

CONTENT RELEASE NOTIFICATION
EXPECTED RELEASE 11/04/2020 AT 5-6 PM PST

IMPLEMENTATION OF THE PROTON PUMP INHIBITORS (PPIS) CPIC GUIDELINE

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

Category	Therapeutic Class	Gene	Drug(s)	Update
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Dexlansoprazole (Dexilant®, Kapidex®)	<i>Updated guidance for dexlansoprazole implements the new CPIC guideline.</i>
				<i>Update guidance provides dose adjustments for CYP2C19 normal, intermediate, poor, and rapid metabolizers in certain therapy managements.</i> <i>Pediatric guidance is now available.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Esomeprazole (Nexium®)	<i>Guidance for esomeprazole implements the new CPIC guideline.</i>
				<i>No changes to the recommendation, the language of the recommendations have been harmonized.</i> <i>Pediatric guidance is now available.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Lansoprazole (Prevacid®)	<i>Updated guidance for lansoprazole implements the new CPIC guideline.</i>
				<i>Update guidance provides dose adjustments for CYP2C19 normal, intermediate, poor, and rapid metabolizers in certain therapy managements.</i> <i>Pediatric guidance is now available.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Omeprazole (Prilosec®)	<i>Updated guidance for omeprazole implements the new CPIC guideline.</i>
				<i>Update guidance provides dose adjustments for CYP2C19 normal, intermediate, poor, and rapid metabolizers in certain therapy managements.</i> <i>Pediatric guidance is now available.</i>

Category	Therapeutic Class	Gene	Drug(s)	Update
				<i>Updated guidance for pantoprazole implements the new CPIC guideline.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Pantoprazole (Protonix®)	<p><i>Update guidance provides dose adjustments for CYP2C19 normal, intermediate, poor, and rapid metabolizers in certain therapy managements.</i></p> <p><i>Pediatric guidance is now available.</i></p>
				<i>Guidance for rabeprazole implements the new CPIC guideline.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Rabeprazole (Aciphex®)	<p><i>No changes to the recommendation, the language of the recommendations have been harmonized.</i></p> <p><i>Pediatric guidance is now available.</i></p>

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
Infections	Antibiotics	G6PD	Silver Sulfadiazine (Silvadene®, SSD®, Thermazene®)	<i>Silver sulfadiazine is used for the prevention and treatment of wound sepsis in patients with second- and third-degree burns.</i>
Infections	Antifungals	DPYD	Flucytosine (Ancobon®)	<i>Flucytosine is used for the treatment of serious infections cause by strains of Candida and/or Cryptococcus.</i>

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)
				<p>Slightly Increased Exposure to Risperidone (CYP2D6 Intermediate Metabolizer) Informational</p> <p><i>The patient's genotype may be associated with a slightly increased risperidone exposure and decreased active metabolite (paliperidone) exposure following standard dosing. Consider prescribing risperidone according to standard label-recommended dosing and administration. Dosing is individualized based on the patient's tolerability and clinical response.</i></p>
Psychiatry	Antipsychotics	CYP2D6	Risperidone (Risperdal®)	<p>Increased Exposure to Risperidone (CYP2D6 Poor Metabolizer) Warning</p> <p><i>The patient's genotype is associated with an increased risperidone exposure and decreased active metabolite (paliperidone) exposure following standard dosing. Consider an initial 25-35% dose reduction. If CNS adverse effects occur, consider a further dose reduction to 50% of standard dose. Dosing is individualized based on the patient's tolerability and clinical response.</i></p>
				<p>Reduced Exposure to Risperidone (CYP2D6 Ultra-Rapid Metabolizer) Critical</p> <p><i>The patient's genotype is associated with a decreased risperidone exposure and increased active metabolite (paliperidone) exposure following standard dosing. Consider an alternative medication.</i></p>

UPDATED DRUGS WITHOUT GENOTYPE-GUIDED RECOMMENDATIONS

We have updated the **interpretation** for several drugs that documents their pathway of elimination and sensitivity to drug-drug interactions. These include:

Category	Therapeutic Class	Drug(s)	Update (highlighted in yellow)
Cardiovascular	Statins	Fluvastatin (Lescol®)	<p>Pharmacogenetic guidance: Fluvastatin is partially metabolized by CYP2C9 and also transported by ABCG2 and SLCO1B1. Genetic polymorphisms of the SLCO1B1 gene have not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are recommended...</p>

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)
Dexlansoprazole (Dexilant®, Kapidex®)	CYP2C19 Normal Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Intermediate Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Poor Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Ultra-Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase.</i>
Lansoprazole (Prevacid®)	CYP2C19 Normal Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Intermediate Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Poor Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Ultra-Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase.</i>
Omeprazole (Prilosec®)	CYP2C19 Normal Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>

	CYP2C19 Intermediate Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Poor Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Ultra-Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase.</i>
	CYP2C19 Normal Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
Pantoprazole (Protonix®)	CYP2C19 Intermediate Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Poor Metabolizer	<i>Test results do not indicate an increased risk of adverse effects. Monitor for adverse effects and consider a dose decrease in the setting of chronic PPI therapy.</i>
	CYP2C19 Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase in certain conditions.</i>
	CYP2C19 Ultra-Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase.</i>
Risperidone (Risperdal®)	CYP2D6 Poor Metabolizer	<i>Test results indicate an increased risk of adverse effects. Consider an initial dose reduction with monitoring for adverse effects.</i>
	CYP2D6 Ultra-Rapid Metabolizer	<i>Test results indicate an increased risk of therapeutic failure. Consider an alternative medication.</i>

UPDATED PRE-TEST ALERT

We have updated the following pre-test alerts:

Category	Therapeutic Class	Gene(s)	Drug(s)	Update
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Lansoprazole (Prevacid®)	<i>The following fields will be updated: Prevalence, Clinical Effect and Confounding Factors.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Omeprazole (Prilosec®)	<i>The following fields will be updated: Prevalence, Clinical Effect and Confounding Factors.</i>
Gastrointestinal	Proton Pump Inhibitors	CYP2C19	Pantoprazole (Protonix®)	<i>The following fields will be updated: Prevalence, Clinical Effect and Confounding Factors.</i>
Psychiatry	Antipsychotics	CYP2D6	Risperidone ¹ (Risperdal®)	<i>The following fields will be updated: Issue, Prevalence and Clinical Effect.</i>

UPDATED HAPLOTYPES

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

Gene(s)	Update
CYP2D6	<i>The CYP2D6 *96 haplotype is now supported. The functionality of this haplotype is classified as no-function.</i>
CYP3A4	<i>CYP3A4*1B will be deprecated and no longer supported. The presence of the *1B allele will now result in a *1 haplotype call.</i>

¹ Note: Risperidone was previously removed from pre-test alerts during the October 3, 2019 Content Release but it is now re-released as a pre-test alert to reflect the latest DPWG guideline ([Link](#)).

CORRECTED ISSUES

We have corrected the following **issues** for the following drug-gene associations (correction highlighted in yellow):

Drug(s)	Gene	Associated Genotype or Phenotype	Issue	Correction	Date Effective
Amitriptyline (Elavil®)	CYP2D6	Intermediate Metabolizer (Activity Score = 1.0)	The dosing guidance for CYP2D6 intermediate metabolizer with an activity score of 1.0 said “CYP2D6 intermediate or normal metabolizer”.	Corrected the phrase to “CYP2D6 intermediate metabolizer”.	July 23, 2020
Clomipramine (Anafranil®)	CYP2D6	Intermediate Metabolizer (Activity Score = 1.0)	The dosing guidance for CYP2D6 intermediate metabolizer with an activity score of 1.0 said “CYP2D6 intermediate or normal metabolizer”.	Corrected the phrase to “CYP2D6 intermediate metabolizer”.	July 23, 2020
Doxepin (Silenor®)	CYP2D6	Intermediate Metabolizer (Activity Score = 1.0)	The dosing guidance for CYP2D6 intermediate metabolizer with an activity score of 1.0 said “CYP2D6 intermediate or normal metabolizer”.	Corrected the phrase to “CYP2D6 intermediate metabolizer”.	July 23, 2020
Imipramine (Tofranil®)	CYP2D6	Intermediate Metabolizer (Activity Score = 1.0)	The dosing guidance for CYP2D6 intermediate metabolizer with an activity score of 1.0 said “CYP2D6 intermediate or normal metabolizer”.	Corrected the phrase to “CYP2D6 intermediate metabolizer”.	July 23, 2020
Siponimod (Mayzent®)	CYP2C9	Poor Metabolizer (Activity Score = 0.5)	The dosing guidance for CYP2C9 poor metabolizer with an activity score of 0.5 said “The FDA label recommendation for CYP2C9 *1/*3 genotype was applied to this patient.” The recommendation itself was correct. The preceding information listed the incorrect diplotype.	Corrected the phrase to “The FDA label recommendation for CYP2C9 *2/*3 genotype was applied to this patient.”	September 23, 2020
Trimipramine (Surmontil®)	CYP2D6	Intermediate Metabolizer (Activity Score = 1.0)	The dosing guidance for CYP2D6 intermediate metabolizer with an activity score of 1.0 said “CYP2D6 intermediate or normal metabolizer”.	Corrected the phrase to “CYP2D6 intermediate metabolizer”.	July 23, 2020

Official symbols and names of genes included in this notification:

CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19

CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6

DPYD: Dihydropyrimidine Dehydrogenase

G6PD: Glucose-6-Phosphate Dehydrogenase