Department of Origin: Integrated Healthcare Services	**Effective Date:** 05/29/24
Approved by: Medical Policy Quality Management Subcommittee	**Date Approved:** 03/05/24
Clinical Policy Document: Pharmacogenetic Testing, CYP2C19 and CYP2D6 Genotyping	**Replaces Effective Clinical Policy Dated**: 03/05/24
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PURPOSE:
The intent of this clinical policy is to ensure services are medically necessary.

Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.

POLICY:
Benefits must be available for health care services. Health care services must be ordered by a provider. Licensed Genetic Counselors may also order genetic tests if it is within the scope of practice of their state licensure. Health care services must be medically necessary, applicable conservative treatments must have been tried, and the most cost-effective alternative must be requested for coverage consideration.

GUIDELINES:
Medical Necessity Criteria – Requests for pharmacogenetic genotyping for CYP2C19 and CYP2D6 polymorphisms - Must satisfy all of the following: I, and any of II - IV

I. After history, physical examination and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain and a valid specific test exists for the suspected condition – as evidenced by all of the following: A – C

   A. Each test has been approved for its intended use by the appropriate *regulatory/oversight body* (implies *analytic validity*); and

   B. Each test has sufficient sensitivity or specificity (*clinical validity*) for targeting the member's specific clinical condition; and

   C. The results of each test will directly impact clinical decision-making and clinical care (*clinical utility)* for the individual.

   [Note: Genetic counseling is not required for well-defined populations.]

II. The use of the test is to guide therapy decisions for antidepressant or antipsychotic medications - must satisfy all of the following: A - C

   A. The member has a diagnosis of major depressive disorder (MDD) or generalized anxiety disorder (GAD); and

   B. The member has failed at least one prior medication to treat their condition; and

   C. If a multi-gene panel is requested, the panel has no more than 15 genes, two of which must be CYP2C19 and CYP2D6

III. CYP2C19 genotyping is medically necessary to detect polymorphisms in members who are considering Plavix (clopidogrel)[7].

IV. CYP2D6 genotyping is medically necessary to detect polymorphisms for either of the following: A or B

A. In members who have been prescribed treatment with Xenazine (tetrabenazine) in doses of greater than 50 mg per day[8]; or

B. In members who are considering Cerdelga (eliglustat) for the treatment of Gaucher disease type 1[9].

EXCLUSIONS (not limited to):
Refer to member's Certificate of Coverage or Summary Plan Description

I. CYP2C19 and CYP2D6 genotyping to detect polymorphisms for all other indications is considered investigative (see Investigative List)

II. Direct-to-consumer testing

DEFINITIONS:
Analytic Validity:
How accurately and reliably the test measures the genotype of interest. A major component in the validation of an analytical technique is the technique's ability to accurately determine the presence of the substance it is seeking. It must measure the target substance without a great range of variation over a number of trials. The technique also must be proven to work reliably at multiple labs to be validated by this testing.

Clinical Utility:
The evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decision-making compared with current management without the testing.

Clinical Validity:
How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.

Cytochrome P450 (CYP450):
The cytochrome P450s (CYPs) are members of a superfamily of oxidative enzymes, which represent the major system for oxidative metabolism of therapeutic substances. Sequencing of the human genome has revealed 58 different human CYP genes, which encode various CYP isoenzymes. CYP enzyme activity can be affected by genetic and environmental factors. One of the more common environmental influences occurs through drug-drug interactions.

Epigenetic changes:
Affect genes without altering the gene sequence. This may occur via changes in gene methylation or histone modification (methylation, acetylation), either of which can influence the rate of transcription or silencing of gene expression. Other epigenetic changes include the alterations in noncoding RNAs and telomere length. These epigenetic changes can be passed on from parents to offspring but can also result from environmental influences on the epigenome. An example of an epigenetic change that affects drug metabolism is reduced sensitivity of a tumor to a chemotherapeutic drug due to gene methylation

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Pharmacogenetics:
A subcategory of pharmacogenomics that refers to the role of genetic variation in response to a drug. Pharmacogenetics generally is used to refer to a specific DNA polymorphism or coding variant rather than epigenetic or transcriptomic changes across the genome. In practice, pharmacogenetics and pharmacogenomics are often used interchangeably.

Pharmacogenomics:
The role of various components of the genome on response to a drug. Among the most commonly studied are genetic sequence variants, structural changes in chromosomes (eg, translocations), epigenetic variants (eg, changes in gene methylation), and variation in the expression profile of genes (changes in messenger RNA [mRNA] levels) or noncoding RNA (eg, changes in microRNA). The genetic variation can be inherited through the germline or acquired (eg, somatic mutation in a tumor). The availability of high-throughput techniques to interrogate the entire genome has facilitated many pharmacogenomic studies.

BACKGROUND:
Pharmacogenomic influences on drug responses have traditionally been divided into four categories based upon the impact of genetic variability on the pharmacologic properties of a drug.

- Effect on drug pharmacokinetics; an example is a genetic variant that alters drug metabolism, affecting plasma concentration.
- Effects on pharmacodynamics; an example is a genetic variation that reduces binding of the drug to its receptor, thereby decreasing therapeutic efficacy.
- Effects on idiosyncratic reactions, such as the likelihood of a hypersensitivity reaction to a certain drug.
- Effects on disease pathogenesis or severity and response to specific therapies; these include specific molecular defects related to the pathogenesis of certain malignancies for which specific targeted therapies have been developed

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Prior Authorization: Yes, per network provider agreement

CODING:
CPT®
CYP2C19
81225 CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg *2,*3,*4,*8,*17)

CYP2D6
81226 CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg *2,*3,*4, *5, *6, *9, *10,*17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
0070U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, common and select rare variants (eg *2,*3,*4,*4N, *5, *6, *7, *8, *9, *10,*11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *83, *xN)
0071U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, full gene sequence
0072U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene)
0073U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, targeted sequence analysis (ie, CYP2D6-2D6 hybrid gene)
0074U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans)
0075U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication)
0076U CYP2D6 (cytochrome P450, family 2, subfamily A, polypeptide 6) (eg, drug metabolism), gene analysis, targeted sequence analysis (ie, 3' gene duplication/multiplication)

Panels
81418 Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
81479 When used for a panel that contains 15 genes or less
0029U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1, and rs12777823) https://www.mayocliniclabs.com/test-catalog/overview/610057
0173U Psychiatry, (ie, depression, anxiety) genomic analysis panel, includes variant analysis of 14 genes (Psych HealthPGx Panel, RPRD Diagnostics) https://www.rprdx.com/testing/psych/
0175U Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes (Genomind Professional PGx Express CORE) https://www.genomind.com/products/core-anxiety-depression-report
0345U Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (GeneSight Psychotropic)
0392U Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
0411U Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6

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0419U Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
0423U Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition
0438U Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions

REFERENCES:

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5. Rush AJ. Unipolar major depression in adults: choosing initial treatment. (Topic 1725 Version 87.0; last updated 10/17/23). In: Soloman D, ed. UpToDate. Waltham, MASS.: UpToDate; 2021 www.uptodate.com. Accessed 12-27-23.
6. Murphy LE, Foneska TM, Bousman CA, Müller DJ. Gene-drug pairings for antidepressants and antipsychotics: level of evidence and clinical application. *Mol Psychiatry* 27,593-605 (2022). https://doi.org/10.1038/s41380-021-01340-6. Accessed 12-27-23.
7. Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi; 2022.
8. Xenazine [package insert]. Deerfield, IL: Lundbeck; 2017
9. Cerdelga [package insert]. Waterford, Ireland: Genzyme Ireland, Ltd.; 2018

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Nondiscrimination & Language Access Policy

Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity. *We* do not exclude people or treat them differently because of race, color, national origin, age, disability, sex, sexual orientation, or gender identity.

We will:
Provide free aids and services to people with disabilities to communicate effectively with us, such as:
- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provide free language services to people whose primary language is not English, such as:
- Qualified interpreters
- Information written in other languages

If *you* need these services, contact *us* at the phone number shown on the inside cover of this *contract*, *your* id card, or aspirushealthplan.com.

If *you* believe that *we* have failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity, *you* can file a grievance with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1062
Minneapolis, MN 55440
Phone: 1.866.631.5404 (TTY: 711)
Fax: 763.847.4010
Email: customerservice@aspirushealthplan.com

You can file a grievance in person or by mail, fax, or email. If *you* need help filing a grievance, the Nondiscrimination Grievance Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1.866.631.5404 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً . اتصل بن اعلى رقم الهاتف 1.866.631.5404(رقم هاتف الصم والبك : 711)

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Hindi: _यान द_: य_द आप ि◌हंदी बोलते ह_ तो आपके ि◌लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_। 1.866.631.5404 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1.866.631.5404 (TTY: 711).

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Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.866.631.5404 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1.866.631.5404 (TTY: 711)

Traditional Chinese: 注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請 致電 1.866.631.5404 (TTY:711).

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1.866.631.5404 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1.866.631.5404 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັ້ງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1.866.631.5404 (TTY:711).