GENETIC TESTING: PHARMACOGENETICS

OVERVIEW

Pharmacogenetic tests are germline genetic tests that are developed to aid in assessing an individual's response to a drug treatment or to predict the risk of toxicity from a specific drug treatment. Testing may be performed prior to initiation of treatment to identify if an individual has genetic variants that could either affect response to a particular drug and/or increase the risk of adverse drug reactions. Testing may also be performed during treatment to assess an individual who has had an adverse drug reaction or to assess response to treatment. Test methodology includes genotyping and single nucleotide variant testing.

POLICY REFERENCE TABLE

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Pharmacogenetic Panel Tests	GeneSight Psychotropic Panel (Myriad Genetics)	81225, 81226, 81227, 81230, 81479. 0345U	F01-F69, F80-F99, Z81.8, Z86.59	29, 30, 31, 32 33
	Professional PGX™ (formerly Genecept™ Assay) (Genomind)			
	PGxOne™ (Admera Health)	81249, 81291, 81404, 81408, 81479	B20, C00.0-C96.9, D00.0-D49.9, E75.22, F01-F99, G10, G71.14, G89.0-G89.4, I20.0, I21.01-I22.9, I24.1, I25.110, I26.01-I26.99, I48.0, I60.00-I66.99, I73,	
	OneOme RightMed Pharmacogenomic Test {OneOme)	81232, 81240, 81241, 81291, 81479,0347U, 0348U, 0349U,		

		0350U	I82.210-I82.91, K50.00-K50.019 K51.00-K51.319, R52, R79.9, T46.6X1A-T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8, Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79	
	Focused Pharmacogenomics Panel (Mayo Clinic Laboratories)	0029U	I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73	
	Warfarin Response Genotype (Mayo Medical Laboratories)	0030U	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	
	Psych HealthPGx Panel, RPRD Diagnostics	0173U	F01-F69, F80-F99, Z81.8, Z86.59	
	Cytochrome P450 Genotyping Panel (ARUP Laboratories)	81225, 81226, 81227, 81230, 81231, 81479	I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73	
Pharmacogenetic Single Gene Tests				
CYP2C9 Variant Analysis	Cytochrome P450 2C9 Genotype (Quest Diagnostics)	81227	G35, I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	3, 4, 5, 21, 22, 25
CYP2C19 Variant Analysis	CYP2C19 Single Gene Test (Blueprint Genetics)	81225, 81479	I21.0-I22.9, I24.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	1, 6, 10, 8, 20, 27
CYP2D6 Variant Analysis	CYP2D6 (ARUP Laboratories)	81226	C50.011-C50.929, C79.81, D05.00-D05.92, D07.30-D07.39,	1, 2, 9, 10, 11, 24, 26
	CYP2D6 Common Variants and Copy Number (Mayo Clinic Laboratories)	0070U		

	CYP2D6 Full Gene Sequencing (Mayo Clinic Laboratories)	0071U	E75.22, G10, I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73, Z13.71-Z13.79, Z80.3, Z85.3, Z86.000	
	CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis (Mayo Clinic Laboratories)	0072U		
	CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis (Mayo Clinic Laboratories)	0073U		
	CYP2D6 CYP2D6 Nonduplicated Gene Analysis (Mayo Clinic Laboratories)	0074U		
	CYP2D65 gene duplication/multiplication targeted sequence analysis (Mayo Clinic Laboratories)	0075U		
	CYP2D63 gene duplication/multiplication targeted sequence analysis (Mayo Clinic Laboratories)	0076U		
CYP4F2 Variant Analysis	CYP4F2 Single Gene Test (Blueprint Genetics)	81479	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	4, 25
DPYD Variant Analysis	DPD 5-Fluorouracil Toxicity (LabCorp)	81232	C00.0-C96.9, D00.0-D49.9	12, 13, 28
*HLA-B**15:02 Variant Analysis	HLA-B*15:02, Carbamazepine Sensitivity (LabCorp)	81381	G40	14, 21
*HLA-B**15:02 and *HLA-A**31:01 Variant Analysis	Carbamazepine Hypersensitivity Pharmacogenomics (Mayo Medical Laboratories)	81381	G40	14

*HLA-B**57:01 Variant Analysis	HLA-B*57:01 Typing (Quest Diagnostics)	81381	B20, Z21	21
*HLA-B**58:01 Variant Analysis	HLA-B*58:01 Typing (Quest Diagnostics)	81381	M10, N20-N22	22
TPMT and *NUDT15* Variant Analysis	Thiopurine S-Methyltransferase (*TPMT*) Genotype (Quest Diagnostics)	81335	C91.0, K50.00-K50.90 K51.00-K51.319, M35.9, M05-M06.9, C85.90	17, 18
	TPMT and *NUDT15* (ARUP Laboratories)	81335, 81306		
	Thiopurine Methyltransferase (*TPMT*) and Nudix Hydrolase (*NUDT15*) Genotyping (Mayo Clinic Laboratories)	0034U		
	NT panel (*NUDT15* and *TPMT*) (RPRD Diagnostics)	0169U		
UGT1A1 Variant Analysis	UGT1A1 Irinotecan Toxicity (LabCorp)	81350	B20, C18, C19, C20, E80.4	23
VKORC1 Variant Analysis	VKORC1 Single Gene Test (Blueprint Genetics)	81355, 81479	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	4
Other Single Gene Variant Analysis	Catechol-O-Methyltransferase (COMT) Genotype (Mayo Clinic Laboratories)	0032U	F01-F69, F80-F99, G20, Z81.8, Z86.59	12, 13 , 19, 24
	Cytochrome P450 1A2 Genotype (Mayo Clinic Laboratories)	0031U	F01-F69, F80-F99, Z81.8, Z86.59	
	Cardio IQ KIF6 Genotype (Quest Diagnostics)	81479	E78.0-E78.9, R79.9, Z82.49	
	Opioid Receptor, mu OPRM1 Genotype, 1 Variant (ARUP Laboratories)	81479	G89.0-G89.4	
	SLCO1B1, 1 Variant (ARUP Laboratories)	81328	E78.00-E78.5, G71.14, R79.9,	

			T46.6X1A-T46.6X6S, Z82.49	
	TYMS Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81479	C00.0-C96.9, D00.0-D49.9	

OTHER RELATED POLICIES

This policy document provides coverage for tests that determine the dosage of or the selection of a specific drug based on pharmacogenetic testing. For other related testing, please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for coverage criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hematologic Conditions (non-cancerous)*** for coverage criteria related to diagnostic testing for non-cancerous genetic blood disorders.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for cystic fibrosis, and related therapies.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to *MTHFR* testing.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to pharmacogenetic testing that are not specifically discussed in this or other specific policies.

COVERAGE CRITERIA

PHARMACOGENETIC PANEL TESTS

I. The use of pharmacogenetic testing panels (81225, 81226, 81227, 81230,81231,81232, 81249, 81291, 81240, 81241, 81291,81479, 81404, 81408,

0029U, 0030U, 0173U, 0345U, 0347U, 0348U, 0349U, 0350U) is considered **investigational** for all indications.

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PHARMACOGENETIC SINGLE GENE TESTS

CYP2C9 Variant Analysis

I. *CYP2C9* variant analysis (81227) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for treatment with siponimod* (Mayzent®).

II. *CYP2C9* variant analysis (81227,) for the purpose of managing the administration and dosing of warfarin is considered **investigational**.

III. *CYP2C9* variant analysis (81227) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals diagnosed with multiple sclerosis

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CYP2C19 Variant Analysis

I. *CYP2C19* variant analysis (81225, 81479) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for or is currently undergoing treatment with clopidogrel (Plavix®), **AND**

   B. The member has all of the following:

      1. Will be undergoing percutaneous coronary intervention (PCI), **AND**

      2. Has acute coronary syndromes (ACS), **AND**

3. Is at high risk for poor outcomes (e.g., urgent PCI for an ACS event, elective PCI for unprotected left main disease or last patent coronary artery)

II. *CYP2C19* variant analysis (81225, 81479) to determine drug metabolizer status is considered **investigational** for all other indications.

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CYP2D6 Variant Analysis

I. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member has Gaucher disease and is being considered for treatment with eliglustat (Cerdelga™), **OR**

   B. The member has Huntington disease and is being considered for treatment with tetrabenazine (Xenazine®) in a dosage greater than 50 mg per day, **OR**

   C. The member is being considered for treatment with codeine.

II. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer is considered **investigational**.

III. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) for the purpose of managing the administration and dosing of tramadol is considered **investigational**.

IV. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status is considered **investigational** for all other indications.

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CYP4F2 Variant Analysis

I. *CYP4F2* variant analysis (81479) for the purpose of managing the administration and dosing of warfarin is considered **investigational**.

II. *CYP4F2* variant analysis (81479) to determine drug metabolizer status is considered **investigational** for all other indications.

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DPYD Variant Analysis

I. *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member being considered for treatment with any 5-FU containing therapy* (e.g., Fluorouracil®, Xeloda®).

II. *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals diagnosed with colorectal, breast, and aerodigestive tract tumors

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*HLA-B*15:02* Variant Analysis

I. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for treatment with any carbamazepine containing therapy* (e.g., Tegretol®, Carbatrol®), **OR**

   B. The member is being considered for treatment with phenytoin** (e.g., Dilantin®, Phenytek®).

II. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder

**Commonly prescribed for treatment of neonatal seizures

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*HLA-B*15:02* and *HLA-A*31:01* Variant Analysis

I. *HLA-B*15:02* and *HLA-A*31:01* variant analysis (81381, 81374) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for treatment with any carbamazepine containing therapy* (e.g., Tegretol®, Carbatrol®).

II. *HLA-B*15:02* and *HLA-A*31:01* variant analysis (81381, 81374) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder

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*HLA-B*57:01* Variant Analysis

I. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for treatment with abacavir* (Ziagen®).

II. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals with HIV

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*HLA-B*58:01* Variant Analysis

I. *HLA-B*58:01* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is being considered for treatment with any allopurinol* (e.g. Aloprim® and Zyloprim®) containing therapy.

II. *HLA-B*58:01* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for individuals with hyperuricemia, gout, or kidney stones

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TPMT and *NUDT15* Variant Analysis

I. *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is beginning therapy with azathioprine* (e.g. Imuran and Azasan), mercaptopurine* (e.g. Purinethol® and Purixan®), or thioguanine* (e.g. Tabloid®), **OR**

B. The member is on thiopurine therapy and has had abnormal complete blood count results that do not respond to dose reduction.

II. *TPMT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for patients with autoimmune disorders (e.g. inflammatory bowel disease, Crohn's disease, rheumatoid arthritis) and for treatment of hematologic malignancies (e.g., leukemia and lymphoma)

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UGT1A1 Variant Analysis

I. *UGT1A1* variant analysis (81350) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is beginning irinotecan therapy (e.g., Onivyde®, Camptosar®) for elevated serum bilirubin or Gilbert syndrome or for cancer treatment (example: colon cancer), **OR**

B. The member is beginning therapy with atazanavir* (e.g. Reyataz®).

II. *UGT1A1* variant analysis (81350) to determine drug metabolizer status is considered **investigational** for all other indications.

*Commonly prescribed for patients with HIV

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VKORC1 Variant Analysis

I. *VKORC1* variant analysis (81355, 81479) for the purpose of managing the administration and dosing of warfarin is considered **investigational**.

II. *VKORC1* variant analysis (81355, 81479) to determine drug metabolizer status is considered **investigational** for all other indications.

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Other Single Gene Variant Analysis

I. Variant analysis of all other genes for drug metabolizer status is considered **investigational**, including but not limited to:

A. *COMT* (0032U)
B. *CYP1A2* (0031U)
C. *KIF6* (81479)
D. *OPRM1* (81479)
E. *SLCO1B1* (81328)
F. *TYMS* (81479)

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BACKGROUND AND RATIONALE

Pharmacogenetic Panel Testing

There are no professional society guidelines that address the clinical utility of large pharmacogenetic testing panels for the general population or for a specific population. The US Food and Drug Administration (FDA) also does not address the usage of pharmacogenetic panels.

There are several recent studies that investigated the usefulness of pharmacogenetic panels [for example, Greden et al (2019), Perlis et al (2020), Shan et al (2019), Tiwari et al (2022), Oslin (2022)]. However, these studies had different study designs and often conflicting results regarding clinical utility, making it difficult to determine whether there is clinical utility for a given patient with a given indication for a given panel.

However, there are several single gene pharmacogenetic tests where the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the FDA describe the clinical utility of the test results for a given gene/drug/testing indication. These are described below.

CYP2C9 Variant Analysis

US Food and Drug Administration (FDA)

The FDA approved siponimod (Mayzent) in March 2019 for the treatment of relapsing forms of multiple sclerosis in adults. This approval was based on a double-blind, randomized, phase 3 study and the *CYP2C9* genotype has an impact on the metabolism of siponimod. As part of the FDA approval, *CYP2C9* genotype determination should be assessed prior to administration. Dosing regimen is dependent on genotype *CYP2C9*, specifically *1/*3 or *2/*3 genotype while the presence of *CYP2C9**3/*3 is contraindicated.

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2017) updated guidelines for pharmacogenetics-guided warfarin dosing what states that "Although there is substantial evidence associating *CYP2C9* and *VKORC1* variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2014) published a guideline on phenytoin prescribing based on HLA-B*1502 and *CYP2C9* genotype which recommends against prescribing phenytoin in individuals who are HLA-B*1502 carriers

(strong recommendation) and recommends *considering* adjusting starting dose in individuals who are HLA-B*1502 non-carriers who have *CYP2C9* poor metabolizer genotype (strong recommendation) or *CYP2C9* intermediate metabolizer genotype (moderate recommendation).

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2020) published a therapeutic recommendations for NSAIDs based on *CYP2C9* genotype stating that, “The quality of evidence linking genotype to NSAID therapeutic response and adverse events was graded as weak in most cases.”

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics (2008) policy statement on pharmacogenetic testing concluded: "There is insufficient evidence, at this time, to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients."

CYP2C19 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (Lee et al, 2020) updated guideline on antiplatelet therapy dosage recommends the following:

> “As the FDA boxed warning does not require genetic testing to initiate clopidogrel therapy, if a patient’s genotype is not known, the decision to perform *CYP2C19* testing is at the discretion of the treating clinician. Although clinical guidelines from the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology recommend against routine *CYP2C19* testing, these groups have noted that use of *CYP2C19* testing to guide selection of prasugrel or ticagrelor in *CYP2C19* IMs and PMs may be considered in select patients undergoing PCI and with ACS at high risk for poor outcomes (e.g., urgent PCI for an ACS event, elective PCI for unprotected left main disease or last patent coronary artery).31–33 Recent meta- analyses have demonstrated that *CYP2C19* genotype- guided therapy could identify patients undergoing PCI who benefit most from alternative antiplatelet therapy.”

The Clinical Pharmacogenetics Implementation Consortium (2016) updated guideline on Voriconazole dosage based on *CYP2C19* genotypes stating that, “Clinical studies have not consistently demonstrated an association between *CYP2C19* genotype and adverse

reactions. However, as individual patients who are poor metabolizers may have elevated levels leading to toxicity, the use of another antifungal agent is recommended."

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2015) conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy and provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on *CYP2D6* and *CYP2C19* genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2016) also conducted a systematic literature review of the influence of *CYP2D6* and *CYP2C19* genotype on the dosing of tricyclic antidepressants and provided dosing recommendations for tricyclic antidepressants based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers.

American College of Cardiology Foundation and American Heart Association

The American College of Cardiology Foundation/American Heart Association ACS guidelines (2012) noted that genetic testing for *CYP2C19* loss-of-function alleles may be considered on a case-by-case basis, especially for patients who experience recurrent ACS events despite ongoing therapy with clopidogrel. In addition, the committee recommended that genotyping might be considered if results of testing may alter management, which they suggest until better clinical evidence exists to provide a more scientifically derived recommendation.

CYP2D6 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2018) published a guideline for tamoxifen prescribing based on *CYP2D6* genotype/metabolic phenotype. The guideline acknowledged that there was moderate evidence that *CYP2D6* poor metabolizers have a higher risk of breast cancer recurrence or worse event-free survival. However, the evidence was considered weak regarding an association between *CYP2D6* metabolizer groups and clinical outcome.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2014) published a guideline for codeine therapy based on *CYP2D6* genotype/metabolic phenotype. The guideline states that “the association of *CYP2D6* metabolizer phenotype with formation of morphine from codeine is well defined” and recommends “using alternative analgesics to codeine in patients who are *CYP2D6* poor or ultrarapid metabolizers.

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2015) conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy and provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on *CYP2D6* and *CYP2C19* genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2016) also conducted a systematic literature review of the influence of *CYP2D6* and *CYP2C19* genotype on the dosing of tricyclic antidepressants and provided dosing recommendations for tricyclic antidepressants based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers.

National Comprehensive Cancer Network (NCCN)

NCCN breast cancer guidelines (2.2021) recommend against *CYP2D6* genotype testing for women being considered for tamoxifen treatment.

American Society of Clinical Oncology (ASCO)

The guidelines from the American Society of Clinical Oncology (2016) on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer stated that "The clinician should not use *CYP2D6* polymorphisms to guide adjuvant endocrine therapy selection and at this point, data do not support the use of *CYP2D6* testing to select patients who may or may not benefit from tamoxifen therapy."

DPYD Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (2017) updated guideline on *DYPD* and Fluoropyrimidine dosing noted that genetic testing for *DPYD* may include "resequencing of the complete coding regions" or may be confined to analysis of particular risk variants which may affect 5-fluorouracil toxicity. The guideline further noted that, while other genes (*TYMS*, *MTHFR*) may be tested for variants, the clinical utility of such tests is yet unproven. The guideline further stated that in patients who have undergone genetic testing and who are known carriers of a *DPYD* risk variant, it is recommended to adjust the dosage of 5-fluorouracil-based treatments, or exclude them, depending on the patient's level of *DPYD* activity.

National Comprehensive Cancer Network

NCCN colon cancer guidelines (2.2021) do not recommend use of area under the curve guidance for 5-fluorouracil (5-FU) dosing. NCCN recognizes that pretreatment *DPYD* testing has the potential to identify the 1-2% of individuals with truncating alleles that may have an increased risk of severe toxicity, but does not currently recommend universal pretreatment genotyping of *DPYD* or *TYMS* variants in patients with colon cancers.

HLA-B*15:02 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) updated the guideline on HLA-B genotyping and carbamazepine dosing (2017) which reaffirmed the original recommendation (2013) and stated the following: "If a patient is carbamazepine-naive…and HLA-B*15:02 positive, carbamazepine…should be avoided."

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2014) published a guideline on phenytoin prescribing based on HLA-B*1502 and *CYP2C9* genotype which states: "If a patient is phenytoin-naive and HLA-B*15:02 positive, the patient is at an increased risk of SJS/TEN [Stevens-Johnson syndrome and toxic epidermal necrolysis] and the recommendation is to consider using an anticonvulsant other than phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks."

HLA-B*57:01 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetic Implementation Consortium (CPIC) updated the guideline on HLA-B genotyping and abacavir dosing (2014) and reaffirmed the CPIC 2012

guidelines which recommend that “HLA-B*5701 screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy.”

HLA-B*58:01 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (2016) revalidated the original 2013 recommendation that, “given the high specificity for allopurinol-induced SCAR, allopurinol should not be prescribed to patients who have tested positive for HLA-B*58:01.”

TPMT and NUDT15 Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines on acute lymphoblastic leukemia (1.2022) recommend consideration of *TPMT* gene polymorphisms in patients receiving 6-MP (mercaptopurine), especially in patients who develop severe neutropenia after starting 6-MP. NCCN recommends consideration of *TPMT* and *NUDT15* genotyping for all patients starting 6-MP. Finally they state that quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism.

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2018) published a guideline on thiopurine dosing based on *TPMT* and *NUDT15* genotypes, with recommendations for starting doses of thiopurines based on an individual’s status as a normal, intermediate, or poor metabolizer. (page 14) Current Acute Lymphoblastic Leukemia NCCN Guidelines (1.2022) states that testing for *TPMT* polymorphisms is especially recommended for individuals who develop severe neutropenia (low white blood cell count) after beginning mercaptopurine (also called 6-MP).

UGT1A1 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium (CPIC) (2015) guidelines for *UGT1A1* genotypes and atazanavir prescribing recommended that poor metabolizers consider an alternative agent particularly where jaundice would be of concern to the patient. “A *UGT1A1* genotype is most helpful if available before atazanavir is prescribed” and that “individuals who are homozygous for *UGT1A1*28* or *UGT1A1*6* are very likely to have Gilbert syndrome. Knowing an individual’s *UGT1A1* genotype prior to prescribing may have implications for selection and dosing for drugs known to be *UGT1A1* substrates or inhibitors, such as irinotecan and nilotinib.”

VKORC1 Variant Analysis

Clinical Pharmacogenetic Implementation Consortium (CPIC)

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2017) updated guidelines for pharmacogenetics-guided warfarin dosing what states that "Although there is substantial evidence associating *CYP2C9* and *VKORC1* variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."

Other Single Gene Variant Analysis

Clinical Pharmacogenomics Implementation Consortium (CPIC)

The Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium (CPIC) (2014) updated guidelines for *SLCO1B* genotypes and simvastatin-induced myopathy recommended prescribing a lower dose or considering an alternative statin and considering routine creatinine kinase surveillance in patients with *SLCO1B* genotypes consistent with intermediate or low statin metabolism.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2021) published a guideline for codeine therapy based on *OPRM1* and *COMT* genotype/metabolic phenotype. The guideline states that "*OPRM1* variants inconsistently have been shown to alter postoperative dose requirements for some opioids. There is evidence for a small increase in postoperative morphine dose requirements (~ 10%) in some clinical studies in patients carrying at least one copy of the *OPRM1* rs1799971 G allele, although the alteration in morphine dose is so modest as to not be clinically actionable. There is also

insufficient evidence at this time to conclude altered analgesic response to other opioids in relation to rs1799971, or other *OPRM1* variants. For the most highly studied *COMT* variant, rs4680, there is no evidence to support an association of this variant with opioid adverse events, and there is mixed evidence for an association between *COMT* rs4680 genotype and analgesia or opioid dose requirements. For all other *COMT* variants, there is mixed evidence for an association between *COMT* genotype and analgesia, opioid dose requirements, or adverse events."

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