pain.
- Institute for Clinical Systems Improvement (ICSI) guidelines for assessment of chronic in adults. The guidelines state “there is no diagnostic test for chronic pain”.
- PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care.
- Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians (2017).
- The HHS pain management best practice Inter-Agency Task force report calls for patient-centered and individualized care.

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. This report utilized clinical literature from January 1, 2018 to May 18, 2023 which included a full text case control study and a cohort study. The report expresses concerns about the very low quality evidence and reporting on too few patients to establish clinical validity of the 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 was not included in the analysis because it did not report on outcomes of interest.

In conclusion, the analysis from the 4 studies, 2 retrospective observational studies, a cross-sectional observational study, and a randomized controlled trial did not show established evidence to support a role of urinary biomarkers for

management of chronic pain. The studies were limited by including retrospective design, high risk of biased, and multiple confounding aspects. The randomized controlled trial is not supported by robust evidence and is challenged by lack of blinding and potential risk for bias. The authors do not explain how chronic pain, underlying co-morbidities, mental health concerns contribute to the results nor cite the source of the CPV and education used. The authors do not compare outcomes for patients who received the test to those who did not and if test results would improve patient outcomes. To establish clinical utility the test must influence not only the management of the patient based on the test result, which this study does demonstrate, but in addition there should be improvement in patient outcomes over time, which was not addressed.

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

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.

PharmGKB clinical annotations assigns *CYP1A2* level 3 (low level of evidence) and 4 (unsupported) for various drugs. Drug label annotations assigns *CYP1A2* PGx level = Informative 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.

Pharmacogenetic Panel Testing (Psychiatry)

Up to 42% of variance in therapy response for major depressive disorders (MDD) can 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. Prospective randomized clinical trials have been performed to validate the clinical validity and utility of a number of PGx Multi-Gene Panels.

In a 2023 systematic review and meta-analysis of randomized controlled trials (RCT), Wang et al. investigated the impact of using pharmacogenetic testing to guide treatment on clinical outcomes of individuals with major depressive disorder (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 1.32, 95%CI 1.15–1.53, eight studies, 4328 participants) and week 12 (OR 1.36, 95%CI 1.15–1.62, four studies, 2814 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, 3971 participants) and week 12 (OR 2.23, 95%CI 1.23–4.04, five studies, 2664 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, 2862 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.

Menchón et al. (2019) examined the influence of patient characteristics such as age, baseline severity, and duration of episode on the clinical utility of PGx testing for psychiatric drugs from the AB-GEN study, a randomized 12-week long study comparing TAU to PGx guided therapy selection in 280 adults with MDD. The primary outcomes analyzed were the Patient Global Impression of Improvement (PGI-I) scale and the HAMD-17). Patients generally showed no difference in sustained response at the 12-week endpoint between the TAU and PGx group (Pérez et al., 2017). However, the PGx group had a higher response rate than TAU, and when subjects were removed whose physicians did not follow the genetic testing recommendations, the response rate improved further. Side effects were less in the PGx group by 6 weeks, which was maintained at week 12. The primary dependent variable identified was the number of previously failed medication trials. In the Menchón et al. reanalysis by patient demographics, additional important variables were identified. Age was important as PGx testing significantly improved outcomes in those under age 60, but not over age 60. Outcomes were also improved in those with moderate to severe depression, but not in those with mild depression. Genetic testing improved PGI-I in one year or less from diagnosis, but not HAMD-17. The effect on HAMD-17 was not significant until the cutoff from time of diagnosis was increased to 5 years. After this, however, a null effect was seen, and individuals who were more than 5 years from their diagnosis were actually worse off in the PGx arm than TAU. To determine which type of patient is most likely to benefit from PGx testing for psychiatric therapies, more prospective, randomized trials are needed.

GUIDED is a 24-week RCT conducted between April 2014 and February 2017 comparing active treatment groups guided by PGx information, to active treatment groups receiving usual care (TAU) for MDD (Greden et al., 2019, included in the Wang, 2023 systematic review discussed above. Sixty sites participated, and patients were referred to the study when it was self, or clinician reported to have inadequate response to at least one antidepressant. The average number of medications failed in the cohort was three, making this a difficult to treat population. Genotyping was for eight genes, *CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A*, and *SLC6A4* and results were evaluated and reported using a proprietary PGx algorithm from Assurex Health. Participants were blinded to the study arm, but clinicians were not, since they needed to consult the PGx results to guide treatment. Using the results to guide treatment was not mandated. Patients were assessed at 4, 8, 12 and 24 weeks using the HAMD-17, which was administered by blinded raters. A total of 1167 enrolled patients made it through week 8 with 607 in TAU and 560 in PGx guided. HAMD-17 scores decreased in the TAU arm by 24% and in the PGx arm by 27%, but the difference was not statistically significant. Treatment response, defined as ≥ 50% decrease in depression, was greater in the PGx arm (26%) than TAU (20%). The depression remission rate, defined as score of ≤ 7 for HAMD-17, was 10% with TAW and 15% with PGx (p = .007). Additionally, at week 8, there was no difference between the groups in reported side effects. When patients taking incongruent medications were evaluated as a separate cohort, those who switched to congruent medications by week 8 experienced significantly fewer side effects. Medication prescriptions that aligned with PGx results at baseline were 77% in the TAU group and 79% in the PGx group. By week 8, the PGx group increased to 91%, and the TAU group was unchanged. After 8 weeks, clinicians in the TAU arm were unblinded and could use the PGx results if they chose. A total of 913 participants completed through week 24 with 456 in TAU and 457 in the PGx guided arm. Overall, in the PGx group, HAMD-17 scores decreased by 43% at week 24 relative to baseline. Response and remission increased by 70% and 100%, respectively, from week 8 to week 24. While the primary outcome being analyzed, symptom improvement at week 8, was not different between the two groups, there was significant difference in response and remission in the PGx group on other measures.

Researchers enrolled 528 (outpatients and inpatients) from 18 hospitals and associated mental health centers in Spain from July 2014 to June 2015 in the AB-GEN study, a 12-week, double-blind, parallel, multi-center RCT to evaluate the effectiveness of PGx testing for drug therapy guidance for MDD. Individuals with a CGI-S ≥ 4 and requiring antidepressant medication de novo or changes in their medication were randomized to a PGx or TAU group. PGx testing was conducted by Neuropharmagen, and results were reported using their web-based clinical decision support tool. Thirty genes and relevant single nucleotide polymorphisms were analyzed. The primary endpoint was measuring a sustained response on the Patient Global Impression of Improvement (PGI-I) of ≤ 2 within the 12-week follow-up. Follow up was conducted by phone, and the interviewer was blinded to the participant's study arm. A patient was considered to have a sustained response with a PGI-I score of 2 or less if they reported their condition to be "much better" or "very much better." Only 280 of 528 patients completed the study. A difference in sustained response was not observed between PGx and TAU at 12 weeks. Overall, the PGx group had a much higher response rate, and this improved when removing the patients whose physicians did not follow the PGx recommendations. Effects were greatest in patients who had failed up to three prior medications. Of those who reported side effects at baseline, the PGx group was more likely to report fewer side effects than the TAU group (Pérez et al., 2017). This study is interesting as it uses real world practices and clinicians, a heterogeneous population with variable disease states and prior treatment failures, and clinicians could choose to not

follow the PGx recommendations. Additional studies are needed to replicate these findings across larger, ethnically diverse study groups.

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 states that “pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose.” Drug labeling may contain information on genomic biomarkers and can describe the following as listed per the FDA: “Drug exposure and clinical response variability, risk for adverse events, genotype-specific dosing, mechanisms of drug action, polymorphic drug target and disposition genes, trial design features.”

FDA safety communications have been published that warn against the use of many genetic tests with unapproved claims to predict patient response to specific medications. According to the FDA, the number of cases are limited for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications. The FDA provides descriptions for how to use genetic information to manage therapeutic treatment and can appear in different sections of the labeling depending on the actions. For instance, from an October 31, 2018 communication: “The FDA is alerting patients and health care providers that claims for many genetic tests to predict a patient's response to specific medications have not been reviewed by the FDA, and may not have the scientific or clinical evidence to support this use for most medications. Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient.” And, “There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications. The FDA authorized labels for these medical products may provide general information on how DNA variations may impact the levels of a medication in a person's body, or they may describe how genetic information can be used in determining therapeutic treatment, depending on the available evidence."

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: Table of Pharmacogenetic Associations (FDA).

The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling identifies *CYP1A2* with rucaparib. Refer to the following website for more information: Table of Pharmacogenomic Biomarkers in Drug Labeling (FDA).

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: label (fda.gov).

References

American Society of Anesthesiologists Task Force on Chronic Pain Management; American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010 Apr;112(4):810-33.

Amirdelfan K, Pope JE, Gunn J, et al. Clinical validation of a multi-biomarker assay for the evaluation of chronic pain patients in a cross-sectional, observational study. Pain Ther 2020;9(2):511-29.

Argoff CE, Alford DP, Fudin J, et al. Rational urine drug monitoring in patients receiving opioids for chronic pain: consensus recommendations. Pain Med. 2018 Jan 1;19(1):97-117.

Aroke EN, Powell-Roach KL. The metabolomics of chronic pain conditions: a systematic review. Biol Res Nurs 2020;22(4):458-71.

Binvignat M, Emond P, Mifsud F, et al. Serum tryptophan metabolites are associated with erosive hand osteoarthritis and pain: results from the DIGICOD cohort. Osteoarthritis Cartilage 2023.

Bousman CA, Stevenson JM, Ramsey LB, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants. Clin Pharmacol Ther. 2023 Jul;114(1):51-68.

Brain K, Burrows T, Rollo M, et al. A systematic review and meta-analysis of nutrition interventions for chronic noncancer pain. Journal of Human Nutrition and Dietetics 2019;32(2):198-225.

Carville S, Constanti M, Kosky N, et al.; Guideline Committee. Chronic pain (primary and secondary) in over 16s: summary of NICE guidance. BMJ. 2021 Apr 21;373:n895.

Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline development process. Curr Drug Metab. 2014;15(2):209-217.

Caudle KE, Gammal RS, Whirl-Carrillo M, et al. Evidence and resources to implement pharmacogenetic knowledge for precision medicine. Am J Health Sys Pharm. 2016;73(23)1977-1985.

Cheng J, Rutherford M, Singh VM. The HHS Pain Management Best Practice Inter-Agency Task Force Report Calls for Patient-Centered and Individualized Care. Pain Med. 2020 Jan 1;21(1):1-3.

Clinical Pharmacogenetics Implementation Consortium (CPIC®). Available at: CPIC (cpicpgx.org). Accessed June 28, 2024.

Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther. 2022 May;111(5):1007-1021.

Crawford C, Boyd C, Paat CF, et al. Dietary ingredients as an alternative approach for mitigating chronic musculoskeletal pain: evidence-based recommendations for practice and research in the military. Pain Medicine 2019;20(6):1236-47.

Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021 Oct;110(4):888-896.

ECRI. Genetic Test Assessment: Foundation Pain Index (Ethos Laboratories) for Guiding Management of Chronic Pain. Secondary Genetic Test Assessment: Foundation Pain Index (Ethos Laboratories) for Guiding Management of Chronic Pain June 2023. https://www.ecri.org/.

Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019 Jan 4; 111:59-67.

Green M, Ma S, Goble S, et al. Population pharmacokinetics of rucaparib in patients with advanced ovarian cancer or other solid tumors. Cancer Chemother Pharmacol. 2022 May;89(5):671-682.

Groven N, Reitan SK, Fors EA, et al. Kynurenine metabolites and ratios differ between chronic fatigue syndrome, fibromyalgia, and healthy controls. Psychoneuroendocrinology 2021;131:105287.

Gunn J, Hill MM, Cotten BM, et al. An analysis of biomarkers in patients with chronic pain. Pain Physician 2020;23(1):E41-E49.

Hagedorn JM, Gunn J, Budwany R, et al. How well do current laboratory biomarkers inform clinical decision-making in chronic pain management? Journal of Pain Research 2021:3695-710.

Jannetto PJ, Langman LJ. Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients. J Appl Lab Med. 2018 Jan 1;2(4):471-472.

Korownyk CS, Montgomery L, Young J, et al. PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care. Can Fam Physician. 2022 Mar;68(3):179-190.

Lambert M. ICSI releases guideline on chronic pain assessment and management. Am Fam Physician. 2010 Aug 15;82(4):434-9.

McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. 2020

Menchón JM, Espadaler J, Tuson M, et al. Patient characteristics driving clinical utility in psychiatric pharmacogenetics: a reanalysis from the AB-GEN multicentric trial. J Neural Transm (Vienna). 2019 Jan;126(1):95-99.

Park JS, Park D, Ko PW, et al. Serum methylmalonic acid correlates with neuropathic pain in idiopathic Parkinson's disease. Neurol Sci 2017;38(10):1799-804.

Peabody J, Paculdo D, Tamondong-Lachica D, et al. Randomized trial on the clinical utility of a novel biomarker panel to identify treatable determinants of chronic pain. Diagnostics (Basel) 2020;10(8).

Pérez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. 2017 Jul 14;17(1):250.

Pope JE FM, Gunn JA, Cotten BM, et al. Cross validation of foundation pain index with PROMIS-29 in chronic pain patients. J Pain Res 2021;14(August 29):62677-2685.

PharmGKB Clinical Annotation Levels of Evidence. Available at: Clinical Annotation Levels of Evidence (pharmgkb.org) Accessed May 16, 2024.

Qaseem A, Wilt TJ, McLean RM, et al.; Clinical Guidelines Committee of the American College of Physicians; Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017 Apr 4;166(7):514-530.

Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther. 2019 May;105(5):1095-1105.

Schünemann H BJ, Guyatt G, Oxman A, editors. The GRADE Working Group, GRADE handbook for grading quality of evidence and strength of recommendations. Secondary GRADE handbook for grading quality of evidence and strength of recommendations. 2013. Available from guidelinedevelopment.org/handbook.

[Software]. GGGGDT. Secondary 2022. gradepro.org.

Staats Pires A, Heng B, Tan VX, et al. Kynurenine, tetrahydrobiopterin, and cytokine inflammatory biomarkers in individuals affected by diabetic neuropathic pain. Front Neurosci 2020;14:890.

Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. Biol Psychiatry. 2013 Apr 1;73(7):679-82.

The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications: FDA safety communication. 2018. The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication | FDA (archive-it.org). Accessed June 28, 2024.

Üstün Özek S. A study on the correlation between pain frequency and severity and vitamin B12 levels in episodic and chronic migraine. Arquivos de Neuro-Psiquiatria 2022;80:586-92.

Wang J, Wu Y, Liu S, et al. Vitamin B12 for herpetic neuralgia: A meta-analysis of randomised controlled trials. Complementary therapies in medicine 2018;41:277-82.

Policy History/Revision Information

Date	Summary of Changes
10/01/2024	**Coverage Rationale** ***CMS Local Coverage Determinations (LCDs) and Articles*** • Added instruction to refer to the coverage rationale [listed in the policy] for coverage guidelines for states/territories with no Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) **Centers for Medicare and Medicaid Services (CMS) Related Documents** • Added notation to indicate 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 **Supporting Information** • Archived previous policy version MMP391.12

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:

- Medical necessity coverage guidelines; including documentation requirements, and/or
- Medicare coding or billing requirements.

Medicare Advantage Policies are applicable to UnitedHealthcare Medicare Advantage Plans offered by UnitedHealthcare and its affiliates. This Policy is provided for informational purposes and does not constitute medical advice. It is intended to serve only as a general reference and is not intended to address every aspect of a clinical situation. Physicians and patients should not rely on this information in making health care decisions. Physicians and patients must exercise their

independent clinical discretion and judgment in determining care. Treating physicians and healthcare providers are solely responsible for determining what care to provide to their patients. Members should always consult their physician before making any decisions about medical care.

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 member specific benefit plan document identifies which services are covered, which are excluded, and which are subject to limitations. In the event of a conflict, the member specific benefit plan document supersedes this policy. For more information on a specific member's benefit coverage, please call the customer service number on the back of the member ID card or refer to the Administrative Guide.

Medicare Advantage Policies are developed as needed, are regularly reviewed, and updated, and are subject to change. They represent a portion of the resources used to support UnitedHealthcare coverage decision making. UnitedHealthcare may modify these Policies at any time by publishing a new version on this website. Medicare source materials used to develop these policies may include, but are not limited to, CMS statutes, regulations, National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and manuals. This document is not a replacement for the Medicare source materials that outline Medicare coverage requirements. The information presented in this Policy is believed to be accurate and current as of the date of publication. Where there is a conflict between this document and Medicare source materials, the Medicare source materials apply. Medicare Advantage Policies are the property of UnitedHealthcare. Unauthorized copying, use, and distribution of this information are strictly prohibited.

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.