CONTENT RELEASE NOTIFICATION
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IMPLEMENTATION OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) CPIC GUIDELINE

We have updated **genotype-guided recommendations** (pharmacogenetic interpretation) for the following drug-gene associations:

Category	Therapeutic Class	Gene	Drug(s)	Update
Pain	NSAIDs	CYP2C9	**Celecoxib** (Celebrex®)	*Updated guidance for celecoxib implements the new CPIC guideline.* *Guidance will be provided for the following indications: osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, primary dysmenorrhea, and acute migraine. Guidance for the co-formulation with amlodipine for osteoarthritis and hypertension is also included.* *Pediatric guidance will also be updated.*
Pain	NSAIDs	CYP2C9	**Flurbiprofen** (Ansaid®)	*Updated guidance for flurbiprofen implements the new CPIC guideline.* *Guidance will be provided for the following indications: osteoarthritis and rheumatoid arthritis.*
Pain	NSAIDs	CYP2C9	**Ibuprofen** (Advil®, Motrin®)	*Updated guidance for ibuprofen implements the new CPIC guideline.* *Guidance will be provided for the following indications: pain, dysmenorrhea, rheumatoid arthritis, osteoarthritis, fever, and other anti-inflammatory uses.* *Pediatric guidance will be available.*
Pain	NSAIDs	CYP2C9	**Meloxicam** (Mobic®)	*Updated guidance for meloxicam implements the new CPIC guideline.* *Guidance will be provided for the following indications: osteoarthritis and rheumatoid arthritis.* *Pediatric guidance will be available.*
Pain	NSAIDs	CYP2C9	**Piroxicam** (Feldene®)	*Updated guidance for piroxicam implements the new CPIC guideline.* *Guidance will be provided for the following indications: osteoarthritis and rheumatoid arthritis.*

We have updated the decision support content for several drugs that documents their pathway of elimination and sensitivity to drug-drug interactions. Pharmacogenetic testing is not recommended or needed prior to prescribing the following medications. To avoid any confusion, the following drugs will be presented on the report as a "non-PGx drug." This change does not affect the previous recommendations provided based on genotype results. The full list of publications reviewed for this drug is available upon request. These include:

Category	Therapeutic Class	Drug(s)	Update (highlighted in yellow)
Pain	NSAIDs	**Diclofenac** (Voltaren®)	***Pharmacogenetic guidance**: Diclofenac is extensively metabolized by hydroxylation and direct glucuronidation. About 50% of diclofenac is eliminated as a 4-hydroxymetabolite, a reaction mediated by CYP2C9. Other CYP enzymes including CYP2C8, CYP2C19 and CYP3A4 are also involved in the formation of a 5-hydroxymetabolite. A substantial portion of the drug is also directly glucuronidated by UGT2B7 and UGT2B4. Genetic polymorphisms of CYP2C9 have not been found to affect the response to diclofenac. No dosing recommendations or genetically guided drug selection are recommended. **Polypharmacy Guidance**: Co-administration of diclofenac with CYP2C9 inhibitors may enhance the drug exposure and toxicity of whereas co-administration with CYP2C9 inducers may lead to compromised efficacy of diclofenac. A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors or inducers.* *This change does not affect the previous recommendations provided based on CYP2C9 results.*
Pain	NSAIDs	**Indomethacin** (Indocin®)	***Pharmacogenetic Guidance**: Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethyl indomethacin, a reaction catalyzed by CYP2C9. Genetic polymorphisms of CYP2C9 have not been found to affect the response to indomethacin. No genetically guided drug selection or dosing recommendations are available.* *This change does not affect the previous recommendations provided based on CYP2C9 results.*

NEW DRUGS WITH GENOTYPE-GUIDED RECOMMENDATIONS

We have added **genotype-guided recommendations** (pharmacogenetic interpretation) for the following drug-gene associations:

Category	Therapeutic Class	Gene(s)	Drug(s)	Use
Anticancer Agents	Topoisomerase Inhibitors	UGT1A1	**Sacituzumab Govitecan-hziy** (Trodelvy®)	*Sacituzumab govitecan-hziy is used for the treatment of metastatic triple negative breast cancer who received at least two prior therapies for metastatic disease.*
Infections	Antimalarials	G6PD	**Hydroxychloroquine** (Plaquenil®)	*Hydroxychloroquine is used for the treatment of uncomplicated malaria or prophylaxis of malaria, chronic discoid lupus erythematosus and systemic lupus erythematosus and acute and chronic rheumatoid arthritis.*

UPDATED DRUGS WITH GENOTYPE-GUIDED RECOMMENDATIONS

We have updated **genotype-guided recommendations** (pharmacogenetic interpretation) for the following drug-gene associations:

Category	Therapeutic Class	Gene	Drug(s)	Update (highlighted in yellow)
Cardiovascular	Angiotensin II Receptor Antagonists	CYP2C9	**Losartan** (Cozaar®, Hyzaar®)	**CYP2C9 Intermediate Metabolizer* | Informational** *Losartan is metabolized to its active metabolite by CYP2C9 and CYP3A4. The patient's genotype predicts a non-clinically significant change in losartan's active metabolite exposure. Losartan can be prescribed at label-recommended dosage and administration with additional monitoring of the patient's response.* *Note: Includes intermediate metabolizers who carry 1 copy of a normal function allele and 1 copy of a decreased function allele, example = CYP2C9*1/*2.
Cardiovascular	Diuretics	CYP2C9	**Torsemide** (Demadex®)	**CYP2C9 Poor Metabolizer** *The patient's genotype predicts a reduced CYP2C9 function, which may result in reduced torsemide clearance and increased torsemide plasma concentrations. There is insufficient data documenting whether such changes are clinically significant. Torsemide can be prescribed at label-recommended dosage and administration with additional monitoring of the patient's response.*

Category	Therapeutic Class	Gene	Drug(s)	Update (highlighted in yellow)
Cardiovascular	Statins	CYP2C9	**Fluvastatin** (Lescol®)	**CYP2C9 Intermediate Metabolizer or CYP2C9 Poor Metabolizer** *Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myopathy/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects, and adjust dose based on tolerability and response. Other adverse events and predisposing factors include advanced age (≥65), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female gender.*
Gastrointestinal	Antiemetics	CYP2C9	**Dronabinol** (Marinol®)	**CYP2C9 Intermediate Metabolizer | Warning** *The patient's genotype predicts a reduced CYP2C9 metabolic activity. Increased drug exposure may occur in this patient leading to prolonged sedation. Consider standard label-recommended dosing and close monitoring for adverse effects.*
Infections	Antimalarials	G6PD	**Quinine** (Qualaquin®)	*The latest FDA label was updated and removed the G6PD contraindication.* **G6PD Decreased Function | Warning** *Male: the patient carries one deficient G6PD allele (class II-III). Female: the patient carries two deficient G6PD alleles (class II-III). The patient has a G6PD enzyme deficiency (<10-60% of normal enzyme activity). The patient is at risk of hemolytic anemia in response to quinine treatment. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.* **G6PD Poor Function | Warning** *Male: the patient carries one deficient G6PD allele (class I). Female: the patient carries two deficient G6PD alleles (class I). The patient has a severe G6PD enzyme deficiency (<10% of normal enzyme activity). The patient is at risk of hemolytic anemia in response to quinine treatment. Closely observe patients with G6PD deficiency for signs of hemolytic anemia. This genotype is also associated with chronic nonspherocytic hemolytic anemia (CNSHA) in absence of any medication.* **G6PD Normal or Decreased Function | Warning** *Female: the patient carries one nondeficient G6PD allele (class IV) and one deficient G6PD allele (class I-III variants). The patient may or may not have a G6PD enzyme deficiency and the patient's risk of hemolytic anemia in response to quinine treatment cannot be predicted accurately. To ascertain that G6PD status is normal, enzyme activity must be measured. Closely observe patients with G6PD deficiency for signs of acute hemolytic anemia.*

UPDATED SHORT CDS RECOMMENDATIONS

We have updated the **short CDS recommendations** for the following drug-gene associations (updates highlighted in yellow):

Drug(s)	Associated Genotype or Phenotype	Update (highlighted in yellow)
Dronabinol (Marinol®)	CYP2C9 Intermediate Metabolizer	*Test results indicate an increased risk of adverse effects. Monitor closely for adverse effects.*
Quinine (Qualaquin®)	G6PD Decreased Function and G6PD Poor Function	*Test results indicate an increased risk of acute hemolytic anemia. Consider standard prescribing practices and carefully monitor patients.*
Tramadol (Ultram®)	CYP2D6 Ultra-Rapid Metabolizer	*Test results indicate an increased risk of adverse effects. Consider an alternative medication or consider a 60% dose reduction and monitor carefully.*

NEW AND UPDATED GENE MONOGRAPHS

To accommodate the new drug-gene pairs for the release, we have added or updated the monographs for the following genes:

Gene(s)	Update (Highlighted in Yellow)
CYP2C9	**Clinical Utility** *The cytochrome P450 2C9 (CYP2C9) is involved in the metabolism of 15% of clinically important medications. This enzyme is highly polymorphic: to date, 60 alleles have been identified. The CYP2C9 assay identifies some common variants that are associated with variability in CYP2C9 enzyme activity, which has important pharmacological and toxicological implications for anticonvulsants, anticoagulants, and certain antidiabetics.* **Assay Interpretation** *CYP2C9 enzyme activity defines a normal or abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2C9 isoforms that functionally are fully active, partially active, or inactive. The CYP2C9 *1 (wild-type) and CYP2C9*9 alleles encode functionally active enzymes. A number of CYP2C9 alleles such as *2, *4, *5, *8, *11, *12 and *31 encode partially active enzymes and are classified as decreased function alleles. Other CYP2C9 alleles such as *3, *6, *13, *15 and *25 are considered no-function alleles encoding inactive enzymes. Many other alleles with an unknown/uncertain functional effect have also been identified and can be revealed from testing.* *…* *The genotype-phenotype relationship is established based on the allele's function. Individuals with two normal function alleles are considered normal (extensive) metabolizers (AS = 2.0). Individuals with one normal function allele with one decreased function allele are considered intermediate metabolizers (AS = 1.5). Individuals with one normal function allele and one no-function allele or two decreased function alleles are considered intermediate metabolizers (AS = 1.0). Individuals with one decreased function allele and one no*

	function allele are considered poor metabolizers (AS = 0.5). Individuals with two no-function alleles are considered poor metabolizers (AS = 0). The phenotype of carriers of one or two CYP2C9 unknown/uncertain function alleles cannot be predicted accurately (unknown phenotype). ***The reference range for CYP2C9 metabolic status is CYP2C9 *1/*1 genotype, which is consistent with an AS of 2.0 and a normal metabolizer.***
CYP2C19	**Assay Interpretation** *CYP2C19 enzyme activity defines a normal or abnormal (intermediate, poor, rapid or ultra-rapid) metabolizer status for a given individual. Several variant alleles have been identified and result in different isoforms of the CYP2C19 enzyme that functionally exhibit normal function, reduction function, no function or increased function. The CYP2C19*1 allele is considered wild-type/reference allele and CYP2C19 *11, *13 and *18 encodes a functionally active enzyme (normal function allele). The alleles *2, *3 *4-*8, *22, *24, and *35-*37 encode an inactive enzyme and are referred to as no function alleles while the *9, *10, *16,*19, *25 and *26 alleles are classified as reduced function alleles. The CYP2C19*17 is an increased function allele.* *A new joint statement by the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), provides a two-tiered classification of CYP2C19 alleles for inclusion during clinical testing. Tier 1 alleles that should be included in all clinical tests, include CYP2C19 *2, *3 and *17. Tier 2 alleles which may also be included in clinical tests include CYP2C19 *4A, *4B, *5, *6, *7, *8, *9, *10 and *35.* … ***The reference range for CYP2C19 metabolic status is CYP2C19 *1/*1 genotype, which is consistent with a normal metabolizer.***

UPDATED GENOTYPE-TO-PHENOTYPE RELATIONSHIP

We have updated the CYP2C9 genotype-to-phenotype assignment rules according to the latest recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) as described in the newest NSAID guideline.[1] The new phenotype assignment uses the concept of an activity score. Each CYP2C9 allele is assigned a score value that describes the extent of change in the enzyme function. A normal function allele is given an activity value of 1.0, decreased function allele is given an activity value of 0.5 and no-function allele is given an activity value of 0. A diplotype is assigned an activity score which is the sum of the score values of its constituent alleles. The activity score is used to predict a likely phenotype

Compared to the previous phenotype assignment rules described in Table 1 of the CPIC phenytoin guideline.[2] The new assignment rules include the following change:

- Individuals with two copies of CYP2C9 decreased function alleles are now considered intermediate metabolizers with an activity score of 1.0, not poor metabolizers.

The following table describes the updated CYP2C9 phenotype definitions.

CYP2C9 Phenotype	Definition	Activity Score Definition	CYP2C9 Diplotype Examples
Normal Metabolizer	*2 copies of normal function alleles*	*2.0*	**1/*1, *1/*9, *9/*9*
Intermediate Metabolizer	*1 copy of a normal function allele and 1 copy of a decreased function allele*	*1.5*	**1/*2, *1/*5, *1/*8*
Intermediate Metabolizer	*1 copy of a normal function allele and 1 copy of a no function allele* *OR* *2 copies of decreased function alleles*	*1.0*	**1/*3, *2/*2, *3/*9*
Poor Metabolizer	*1 copy of a decreased function allele and 1 copy of a no function allele*	*0.5*	**2/*3, *3/*8, *5/*6*
Poor Metabolizer	*2 copies of no function alleles*	*0*	**3/*3, *3/*15, *6/*6*

[1] Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. 2020 Mar 19.

[2] Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT; Clinical Pharmacogenetics Implementation Consortium. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Version 2. Clin Pharmacol Ther. 2014 Nov;96(5):542-8.

The following table illustrates the updates for CYP2C9.

Clinical Functional Status	Activity Value	Alleles
Normal Function	*1.0*	**1, *9*
Decreased Function	*0.5*	**2, *4, *5, *8, *11, *12, *14, *16, *23, *26, *28, *29, *30, *31, *37, *38, *44, *46, *50, *55, *61*
No Function	*0*	**3, *6, *13, *15, *24, *25, *33, *35, *39, *42, *43, *45, *52*
Uncertain Function	*N/A*	**7, *10, *17, *18, *19, *20, *21, *22, *27, *32, *34, *36, *40, *41, *47, *48, *49, *51, *53, *54, *56, *58, *59, *60*
Unknown Function	*N/A*	**57*

UPDATED PHENOTYPE TERMS

We have updated the phenotypes for the following gene(s):

Gene(s)	Update
CYP2C9	*The reporting label of the phenotype will be updated from "Possible Intermediate Metabolizer" to "Intermediate Metabolizer".* *The reporting label of the phenotype will be updated from "Possible Poor Metabolizer" to "Poor Metabolizer"*
CYP2D6	*The reporting label of the phenotype will be updated from "Possible Intermediate or Ultra-Rapid Metabolizer" to "Normal or Intermediate or Ultra-Rapid Metabolizer"*
NUDT15	*The reporting label of the phenotype will be updated from "Possible Intermediate Metabolizer" to "Intermediate Metabolizer".*
TPMT	*The reporting label of the phenotype will be updated from "Possible Intermediate Metabolizer" to "Intermediate Metabolizer".*

NEW PRE-TEST ALERT

We have added the following pre-test alerts:

Category	Therapeutic Class	Gene(s)	Drug(s)
Anticancer Agents	Topoisomerase Inhibitors	UGT1A1	**Sacituzumab Govitecan-hziy** (Trodelvy®)
Infections	Antimalarials	G6PD	**Hydroxychloroquine** (Plaquenil®)
Pain	NSAIDs	CYP2C9	**Meloxicam** (Mobic®)
Pain	NSAIDs	CYP2C9	**Piroxicam** (Feldene®)

UPDATED PRE-TEST ALERT

We have updated the following pre-test alerts:

Category	Therapeutic Class	Gene(s)	Drug(s)	Update
Infections	Antimalarials	G6PD	**Chloroquine**	*The following field will be updated: issue.*
Pain	NSAIDs	CYP2C9	**Celecoxib** (Celebrex®)	*The following fields will be updated: issue, prevalence, and confounding factors.*
Pain	NSAIDs	CYP2C9	**Flurbiprofen** (Ansaid®)	*The following fields will be updated: issue, prevalence, and confounding factors.*

INTERNATIONAL CUSTOMER SPECIFIC CONTENT UPDATES

NEW DRUGS WITH GENOTYPE-GUIDED RECOMMENDATIONS

We have added **genotype-guided recommendations** (pharmacogenetic interpretation) for the following drug-gene associations:

Category	Therapeutic Class	Gene(s)	Drug(s)	Use
Pain	NSAIDs	CYP2C9	**Lornoxicam** (Xefo®)	*Lornoxicam is used for the short-term relief of acute mild to moderate pain, symptomatic relief of pain and inflammation in osteoarthritis and symptomatic relief of pain and inflammation of rheumatoid arthritis.*

Official symbols and names of genes included in this notification:

CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9

CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19

CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6

G6PD: Glucose-6-Phosphate Dehydrogenase

NUDT15: Nudix Hydrolase 15

TPMT: Thiopurine S-Methyltransferase

UGT1A1: UDP Glucuronosyltransferase Family 1 Member A1