CONTENT RELEASE NOTIFICATION
EXPECTED RELEASE 02/26/20 AT 5-6 PM PST

UPDATED DRUGS WITH GENOTYPE-GUIDED RECOMMENDATIONS

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

Category	Therapeutic Class	Gene	Drug(s)	Update (highlighted in yellow)
Anticancer Agents	Protein Kinase Inhibitors	CYP2D6	**Gefitinib** (Iressa®)	*The title and the language of the recommendations will be harmonized. No changes to the decision support content.*
Psychiatry	Antidepressants	CYP2D6	**Fluvoxamine** (Luvox®)	Possible Reduced Response to Fluvoxamine (CYP2D6 Ultra-Rapid Metabolizer) *There is insufficient data documenting fluvoxamine exposure for this phenotype. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug may occur. ~~There is insufficient data to calculate dose adjustments and careful titration is recommended until a favorable response is achieved.~~ An alternative medication not metabolized by CYP2D6 may also be considered.*
Psychiatry	Antipsychotics	CYP2D6	**Aripiprazole** (Abilify®, Aristada®)	Normal Exposure to Aripiprazole (CYP2D6 Intermediate Metabolizer) and (CYP2D6 Ultra-Rapid Metabolizer) *The following sentence is a duplicated in the recommendations and will be removed, "Reduce dose by 50% if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered."*
Psychiatry	Antipsychotics	CYP2D6	**Paroxetine** (Paxil®, Brisdelle®)	Possible Increased Sensitivity to Paroxetine (CYP2D6 Poor Metabolizer) *The last sentence of the recommendations will be removed, "Some studies show that compared to normal metabolizers, poor metabolizers may experience more sexual dysfunction."*
Psychiatry	Antipsychotics	CYP2D6	**Brexpiprazole** (Rexulti®)	*The title and the language of the recommendations will be harmonized. No changes to the decision support content.*

UPDATED DRUGS WITHOUT GENOTYPE-GUIDED RECOMMENDATIONS

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
Diabetes	Sulfonylureas	**Chlorpropamide** (Diabinese®)	***Pharmacogenetic guidance**: Chlorpropamide is metabolized mainly by CYP2C9 and to a lesser extent by CYP2C19. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of chlorpropamide with a strong CYP2C9 and/or CYP2C19 inhibitors may result in higher chlorpropamide concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 and/or CYP2C19 inducers may result in lower chlorpropamide concentrations and a lack of efficacy.* *This change does not affect the previous recommendations provided based on CYP2C9 results.*
Diabetes	Sulfonylureas	**Glipizide** (Glucotrol®)	***Pharmacogenetic guidance**: Glipizide is metabolized by CYP2C9. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of glipizide with a strong CYP2C9 inhibitor may result in higher glipizide concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 inducer may result in lower glipizide concentrations and a lack of efficacy.* *This change does not affect the previous recommendations provided based on CYP2C9 results.*
Infectious Diseases	Antimalarials	**Proguanil** (Malarone®)	***Pharmacogenetic guidance**: Proguanil is a pro-drug that is primarily metabolized by CYP2C19 to its active metabolite, cycloguanil. Preliminary studies indicate that individuals with reduced CYP2C19 function, have reduced cycloguanil exposure compared to subjects with normal CYP2C19 function, but there is considerable overlap of cycloguanil and proguanil metabolic ratios across CYP2C19 metabolizer status. The clinical relevance of this change is not well understood and there is insufficient data to calculate dose adjustments. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of proguanil with a strong CYP2C19 inhibitor may result in lower cycloguanil (higher proguanil) exposure.* *This change does not affect the previous recommendations provided based on CYP2C19 results.*

Category	Therapeutic Class	Drug(s)	Update
Neurology	Anticonvulsants	**Lacosamide** (Vimpat®)	***Pharmacogenetic guidance**: Lacosamide is primarily cleared by renal excretion and metabolized by CYP3A4, CYP2C9 and CYP2C19. While these clearance pathways are diminished in subjects with reduced enzyme activity, these changes have not been shown to be clinically significant. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of lacosamide, in patients with reduced renal function, with strong CYP2C9 and/or CYP3A4 inhibitors may result in higher lacosamide concentrations.* *This change does not affect the previous recommendations provided based on CYP2C19 results.*

UPDATED SHORT CLINICAL DECISION SUPPORT (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)
Escitalopram (Lexapro®)	CYP2C19 Poor Metabolizer	*Test results indicate an increased risk of adverse effects. Consider a 50% dose reduction and monitor closely.*
Fluvoxamine (Luvox®)	CYP2D6 Poor Metabolizer	*Test results indicate an increased risk of adverse effects. Consider a 25-50% reduction of recommended starting dose and titrate to response or consider an alternative medication.*
	CYP2D6 Ultra-Rapid Metabolizer	*Test results indicate a possible risk of therapeutic failure. Consider standard prescribing practices and monitor closely or may select an alternative medication.*
Gefitinib (Iressa®)	CYP2D6 Poor Metabolizer	*Test results indicate a possible increased risk of adverse effects. Consider standard prescribing practices and monitor closely.*
Paroxetine (Paxil®, Brisdelle®)	CYP2D6 Poor Metabolizer	*Test results indicate a possible increased risk of adverse effects. Consider an alternative drug or consider a 50% reduction of recommended starting dose and titrate to response.*
	CYP2D6 Ultra-Rapid Metabolizer	*Test results indicate an increased risk of therapeutic failure. Consider an alternative medication ~~or use a higher dose and monitor closely~~.*
Phenytoin (Dilantin®)	CYP2C9 Poor Metabolizer	*Test results indicate an increased risk of neurotoxicity. Consider a standard loading dose but reduce maintenance doses by 50% and use therapeutic drug monitoring.* *This correction update was made January 22, 2020.*

Drug(s)	Associated Genotype or Phenotype	Update (highlighted in yellow)
Primaquine (Primaquine®)	G6PD Decreased Function	*Test results indicate an increased risk of acute hemolytic anemia. Consider an alternative medication.*
	G6PD Poor Function	*This correction update was made January 22, 2020.*
Sertraline (Zoloft®)	CYP2C19 Poor Metabolizer	*Test results indicate an increased risk of adverse effects. Consider a 50% dose reduction and titrate to response or may consider an alternative medication.*

NEW AND/OR 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)
	Assay Interpretation
CYP2C	*… While the rs12777823 G allele is the reference allele, it has a lower frequency than the A allele in most populations. In Asians, the rs12777823 A allele frequency is about 65%. In Africans and Caucasians, the A allele frequency ranges between 15% and 25%. …*

UPDATED VARIANTS

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

Gene(s)	Update
CYP4F2	*The HGVS name of the CYP4F2 variant rs2108622 will be updated to "c.1297G>A".*

UPDATED HAPLOTYPES

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

Gene(s)	Update
CYP2D6	*The haplotype *14A will be updated to *114 haplotype.* *The haplotype *14B will be updated to *14 haplotype.* *The functional effects of the haplotypes have not changed. The CYP2D6*114 remains as a no function allele and the CYP2D6*14 remains as a decreased function allele. This update is concordant with CPIC, PharmGKB and PharmVar.*

UPDATED PHENOTYPES

We have updated the phenotype(s) the following gene(s):

Gene(s)	Update
IFNL3	*The phenotype labels for IFNL3 will be updated to the following.* *IFNL3 "Homozygous for rs12979860 C allele" will be updated to "Favorable Genotype Response".* *IFNL3 "Heterozygous for rs12979860 T allele" and "Homozygous for rs12979860 T allele" will be updated to "Unfavorable Genotype Response".* *The clinical consequences will be updated as well.*
MTHFR	*The clinical consequences for MTHFR will be harmonized to the latest nomenclature of MTHFR c.665C>T to be consistent with cases and test details table. It was previously listed as MTHFR C677T.*
Other	*We have updated and harmonized the language of the clinical consequences for the following genes.* *CYP2C rs12777823, CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1*

UPDATED GENOTYPE-TO-PHENOTYPE

We have updated the genotype-to-phenotype assignment the following genotypes:

Gene(s)	Update
CYP3A5	*The phenotype assigned to CYP3A5 *3/*5, *5/*5, *5/*6 and *5/*7 will be updated to Unknown Phenotype.*

CYP2D6 PHENOTYPE UPDATE

TSI has updated the CYP2D6 genotype-to-phenotype assignment rules according to the latest Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG)[1].

The new assignment rules include the following changes:

- the value assigned to the CYP2D6*10 allele for activity score calculation will be downgraded from 0.5 to 0.25
- the phenotype assignment for an activity score of 1.0 will be updated from normal metabolizer to intermediate metabolizer
- the phenotype assignment for an activity score of 2.25 will be a normal metabolizer

The following table describes the previous and updated CYP2D6 phenotype definitions.

CYP2D6 Phenotype	Previous Definition (Activity Score)	Updated Definition (Activity Score)	CYP2D6 Diplotype Examples
Ultra-Rapid Metabolizer	>2	> 2.25	**1/*2 XN*
Normal Metabolizer	1 or 1.5 or 2	1.25 ≤ x ≤ 2.25	**1/*10; *1/*41; *10/*41*
Intermediate Metabolizer	0.5	0 < x < 1.25	**9/*9, *1/*5; *4/*10*
Poor Metabolizer	0	0	**4/*4, *3/*5*

Following the publication of the consensus phenotype updates, CPIC published a notification for relevant CYP2D6 -drug pairs, documenting the impact on existing recommendations. These changes are reflected in our recommendations and are available from CPIC's website.

[1] Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020;13(1):116–124.

The following table illustrates the updates for CYP2D6 (*e.g.,* *10, updated haplotypes, etc.)

Functional Status	Activity Value	Alleles
Increased Function	2 or >2	*1xN, *2xN, *35x2, *45x2
Normal or Increased Function	1.5 or >1.5	*41xN
Normal Function	1	*1, *2, *9x2, *17x2, *27, *29x2, *33, *34, *35, *39, *41x2, *45, *46, *48, *53
Decreased Function	0.5	*9, *10x2, *14, *17, *29, *41, *49, *50, *54, *55, *59, *72, *84
Decreased Function	0.25	*10
No Function	0	*3, *3x2, *4, *4xN, *5, *6, *6x2, *7, *8, *11, *12, *13, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *60, *62, *68, *69, *92, *96, *99, *100, *101, *114
Uncertain	N/A	*22, *23, *24, *25, *26, *28, *30, *32, *37, *43, *43x2, *52, *61, *63, *64, *65, *70, *71, *75, *81, *87, *88, *89, *90, *91, *93, *94, *95, *97, *98, *106
Unknown	N/A	*58, *73, *74, *82, *83, *85, *86, *102, *103, *104, *105, *107, *108, *109, *110, *111, *112, *113

UPDATED DRUG NAME(S)

We have updated the following drug(s):

Category	Therapeutic Class	Drug(s)	Update
Anticancer Agents	Fluoropyrimidines	**Fluorouracil**	*The iv after the trade name "Adrucil" was capitalized to "IV".*
Gastrointestinal	Antiemetics	**Fosaprepitant**	*The i.v after the trade name "Emend" will be harmonized and capitalized to "IV".*
Gastrointestinal	Antiemetics	**Fosnetupitant / Palonosetron**	*The i.v after the trade name "Akynzeo" will be harmonized and capitalized to "IV".*

CORRECTION NOTE FOR OCTOBER 03, 2019 RELEASE NOTES

The October 03, 2019 scientific content release notes included recommendation updates represented as percentages for CYP2C19 ultra-rapid metabolizers and the following medications; lansoprazole, omeprazole and pantoprazole (pages 5-6).

The dose changes represented as percentages were only in the scientific content release notes. The decision to update the recommendations to represent the dose changes in fold instead of percentages was decided after the science content release notes were sent to customers. On the day of the science release, the dose changes represented in fold were implemented.

The updated guideline (Link) from The Royal Dutch Pharmacists Association of the KNMP (also known as the Dutch Pharmacogenetics Working Group, DPWG) provided the recommendations for these drugs, representing the dose change in fold, NOT percentages. Therefore, the recommendations in the TSI system were updated to reflect the DPWG guideline.

Lansoprazole (CYP2C19 Ultra-Rapid Metabolizer)

Recommendation in the Release Notes	Correct Recommendation for Release Notes
The patient's genotype is associated with a significantly decreased lansoprazole exposure following standard dosing. • ***For Helicobacter pylori eradication:*** *Consider prescribing at 300% of the standard dose and be alert to insufficient response.* • ***For other indications:*** *Be alert to insufficient response and consider increasing the dose by 300%, if needed.*	*The patient's genotype is associated with a significantly decreased lansoprazole exposure following standard dosing.* • ***For Helicobacter pylori eradication****: Consider prescribing a 4-fold higher dose and be alert to insufficient response.* • ***For other indications****: Be alert to insufficient response and consider increasing the dose by 4-fold, if needed.*

Omeprazole (CYP2C19 Ultra-Rapid Metabolizer)

Recommendation in the Release Notes	Correct Recommendation for Release Notes
The patient's genotype is associated with a significantly decreased omeprazole exposure following standard dosing. • ***For Helicobacter pylori eradication:*** *Consider prescribing at 200% of the standard dose and be alert to insufficient response.* • ***For other indications:*** *Be alert to insufficient response and consider increasing the dose by 200%, if needed.*	*The patient's genotype is associated with a significantly decreased omeprazole exposure following standard dosing.* • ***For Helicobacter pylori eradication****: Consider prescribing a 3-fold higher dose and be alert to insufficient response.* • ***For other indications****: Be alert to insufficient response and consider increasing the dose by 3-fold, if needed.*

Pantoprazole (CYP2C19 Ultra-Rapid Metabolizer)

Note: There was no change to the percentage update for pantoprazole, only the language of the recommendations was harmonized.

Recommendation in the Release Notes	Correct Recommendation for Release Notes
The patient's genotype is associated with a significantly decreased pantoprazole exposure following standard dosing. • ***For Helicobacter pylori eradication:*** *Consider prescribing at 400% of the standard dose and be alert to insufficient response.* • ***For other indications:*** *Be alert to insufficient response and consider increasing the dose by 400%, if needed.*	*The patient's genotype is associated with a significantly decreased pantoprazole exposure following standard dosing.* • ***For Helicobacter pylori eradication****: Consider prescribing a 5-fold higher dose and be alert to insufficient response.* • ***For other indications****: Be alert to insufficient response and consider increasing the dose by 5-fold, if needed.*

The main evidence for the recommendations for dexlansoprazole with CYP2C19 comes from the FDA NDA clinical pharmacology review and literature analysis. For CYP2C19 intermediate and poor metabolizers the language of the recommendations was harmonized. Below are the correct recommendations for the October 3, 2019 release notes. The following recommendations are also the recommendations implemented on the day of the science release.

Dexlansoprazole (CYP2C19 Intermediate Metabolizer)

The correct recommendation for the release notes below,

> *Dexlansoprazole is the R-enantiomer of lansoprazole. The patient's genotype is associated with an increased dexlansoprazole exposure following standard dosing. Consider prescribing dexlansoprazole at standard label-recommended dosage and administration. ~~A positive clinical effect is expected in CYP2C19 intermediate metabolizers.~~*

Dexlansoprazole (CYP2C19 Poor Metabolizer)

The correct recommendation for the release notes below,

> *Dexlansoprazole is the R-enantiomer of lansoprazole. The patient's genotype is associated with an increased dexlansoprazole exposure following standard dosing. Consider prescribing dexlansoprazole at standard label-recommended dosage and administration. ~~A positive clinical effect is expected in CYP2C19 poor metabolizers.~~*

Dexlansoprazole (CYP2C19 Ultra-Rapid Metabolizer)

Recommendation	Correct Recommendation for Release Notes
Dexlansoprazole is the R-enantiomer of lansoprazole. The patient's genotype is associated with a significantly decreased dexlansoprazole exposure following standard dosing. • ***For Helicobacter pylori eradication**: Consider prescribing at 300% of the standard dose and be alert to insufficient response.* • ***For other indications**: Be alert to insufficient response and consider increasing the dose by 300%, if needed.*	*Dexlansoprazole is the R-enantiomer of lansoprazole. The patient's genotype is associated with a significantly decreased dexlansoprazole exposure following standard dosing.* • ***For Helicobacter pylori eradication**: A dose increase can be considered and be alert to insufficient response.* • ***For other indications**: Be alert to insufficient response and a dose increase can be considered, if needed.*

Official symbols and names of genes included in this notification:

CYP2C: Cytochrome P450 Family 2 Subfamily C

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

CYP3A5: Cytochrome P450 Family 3 Subfamily A Member 5

CYP4F2: Cytochrome P450 Family 4 Subfamily F Member 2

DPYD: Dihydropyrimidine Dehydrogenase

G6PD: Glucose-6-Phosphate Dehydrogenase

HLA-A: Major Histocompatibility Complex, Class I, A

HLA-B: Major Histocompatibility Complex, Class I, B

IFNL3: Interferon Lambda 3

MTHFR: Methylenetetrahydrofolate Reductase

NUDT15: Nudix Hydrolase 15

SLCO1B1: Solute Carrier Organic Anion Transporter Family Member 1B1

TPMT: Thiopurine S-Methyltransferase

UGT1A1: UDP Glucuronosyltransferase Family 1 Member A1

VKORC1: Vitamin K Epoxide Reductase Complex Subunit 1