Medical Policy

Subject:	Pain Management Biomarker Analysis		
Document#:	LAB.00048	**Publish Date:**	07/06/2022
Status:	New	**Last Review Date:**	05/12/2022

Description/Scope

This document addresses a new pain biomarker test, the Foundation Pain Index (FPI) which is a test panel of pain functional biomarkers in urine and is intended to identify sources of chronic pain. The FPI involves analysis of urine by liquid chromatography tandem mass spectrometry (LCM/MS) of a panel 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). It is suggested that nutritional deficiencies (such as in Vitamin B12 and B6), oxidative stress and metabolic abnormalities can lead to pain syndromes, and that these abnormalities can be identified through this testing for these pain biomarkers.

Note: This document does not address drug testing for chronic pain. For more information see:

- CG-LAB-09 Drug Testing or Screening in the Context of Substance Use Disorder and Chronic Pain

Position Statement

Investigational and Not Medically Necessary:

The functional pain biomarker urine test panel is considered **investigational and not medically necessary** for chronic pain management and for all other indications.

Rationale

Ethos Laboratories (Newport, KY), in partnership with Ethos R&D, has developed a series of functional biomarker panels, which are intended to identify sources of pain. These laboratory tests provide objective measurements of

biomarkers known to be associated with pain and may be used as part of a pain-specific work-up. Pain Biomarker Assessment provides insight into the possible origins of neuropathic pain, inflammatory pain, and altered pain perception. According to the manufacturer, Ethos Laboratories, "Correction of abnormal levels of functional pain biomarkers using safe, cost-effective therapies could increase the likelihood of successful and prolonged chronic pain management." Ethos laboratories also claims the ability to provide personalized recommendations for adjunctive therapy based on the test results, "Uncovering the biochemical origins of a patient's chronic pain can suggest relevant, personalized treatment approaches." The analytes included in this functional biomarker testing can be classified as markers of the following:

- Chronic inflammation;
- Nerve health;
- Neurotransmitter status;
- Oxidative stress.

Ethos laboratories has based its efficacy on a single retrospective observational study of 17,834 subjects with chronic pain. Results claim that 77% of these subjects with chronic pain exhibited at least one abnormal pain biomarker. In contrast, among healthy people with no history of chronic pain or opioid use, only up to 5% exhibited one or more of these abnormal biomarkers. The most common abnormal biomarker finding was elevated quinolinic acid, which was observed in 29% of subjects (n=5107). Elevated pyroglutamate, indicative of glutathione depletion, was observed in 19% of subjects (n=3314). Elevated xanthurenic acid, indicative of vitamin B6 insufficiency, was observed in 17% of subjects (n=3025). Elevated levels of the acrolein metabolite 3-hydroxypropyl mercapturic acid was observed in 21% of subjects (n=3667). Elevated methylmalonic acid, indicative of a vitamin B12 deficiency, was observed in 10% of subjects (n=1827), whereas abnormally low levels of neurotransmitter metabolites were observed in 8% of subjects (n=1456). The investigators noted that a limitation of this study was that medications and conditions other than those associated with chronic pain were not evaluated as potential causes of abnormal biomarker findings (Gunn, 2020).

There is a lack of evidence in the peer-reviewed published medical literature of the clinical validity and utility of this test. Ethos laboratories also claims the ability to provide personalized recommendations for adjunctive therapy based on the test results, "Uncovering the biochemical origins of a patient's chronic pain can suggest relevant, personalized treatment approaches." However, further study with large, well-designed trials are needed to elucidate the true value of these test findings, as it relates to conventional pain management strategies.

Background/Overview

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

The Foundation Pain Index (PI℠) is intended for use in adults being treated for chronic pain when the treating clinician is attempting to determine the underlying pathogenesis of the pain, attempting to minimize or lower opioid dependence, or wanting to identify targeted, non-opioid therapies for the individual. Specifically, individuals with chronic pain of unknown etiology, new subjects presenting with pain, and those with established chronic pain diagnoses being managed on opioid therapy represent the intended use population for Foundation PI℠. An algorithm is then reported as a Pain Index Score (PIS) with projected likelihood of atypical biochemical function associated with pain. This PIS claims to quantify, in a single number, the collective results of 11 different biomarker tests. Ethos laboratories claims that individual test results, both current and historic, would potentially enable providers to identify changes in an individual's functional biomarkers over time and in response to treatment. The Ethos laboratory purports intended indications would include:

- Identification and validation of objective biomarkers to aid in the diagnosis and treatment of chronic pain;
- With the potential to reshape pain management paradigms, improve patient outcomes, reduce opioid reliance, cut healthcare costs, and further the pursuit of personalized medicine (Ethos Laboratories).

Definitions

Mass Spectrometry: An analytical tool useful for measuring the mass-to-charge ratio (m/z) of one or more molecules present in a sample. Mass spectrometers can be used to identify unknown compounds via molecular weight determination, to quantify known compounds, and to determine structure and chemical properties of molecules.

Tandem Mass Spectrometry (LCM/MS): An analytical tool which is based on coupling mass spectrometers together in a series to analyze complex mixtures. Historically, LCM/MS had been used primarily by research, pharmaceutical, or commercial laboratories. Recent advances in the technology, decreasing costs for basic systems, intelligible software, an increased number of published protocols and methods, and the release of Food and Drug Administration (FDA) approved kits has enabled more clinical laboratories to pursue these instruments as viable clinical analyzers.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider

reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
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℠, Ethos Laboratories
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. 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):511-529.
2. Gunn J, Hill MM, Cotten BM, Deer TR. An analysis of biomarkers in patients with chronic pain. Pain Physician. 2020; 23(1):E41-E49.
3. Hagedorn JM, Gunn J, Budwany R, et al. How well do current laboratory biomarkers inform clinical decision-making in chronic pain management? J Pain Res. 2021; 14:3695-3710.
4. Reckziegel D, Vachon-Presseau E, Petre B, et al. Deconstructing biomarkers for chronic pain: context and hypothesis dependent biomarker types in relation to chronic pain. Pain. 2019; 160(Suppl 1):S37-S48.
5. Sun AL, Ni YH, Li XB, et al. Urinary methylmalonic acid as an indicator of early vitamin B12 deficiency and its role in polyneuropathy in type 2 diabetes. J Diabetes Res. 2014; 2014:1-6.

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Foundation PI℠

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/12/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.