JOHNS HOPKINS HEALTH PLANS	Johns Hopkins Health Plans **Medical Policy Manual** **Medical Policy**	*Policy Number*	CMS04.03
		Effective Date	08/01/2023
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	Subject **Pharmacogenomics**	*Supersedes Date*	11/01/2022
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This document applies to the following Participating Organizations:

EHP US Family Health Plan

Keywords: Genotyping, Pharmacogenomics

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I. ACTION

	New Policy	
x	Revising Policy Number	CMS04.03
	Superseding Policy Number	
	Archiving Policy Number	
	Retiring Policy Number	

II. POLICY DISCLAIMER

Johns Hopkins Health Plans (JHHP) provides a full spectrum of health care products and services for Advantage MD, Employer Health Programs, Johns Hopkins Health Plan of Virginia Inc., Priority Partners, and US Family Health Plan. Each line of business possesses its own unique contract, benefits, regulations, and regulators' clinical guidelines that supersede the information outlined in this policy.

III. POLICY

For Advantage MD refer to: eviCore Guidelines

For Employer Health Programs (EHP) refer to:

- Plan specific Summary Plan Descriptions (SPDs)

For Priority Partners (PPMCO) refer to: eviCore Guidelines

For Johns Hopkins Health Plan of Virginia LLC (JHHPVA) refer to eviCore Guidelines (Effective 1/1/2024)

For USFHP refer to: Tricare Policy Manuals

- TRICARE Operations Manual 6010-62-M, April 1, 2021, Chapter 18, Section 2 Defense Health Agency (DHA) Evaluation Of Non-United States (U.S.) Food and Drug Administration (FDA) Approved Laboratory Developed Tests (LDTs) Demonstration Project.
- TRICARE Policy Manual 6010.63-M, April 2021, Chapter 6, Section 3.1 Genetic Testing and Counseling.
- TRICARE Policy Manual 6010.63-M, April 2021, Chapter 13, Section 1.1 Provisional Coverage for Emerging Services and Supplies.

IV. POLICY CRITERIA

A. Universal Requirements: When benefits are provided under the member's contract, JHHP considers pharmacogenomics genotyping medically necessary when the following criteria are met:
   1. The patient has signs and symptoms of the disorder in question, AND;
   2. A definitive diagnosis cannot be made using conventional medical tests, AND;
   3. The laboratory performing the test meets CLIA requirements (The CDC maintains a searchable database of CLIA-certified laboratories at https://www.cdc.gov/), AND;
   4. There is appropriate documentation of the testing requested including:
      a. Proprietary test name(s)/gene name(s)
      b. Applicable CPT codes
      c. Laboratory performing the test; name of the billing provider
      d. Indication for testing and drugs(s) being considered, and documentation to indicate the clinical validity and utility of the test *(see below for sources that should be referred to*), AND;
   5. The provider documentation includes how the test will be used to change medical management of the member, AND indicates the test has clinical validity and utility based on ONE of the following:
      a. The test is an FDA approved companion diagnostic device.
         i. The FDA maintains a table that lists approved tests and their indication at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. If the use of this test is consistent with the indication, then the testing is considered medically necessary, OR;
      b. The identification of the associated gene biomarker is clinically necessary prior to initiation of therapy as indicated by a PharmGKB assigned PGx level of "testing required" or "testing recommended" based on the FDA drug label.
         i. PharmGKB is a NIH supported resource that provides summaries of FDA drug labels that contain pharmacogenomic information at https://www.pharmgkb.org/labelAnnotations.
            - Each drug is assigned a PharmGKB PGx level tag to indicate if testing is needed.
            - If the PGx level is "testing required" or "testing recommended" for the specific drug(s) that the provider is considering and the indication is met based on information summarized in the annotation from the FDA drug label, then JHHP considers testing for this genetic biomarker medically necessary.
            - The annotation will include whether the drug has an FDA approved companion diagnostic device (test). However, the FDA table will need to be referred to for specific test names.
            - If the PGx level is "actionable PGx" or "informative PGx" and the indication is met based on information summarized in the annotation from the FDA drug label, then JHHP may consider this test medically necessary. (*Medical Director review required*), OR;

c. The identification of the associated gene biomarker is clinically necessary based on the FDA drug label (*Medical Director review required*).
   i. The FDA maintains a searchable Table of Pharmacogenomic Markers in Drug Labeling at https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. This table includes the drugs that contain pharmacogenomic information in their drug labels. If the testing ordered is necessary based on information contained in the FDA approved label, then JHHP considers this test medically necessary, OR;

d. The gene-drug pair are assigned a CPIC level A or B and are discussed in a CPIC Guideline whose recommendations are applicable to the clinical management.
   i. CPIC lists gene-drug pairs and applicable guidelines at https://cpicpgx.org/genes-drugs/. If the use of the test is consistent with the recommendations in the guidelines, then JHHP considers this testing medically necessary, OR;

e. The gene-drug pair is listed in the FDA Table of Pharmacogenetic Associations and the interaction described is applicable to the clinical management (*Medical Director Review Required*).
   i. The FDA maintains a Table of Pharmacogenetic Associations at https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. If the use of the test is consistent with the interaction described, then JHHP considers this testing medically necessary, OR;

f. The associated gene biomarker is discussed in a National Comprehensive Cancer Network (NCCN) guideline or another similarly respected professional organization guideline and is applicable to the clinical management.
   i. The National Comprehensive Cancer Network Treatment by Cancer Type Guidelines are accessible at https://www.nccn.org/guidelines/category_1. If the testing being requested is consistent with the management algorithm presented in the guidelines, then JHHP considers testing medically necessary, OR; *Note*: Genetic biomarkers that are mentioned in the discussion portion of the guidelines without explicit recommendation guidance may be considered medically necessary (*Medical Director review required*).

g. There is sufficient evidence in the scientific literature to support the clinical validity (scientific and predictive accuracy) and clinical utility of the test for the specific indication (*Medical Director Review Required*), OR;

6. The test has received a Hayes rating of A or B for the specific indications.

B. Multi-gene Panels: When benefits are provided under the member's contract, JHHP considers multi-gene panel tests medically necessary when the following conditions are met:
1. The multi-gene panel test is approved by the FDA for the appropriate indication OR recommended in a NCCN management algorithm when the indication is met as medically necessary.
2. Multi-gene tests may also be considered medically necessary if more than one single gene included on the panel has clinical validity and utility based on the criteria listed above in section A 5 including those situations where more than one drug is being considered.
3. Combinatorial pharmacogenomics tests rely on propriety algorithms to help with the interpretation of multiple genes and are not considered medically necessary unless individual genes have demonstrated clinical validity and utility based on the criteria listed above in section A 5.

V. DEFINITIONS

Genomic Biomarker: "A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions." As an example, a genetic biomarker may be a measurement of the expression of a gene, the function of a gene, or the regulation of a gene (FDA, 2008).

Pharmacogenomics and Pharmacogenetics: These terms are often used interchangeably. However, in an effort to have consistent definitions in this field, the US Food and Drug Administration (FDA), through their work on the International

Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) produced a guidance document with key definitions (FDA, 2008)

- Pharmacogenomics (PGx): "The study of variations of DNA and RNA characteristics as related to drug response". (FDA).
- Pharmacogenetics (PGt): "The study of variations in DNA sequence as related to drug response". Pharmacogenetics (PGt) is a subset of pharmacogenomics (PGx).

Pharmacogenetic or Pharmacogenomic Tests vs Genetic Tests: Pharmacogenetic or pharmacogenomic tests are a type of genetic test, but they are distinct from genetic tests in that their intended purpose is to detect genetic variation to guide the choice and dosing of drugs. How individuals metabolize drugs may also be determined by their genes. Some individuals may metabolize drugs quickly or slowly, which may affect their safety and effectiveness profile and what dose is prescribed. Pharmacogenetic or pharmacogenomic tests are helpful when a particular drug is being considered for an individual. The purpose of genetic tests is to detect genetic variation for screening or diagnostic purposes. (ASCO, 2020; FDA, 2007).

VI. BACKGROUND

This policy refers to tests that detect both germline (inheritable) variation that affects an individual's response to a drug and somatic (acquired) mutations used in tailoring cancer management. Please refer to the Genetic Testing Policy criteria for genetic tests done for screening or diagnostic purposes and for a review of genetic testing techniques (e.g. NGS).

The field of pharmacogenomics presents both opportunities and challenges for the practice of precision medicine (Teutsch & Tuckson, 2008). The National Human Genome Research Institute is supporting advancements in genomics research, and pharmacogenomics may help clinicians avoid the trial and error approach of drug prescribing (NIH, 2020). It is an area of active research and reimbursement for these tests is expanding (Empey, 2021). Fortunately, there are respected resources and tools to support physicians' clinical decision making in the appropriate use of pharmacogenetic testing from the National Institutes of Health (NIH), the US Food and Drug Administration (FDA), and the National Comprehensive Cancer Network (NCCN). These resources will be reviewed briefly here in the context of medical necessity determinations and are listed at the end of this section.

The NIH is supporting advancements in this field through the Pharmacogenomics Research Network, the Clinical Pharmacogenetic Implementation Consortium (CPIC), and the Pharmacogenomics Knowledge Base (PharmGKB).

The Clinical Pharmacogenetic Implementation Consortium (CPIC) is a partnership between the Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenomics Research Network. CPIC provides evidence based guidelines regarding the use of pharmacogenetic tests to help facilitate their use in the clinical setting. The quality of evidence and the strength of the recommendations are rated within the guidelines, and the gene-drug pair are assigned a CPIC level (A,B,C, or D). Gene-drug pairs described in CPIC guidelines that have enough evidence to support recommending a change in the use of that drug are assigned a level A or B (CPIC, 2021). According to the CPIC website, "CPIC guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy, rather than whether tests should be ordered." CPIC guidelines are developed with the understanding that pharmacogenomic results will be more widely available on patients prior to when a specific indication arises (Relling, 2011; CPIC, 2021). The effectiveness of preemptively testing patients is an area of research and may contribute to the management of diseases such as diabetes in the future (van der Wouden et al., 2017; Pearson, 2019).

PharmGKB is a NIH supported pharmacogenomics resource that was created as a tool to provide comprehensive information on how specific genes affect drug responses. PharmGKB is an extensive searchable public database that summarizes pharmacogenomics information found in drug labels, clinical guidelines, and published research papers (Whirl-Carrillo, 2012; Thorn, 2013). PharmGKB includes annotations of drug labels from the US Food and Drug Administration, Pharmaceuticals and Medical Devices Agency (Japan), European Medicines Agency, Health Canada (Santé Canada), and the Swiss Agency

of Therapeutic Products and assigns a PGx level to indicate the necessity of testing (i.e. “testing required,” “testing recommended,” “actionable PGx,” or “informative PGx”) based on the information contained in the drug label. FDA approved drugs that contain pharmacogenomic information in the drug label are listed in the Table of Pharmacogenomic Biomarkers in Drug Labeling on the FDA website. PharmGKB annotates all drugs listed in the FDA’s Table of Pharmacogenomic Biomarkers in Drug Labeling and other FDA approved drugs that may not be included in the table or have been removed from the table. Of note, PharmGKB drug annotations based on FDA approved labels are updated as there are changes in the FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling, and there will frequently be an expected lag period between changes made by the FDA and the PharmGKB website (PharmGKB, https://www.pharmgkb.org/). In addition, the FDA has a Table of Pharmacogenetic Associations on their website that summarizes specific gene-drug associations based on their review of the scientific literature that is distinct from the FDA’s Table of Pharmacogenomic Biomarkers in Drug Labeling, and not all gene-drug associations described in this table are incorporated into FDA approved drug labels (FDA, 2020). PharmGKB annotations of FDA approved drug labels, CPIC guidelines, and the FDA Table of Pharmacogenetic Associations are available to support appropriate testing.

Pharmacogenomic tests play a very important role in anticancer treatments. By genotyping tumors, it is possible to prescribe treatments and doses that are optimally effective for individuals (Calvo et al., 2016). The growth of molecular testing in oncology has led to challenges regarding determining appropriate FDA oversight of tests, determining clinical utility, and concerns related to reimbursement by payors (Engstrom et al., 2011). The National Comprehensive Cancer Network (NCCN) is comprised of 31 cancer centers and provides resources to support cancer management. The NCCN Guidelines for Treatment by Cancer Type provide recommendations including pharmacogenetic testing (NCCN, 2021).

Beyond cancer treatment, pharmacogenomic approaches are being considered to improve available treatments for conditions with public health significance such as diabetes (Dawed et al., 2016) and to enhance dosing decisions of widely used drugs such as Warfarin (Stack et al., 2016). In addition, pharmacogenomic testing also has implications for the pediatric population. The Sanford Children’s Genomic Medicine Consortium is comprised of 10 US children’s hospitals and is committed to supporting pediatric pharmacogenomic research and testing (Gregornik et al., 2021b).

Given the promise of personalized medicine, genetic tests have grown in popularity, and in 2018 the FDA issued a cautionary statement to increase awareness among patients and clinicians that not all claims about pharmacogenomic testing have been supported by evidence (FDA, 2018b). In addition to clinical utility, pharmacogenomic tests should be clinically and analytically valid and be consistent with Clinical Laboratory Improvement Amendments (CLIA) requirements. (Association for Molecular Pathology, 2019). A companion diagnostic test “provides information that is essential for the safe and effective use of a corresponding drug", and the FDA has provided guidance about the development of companion tests which ideally are developed and approved concurrently alongside the drug (FDA, 2018a). The FDA has published a discussion paper summarizing the issues related to oversight of laboratory developed tests (FDA, 2018c). The FDA maintains a list of approved companion diagnostic devices with their specific indications, and a full list of all FDA approved nucleic acid based tests. Some of these FDA approved tests are multi-gene panels (FDA, 2021a, FDA 2021b).

Multi-gene panel tests detect genetic variations involving more than one gene at one time. With advances in technology, multi-gene panel testing has become more common, which is adding to the complexity of the field and shifting clinical practice to more of a preemptive testing strategy (Relling & Evans, 2015). The composition of these multi-gene panel tests is variable and may include tests that have strong clinical validity and utility and others where evidence may not be sufficient. Multi-gene panel testing has growing implications in cancer diagnosis and treatment. In the American Society of Clinical Oncology’s policy statement regarding genetic and genomic testing for cancer susceptibility, the appropriate use of these tests, including a description of the challenges with detecting moderate-penetrance mutations and variants of unknown significance are discussed (Robson et al., 2015).

Similar to single gene tests, multi-gene panel tests may be included on the FDA's approved companion diagnostic list or recommended in a NCCN management algorithm for a specific indication. In addition, providers may find the results of multi-gene testing that provide information on genes that are known to affect the metabolism of a particular drug or drug class helpful in certain clinical situations. For example, CPIC guidelines regarding the use of SSRI's provide dosing recommendations based on both CYP2D6 and CYP2C19 genotypes. However, as explained in the guideline "patients on a stable and effective dose of an SSRI most likely will not benefit from additional dose modifications based on CYP2D6 or CYP2C19 genotype results" (Hicks et al., 2015). Similar to single gene tests, multi-gene panel testing should be appropriately used given the complete clinical context.

The effectiveness of a drug may be influenced by many genes and their interaction. Individual gene testing may not capture these effects and interpreting the results of multiple genes on a panel increases the clinical decision making complexity for the provider who is now faced with the challenge of integrating these results. Combinatorial pharmacogenomic testing applies an algorithm to assist in interpretation of the multiple genes included on the panel. Several of these combinatorial multi-gene pharmacogenomic tests have been developed to help treat mental health disorders (e.g. GeneSight) and while these tests indicate exciting advancements in psychiatry, additional studies assessing their clinical utility are still needed (Winner & Dechairo, 2015; Zeier et al., 2018).

Summary of Resources for Pharmacogenetic Testing:

Clinical Pharmacogenetic Implementation Consortium (CPIC) Gene-Drug Pairs and Guidelines: https://cpicpgx.org/genes-drugs/
FDA List of Cleared or Approved Companion Diagnostic Devices: https://www.fda.gov/
FDA Table of Pharmacogenetic Associations: https://www.fda.gov/medical-devices/precision-medicine
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling: https://www.fda.gov/drugs/science-and-research
National Comprehensive Cancer Network Guidelines https://www.nccn.org/
Pharmacogenomics Knowledge Base (PharmGKB) Drug Label Annotations https://www.pharmgkb.org/labelAnnotations

VII. CODING DISCLAIMER

Note: The following CPT/HCPCS codes are included below for informational purposes and may not be all inclusive. Inclusion or exclusion of a CPT/HCPCS code(s) below does not signify or imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member's 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 of payment. Other policies and coverage determination guidelines may apply.

Note: All inpatient admissions require preauthorization.

Adherence to the provision in this policy may be monitored and addressed through post payment data analysis and/or medical review audits
Employer Health Programs (EHP): Specific Summary Plan Descriptions (SPDs) supersedes JHHP Medical Policy. If there are no criteria in the SPD, apply the Medical Policy criteria.
US Family Health Plan (USFHP): Regulatory guidance supersedes JHHP Medical Policy. If there are no TRICARE policies, or other regulatory guidelines, apply the Medical Policy criteria.

VIII. CODING INFORMATION

CPT® CODES ARE FOR INFORMATIONAL PURPOSES	
CPT® CODES	**DESCRIPTION**
81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/ deletion variants
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism),
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha)
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each

81400	Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • ABL (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib resistance), T315I variant
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) • KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma), gene analysis, variant(s) in exon 2 MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), exon 10 sequence VHL (von HippelLindau tumor suppressor) (eg, von Hippel-Lindau familial cancer syndrome), deletion/duplication analysis VWF (von Willebrand factor) (eg, von Willebrand disease types 2A, 2B, 2M), targeted sequence analysis (eg, exon 28)
81405	Molecular pathology procedure, level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) • KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence • OTC (ornithine carbamoy/transferase) (eg, ornithine transcarbamylase deficiency), full gene sequence
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) • BRAF(v-raf murine sarcoma viral oncogene homolog B1) (eg, Noonan syndrome), full gene sequence
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
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
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81479	Unlisted molecular pathology procedure • When used to report testing for a specific gene biomarker which is not otherwise reportable by a specific code and which is noted to be clinically necessary prior to initiating therapy with the drug target as noted in the section heading “Indications and Usage” of the U.S. Food and Drug Administration (FDA)-approved prescribing label.
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
85576	Platelet, aggregation (in vitro), each agent
86352	Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (eg, ATP)
86356	Mononuclear cell antigen, quantitative (eg, flow cytometry), not otherwise specified, each antigen
87900	Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics
87902	Infectious agent genotype analysis by nucleic acid (DNA or RNA); Hepatitis C virus
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology

HCPCS CODES ARE FOR INFORMATIONAL PURPOSES	
HCPCS CODE	**DESCRIPTION**
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)
0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplifie
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider

0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0040U	BCR/ABL1 (t(9; 22) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6),(eg.drug metabolism) gene analysis, common and select rare variants (ie,*2,*3,*4,*4N,*5,*6*7,*8,*9,*10,*11,*12,*13*14A,*14B,*15*17,*29, 35, *41, *57,*63,* 68, *xN)
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
0072U	CYP2D6 (CYTOCHROME P450, FAMILY 2,subfamily D, polypeptide 6) (eg, drug metabolism)gene analysis, targeted sequence analysis (ie, CYPCD6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
0073U	CYP2D6 (cytochrome P450,family 2, subfamily D, polypeptide 6) (eg. drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
0074U	CYPCD6 (cytochrome P450, family 2 subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primay procedure)
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism)gene analysis, targeted sequence analysis (ie, 5'gene duplication/multiplication) (List separately in addition to code for primary procedure)
0076U	CYP2D6 (cytochrome P450,family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/multiplication) (List separately in addition to code for primary procedure)
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
0154U	Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status

0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivitydisorder [ADHD]), genomic analysis panel, variant analysis of 15genes, including deletion/duplication analysis of CYP2D6

IX. REFERENCE STATEMENT

Analyses of the scientific and clinical references cited below were conducted and utilized by the Johns Hopkins Health Plans (JHHP) Medical Policy Team during the development and implementation of this medical policy. The Medical Policy Team will continue to monitor and review any newly published clinical evidence and revise the policy and adjust the references below accordingly if deemed necessary.

X. REFERENCES

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XI. APPROVALS

Historical Effective Dates: 12/04/2015, 09/02/2016, 03/03/2017, 07/01/2019, 08/02/2021, 11/01/2022, 08/01/2023