ADMINISTRATIVE POLICY STATEMENT
Michigan Health Link

Policy Name & Number	Date Effective
Pharmacogenomics-CYP Gene Testing-MI Health Link-AD-1423	07/01/2024
Policy Type	
ADMINISTRATIVE	

Administrative Policy Statement prepared by CareSource and its affiliates are derived from literature based on and supported by clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services include, but are not limited to, those health care services or supplies that are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased or new morbidity, impairment of function, dysfunction of a body organ or part, or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative, and are not provided mainly for the convenience of the member or provider. Medically necessary services also include those services defined in any Evidence of Coverage documents, Medical Policy Statements, Provider Manuals, Member Handbooks, and/or other policies and procedures.

Administrative Policy Statements prepared by CareSource and its affiliates do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Administrative Policy Statement. If there is a conflict between the Administrative Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

According to the rules of Mental Health Parity Addiction Equity Act (MHPAEA), coverage for the diagnosis and treatment of a behavioral health disorder will not be subject to any limitations that are less favorable than the limitations that apply to medical conditions as covered under this policy.

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A. Subject

Pharmacogenomics-CYP Gene Testing

B. Background

Pharmacogenomics is an area of precision medicine that provides information about an individual's genes, influencing therapeutic strategies and assessing the likelihood of benefit or toxicity to a given drug. This form of medication management has been evaluated in a variety of clinical scenarios. As pharmacogenomics expands and laboratories offering testing proliferate, the value of a given test in terms of patient benefit may be obscured by multiple contributing factors, including exaggerated public marketing claims, inconsistencies in test standardization, continued patient variation in response to prescribed medication, incomplete knowledge of drug metabolism, and limitations in regulatory oversight. To manage these challenges, the clinical validity and clinical utility of a specific gene or biomarker with a specific drug target should demonstrate improvement in patient outcomes.

C. Definitions

- **Clinical Utility** – The likelihood that a test will, by prompting an intervention, result in an improved health outcome.
- **Clinical Validity** – The accuracy of a test for a given clinical outcome.
- **Unbundling** – HCPCS/CPT codes should be reported only if all services described by the code are performed. Multiple codes should not be reported if a single code exists that describes the services performed. The codes include all services usually performed as part of the procedure as a standard of medical/ surgical practice and should not be separately reported simply because codes exist for the services.

D. Policy

I. General Guidelines

A. Biomarker testing with uncertain clinical significance in MCG will be considered experimental and investigational.

B. Unbundling of codes in a panel is an incorrect billing practice and may result in payment recovery.

C. Any drug, biologic, device, diagnostic, product, equipment, procedure, treatment, service, or supply used in or directly related to the diagnosis, evaluation, or treatment of a disease, injury, illness, or other health condition which HAP CareSource determines in its sole discretion to be experimental or investigational is not covered by HAP CareSource.

II. Based on review of existing evidence, there are currently no clinical indications for the high-volume tests below, and the current role remains uncertain. Therefore, HAP CareSource considers these requests experimental and investigational, as there is not sufficient evidence for use in the peer reviewed literature. This is not an all-inclusive list.

CPT® Codes	Testing Examples
81225 - CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)	Genecept Assay, OneOme RightMed, PGxOnePlus, CQuentia, IDGenetix, PROOVE, GARSPREDX, PharmacoDx
81226 - CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)	
81227 - CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)	
81230 - CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)	

III. The following codes require review by HAP CareSource and authorization prior to service provision:
   A. 81291 – MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
   B. 0345U – Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6

IV. HAP CareSource applies coding edits to medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. Proper billing and submission guidelines must be followed, including the following:
   A. Use of industry standard, compliant codes on all claims submissions, including CPT codes and/or HCPCS codes.
   B. Services considered to be mutually exclusive, incidental to or integral to the primary service rendered are not allowed additional payment.
   C. Proprietary panel testing requires evidence-based documentation of medical necessity.
   D. Submission of the most accurate and appropriate CPT/HCPCS code(s) for the product or service being provided, including coding to the highest level of specificity.

V. HAP CareSource considers the following not medically necessary (not an all-inclusive list):
   A. Pharmacogenomic testing or screening in the general population.
   B. A non-covered test billed by using unlisted procedure codes.
   C. The use of multi-gene panels for genetic polymorphisms, including, but not limited to, pain management, cardiovascular drugs, anthracyclines, or polypharmacy, for evaluating drug-metabolizer status (eg, PharmacoDx).
   D. Tests considered screening in the absence of clinical signs/symptoms of disease.
   E. Tests that do not confirm new data for decision making but confirm a known diagnosis or information.
   F. Tests to determine risk for developing a disease or condition.
   G. Tests without diagnosis-specific indications.
   H. Tests performed to ensure a tissue specimen matches an individual.

E. Conditions of Coverage

NA

F. Related Policies/Rules

Overpayment Recovery
Medical Necessity Determinations
Experimental and Investigational Item and Service

G. Review/Revision History

	DATE	ACTION
Date Issued	03/27/2024	New policy. Approved at Committee.
Date Revised		
Date Effective	07/01/2024	
Date Archived		

H. References

1. Behavioral Health Medication Pharmacogenetics – Gene Panels: A-0861. MCG Health. 28th ed. Updated February 1, 2024. Accessed March 14, 2024. www.careweb.careguidelines.com
2. Clinical laboratory improvement amendments (CLIA). Centers for Disease Control and Prevention. Reviewed January 16, 2024. Accessed March 14, 2024. www.cdc.gov
3. *Clinical Use of Pharmacogenetic Testing in Prescribing Psychotropic Medications for Children and Adolescents*. American Academy of Child & Adolescent Psychiatry; 2020. Accessed March 14, 2024. www.aacap.org
4. Clinical Utility Evaluation: APOE Genetic Testing for Alzheimer Disease. Hayes; 2018. Updated May 18, 2022. Accessed March 14, 2024. www.hayesinc.com
5. Clinical Utility Evaluation: Genetic Testing for Common Forms of Hereditary Thrombophilia in Adults with Unprovoked Venous Thromboembolism. Hayes; 2019. Updated June 21, 2022. Accessed March 14, 2024. www.evidence.hayesinc.com
6. Clinical Utility Evaluation: Genetic Testing For Common Forms of Hereditary Thrombophilia in Pediatric Patients with Unprovoked Venous Thromboembolism. Hayes; 2019. Updated June 21, 2022. Accessed March 14, 2024. www.evidence.hayesinc.com
7. Clinical Utility Evaluation: Genetic Testing for factor V Leiden in Women with Unexplained Recurrent Pregnancy Loss. Hayes; 2018. Updated October 24, 2022. Accessed March 14, 2024. www.hayesinc.com
8. Clinical Utility Evaluation: *MTHRF* Genetic Testing for Hypertension. Hayes; 2023. Accessed March 14, 2024. www.hayesinc.com
9. Clinical Utility Evaluation: *MTHRF* Genetic Testing for Nondevelopmental Psychiatric Disorders. Hayes; 2023. Accessed March 14, 2024. www.hayesinc.com
10. Clinical Utility Evaluation: *MTHRF* Genetic Testing for Pregnancy Complications. Hayes; 2023. Accessed March 14, 2024. www.hayesinc.com

11. Clinical Utility Evaluation: *MTHRF* Genetic Testing for Severe *MTHFR* Enzyme Deficiency. Hayes; 2023. Accessed March 14, 2024. www.hayesinc.com
12. Clinical Utility Evaluation: *MTHRF* Pharmacogenetic Genotyping for Altering Drug Treatment. Hayes; 2017. Updated May 23, 2021. Accessed March 14, 2024. www.hayesinc.com
13. Clinical Utility Evaluation: Pharmacogenetic and Pharmacogenomic Testing for Opioid Treatment for Pain in Adults – Selected Single-Gene Variants and Pharmacogenomic Panels. Hayes; 2019. Updated October 26, 2022. Accessed March 14, 2024. www.evidenced.hayesinc.com
14. Clinical Utility Evaluation: Pharmacogenetic and Pharmacogenomic Testing to Improve Outcomes Related to Opioid Use Disorder. Hayes; 2020. Updated June 30, 2023. Accessed March 14, 2024. www.evidence.hayesinc.com
15. Clinical Utility Evaluation: Pharmacogenomic Testing for Attention-Deficit/Hyperactivity Disorder. Hayes; 2022. Updated February 27, 2024. Accessed March 14, 2024. www.evidence.hayesinc.com
16. Clinical Utility Evaluation: Pharmacogenomic Testing of Selected Mental Health Conditions. Hayes; 2021. Updated December 1, 2023. Accessed March 14, 2024. www.evidence.hayesinc.com
17. Cytochrome P450 pharmacogenetics – gene tests and gene panel: A-0775. MCG Health. 28th ed. Updated February 1, 2024. Accessed March 14, 2024. www.careweb.careguidelines.com
18. Deoxyribonucleic acid (DNA) fact sheet. National Human Genome Research Institute. Updated August 24, 2020. Accessed March 14, 2024. www.genome.gov
19. Hefti E, Blanco JG. Documenting pharmacogenomic testing with CPT codes. *J AHIMA*. 2016;87(1):56-59. Accessed March 14, 2024. www.pubmed.ncbi.nih.gov
20. Hicks JK, Bishop JR, Sangkuhl K, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther*. 2015;98(2):127-134. doi:10.1002/cpt.147
21. Hippman C, Nislow C. Pharmacogenomic testing: clinical evidence and implementation challenges. *J Pers Med*. 2019;9(3):40. doi:10.3390/jpm9030040
22. Hyperhomocysteinemia – MTHRF gene: A-0629. MCG Health. 28th ed. Updated February 1, 2024. Accessed March 14, 2024. www.careweb.careguidelines.com
23. Kohlmann W, Slavotinek A. Genetic testing. UpToDate. Updated October 7, 2022. Accessed March 14, 2024. www.uptodate.com
24. Laboratory Requirements, 42 C.F.R. § 493 (2024).
25. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Food and Drug Administration. Updated December 21, 2023. Accessed March 14, 2024. www.fda.gov
26. Medical Code Brief: 0345U-PLA (U Codes). Hayes; 2022. Accessed March 14, 2024. www.evidence.hayeinc.com
27. Methotrexate pharmacogenetics – MTHFR gene: A-1009. MCG Health. 28th ed. Updated February 1, 2024. Accessed March 14, 2024. www.careweb.careguidelines.com

28. *MolDx: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR).* Medicare Coverage Database; 2015. LCD ID L35984. Revised July 20, 2023. Accessed March 14, 2024. www.cms.gov
29. *MolDx: Molecular Diagnostic Tests (MDT).* Medicare Coverage Database; 2017. LCD ID L36807. Revised April 27, 2023. Accessed March 14, 2024. www.cms.gov
30. *MolDx: Pharmacogenomics Testing*. Medicare Coverage Database; 2020. LCD ID L38435. Updated August 24, 2023. Accessed March 14, 2024. www.cms.gov
31. *MolDx*: *Repeat Germline Testing*. Medicare Coverage Database; 2020. LCD ID L38429. Revised January 23, 2024. Accessed March 14, 2024. www.cms.gov
32. Molecular Test Assessment: GeneSight Psychotropic (Assurex Health Inc./Myriad Neuroscience). Hayes; 2021. Updated November 13, 2023. Accessed March 14, 2024. www.evidence.hayesinc.com
33. National Cancer Institute (NCI). NCI Dictionary of Genetics Terms. National Institute of Health. Accessed March 14, 2024. www.cancer.gov
34. National Center for Biotechnology Information. Genetic testing registry. National Library of Medicine. Accessed March 14, 2024. www.ncbi.nlm.nih.gov
35. *National Correct Coding Initiative Policy Manual For Medicaid Services*. Centers for Medicaid and Medicare Services. Updated January 1, 2024. Accessed March 14, 2024. www.medicaid.gov
36. Pharmacogenetic testing. American Academy of Child and Adolescent Psychiatry. Updated December 2019. Accessed March 14, 2024. www.aacap.org
37. Pharmacogenomic Testing for Warfarin Response. Medicare Coverage Database; 2009. NCD ID 90.1. Accessed March 14, 2024. www.cms.gov
38. Precision Medicine Research Brief: Genecept Assay (Genomind). Hayes; 2016. Accessed March 14, 2024. www.evidence.hayesinc.com
39. Precision Medicine Research Brief: PGxOne Plus (Admera Health). Hayes; 2017. Accessed March 14, 2024. www.evidence.hayesinc.com
40. Precision Medicine Research Brief: Proove Opioid Risk Test (Proove Biosciences). Hayes; 2016. Accessed March 14, 2024. www.evidence.hayesinc.com
41. Raby B. Personalized medicine. UpToDate. Updated September 06, 2023. Accessed March 14, 2024. www.uptodate.com
42. Tantisira K, Weiss S. Overview of pharmacogenomics. UpToDate. Updated December 20, 2023. Accessed March 14, 2024. www.uptodate.com
43. Warfarin pharmacogenetics-CYP2C9, CYP4F2, and VKORC1 genes: A-0587. MCG Health. 28th ed. Updated February 1, 2024. Accessed March 14, 2024. www.careweb.careguidelines.com