ASCPT 2018

ANNUAL MEETING

MARCH 21 - 24, 2018 · HILTON ORLANDO · ORLANDO, FL

Accommodating substrate-dependence in CYP genotype to activity phenotype translation for pharmacogenetic implementation

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CPIC Director

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Clinical Pharmacogenetics Implementation Consortium

Survey: Challenges to implementing pharmacogenetics in the clinic

What do you think is the most challenging aspect of the implementation of pharmacogenetics into the clinic?

A. Translation of genetic information into clinical action
B. Test cost, test reimbursement or other economic issues
C. Availability of high quality genotyping test (CLIA approved)
D. Electronic medical record use, such as the application of CDS
E. Clinician and patient resistance and/or ethical concerns

Clin Pharmacol Ther. 2011 Mar;89(3):464-7.

Survey: top 3 Challenges to implementing pharmacogenetics in the clinic

- 95% of respondents selected: “process required to translate genetic information into clinical actions”
- Next 2 responses
  - Genotype test interpretation (e.g. using genotype information to impute phenotype)
  - Providing recommendations for selecting the drug/gene pairs to implement

Clin Pharmacol Ther. 2011 Mar;89(3):464-7.

- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  - Not WHETHER tests should be ordered.
- Key Assumption:
  - Clinical high-throughput and pre-emptive genotyping will become more widespread.
  - Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

- As of January 2018:
  - 249 Members
    - Clinicians and scientists
    - 178 institutions
    - 28 countries
  - 10 Observers (NIH and FDA)
  - CPIC Informatics
    - >20 members from 12 organizations

2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – warfarin

2012

- *CYP2D6* – codeine
- *HLA-B* – abacavir
- *SLCO1B1* – simvastatin

2013

- *HLA-B* – allopurinol
- *CYP2D6, CYP2C19* – TCAs
- *HLA-B* – carbamazepine
- *DPYD* -- 5FU / capecitabine
- *TPMT* – thiopurines—UPDATE
- *CYP2C19* – clopidogrel--UPDATE

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin
- *CYP2D6* – codeine--UPDATE
- *HLA-B* – abacavir--UPDATE
- *SLCO1B1* – simvastatin—UPDATE

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir
- *HLA-B* – allopurinol—UPDATE

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

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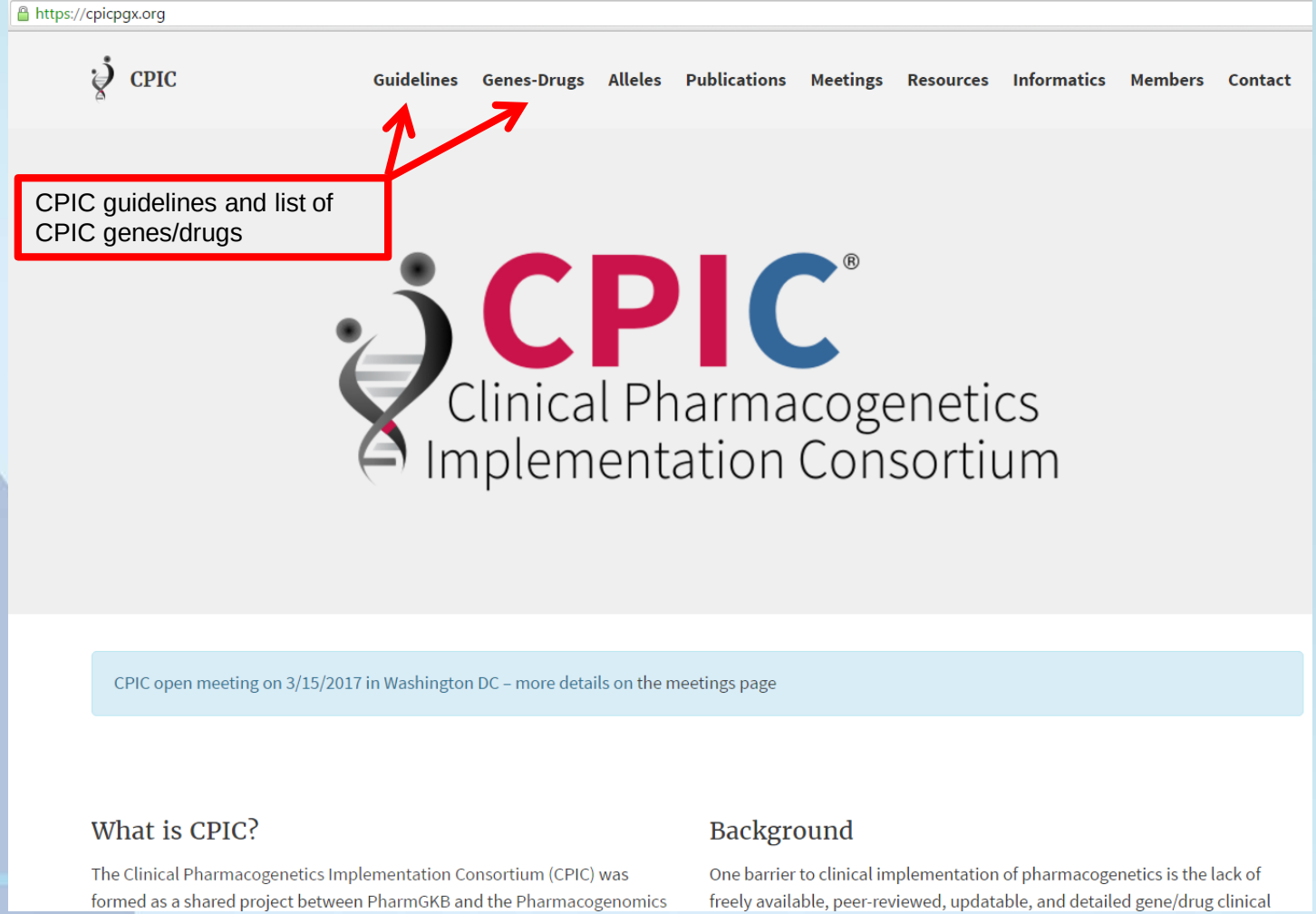
2017

- *CYP2D6* – tamoxifen
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine—UPDATE-in review

2018 (in progress)

- *RYR1*– inhaled anesthetics
- *CYP2B6*—efavirenz
- *TPMT/NUDT15* – thiopurines--UPDATE
- *CYP2D6*—atomoxetine
- *CYP2C19*/PPI
- *CYP2C9*/HLA-phenytoin—UPDATE
- *CYP2C9*/celecoxib

https://cpicpgx.org/guidelines/



CPIC website: www.cpicpgx.org

Supplemental Table S1. Evidence linking *CYP2C19* genotype to voriconazole phenotype

CYP2C19 allele definition table

CYP2C19 allele functionality table

CYP2C19 frequency table

CYP2C19 diplotype-phenotype table

Gene resource mapping

CYP2C19 gene resource mappings

Drug resource mapping

Voriconazole

Clinical decision support:[b]

Voriconazole pre- and post-test alerts and flow chart

...line for Voriconazole and CYP2C19

...tion:

...plementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole

...tions since publication.

...anuscript of the guideline:

...henotype based on genotypes
...oriconazole based on CYP2C19 phenotype for adult patients
...oriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

...macogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and ...ber 2016)

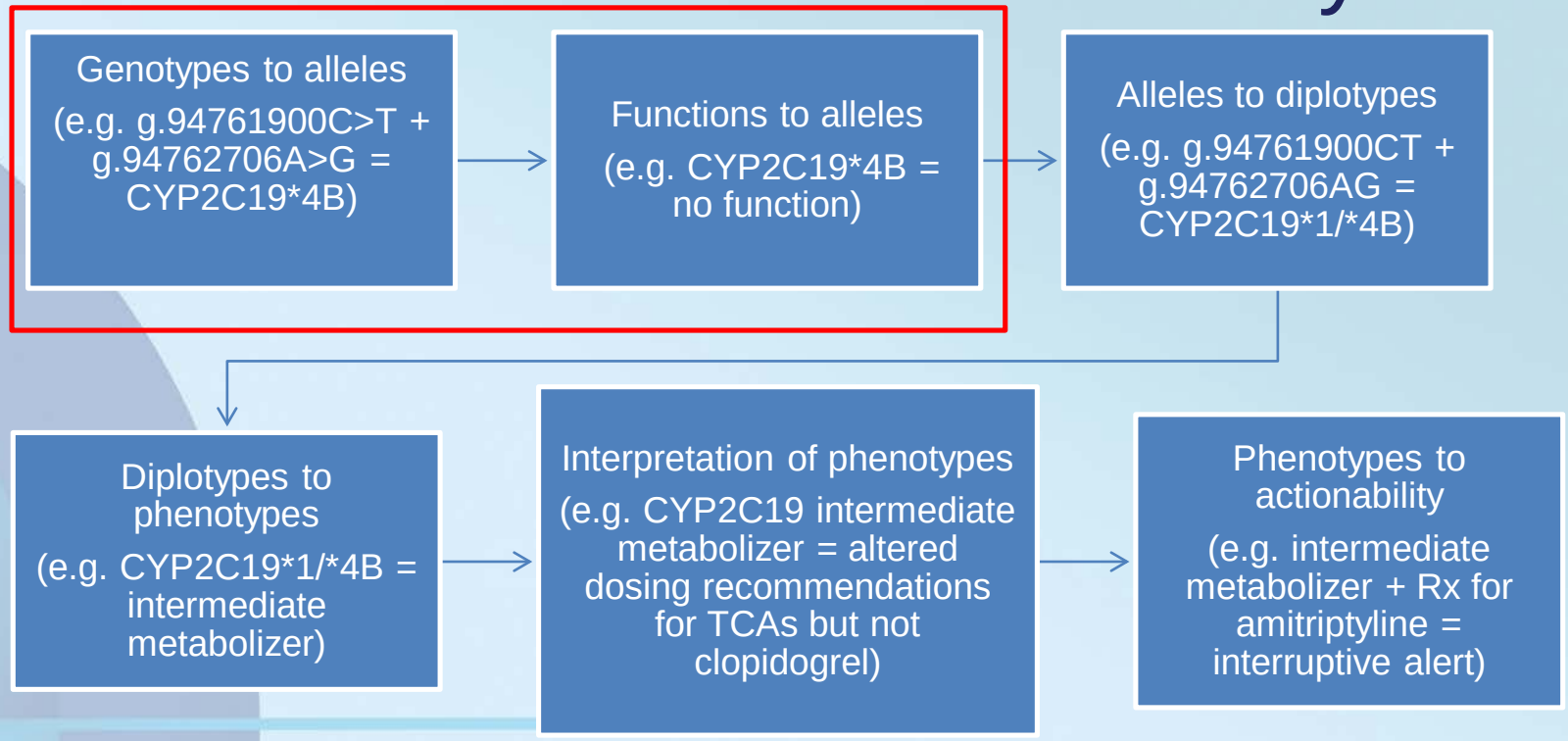
...the guideline publication supplement or referenced in the guideline[a]:

...*CYP2C19* genotype to voriconazole phenotype

Gene resource mapping

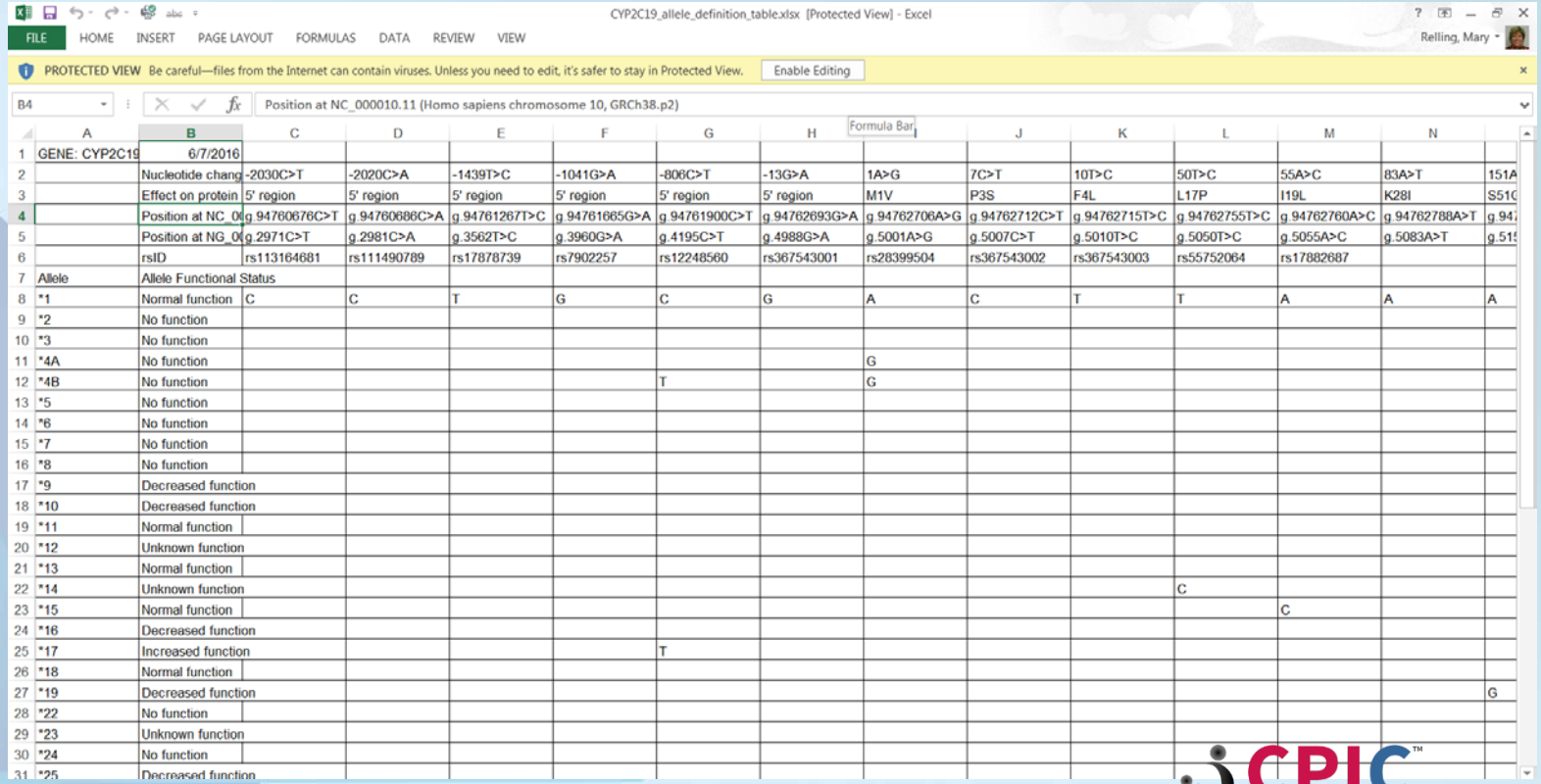
CYP2C19 gene resource mappings

CPIC tables allow translation of genetic test results to actionability



https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials

Allele definition table: genotypes to alleles



CYP2C19_allele_definition_table.xlsx [Protected View] - Excel

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B4 Position at NC_000010.11 (Homo sapiens chromosome 10, GRCh38.p2)

Formula Bar

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	
1	GENE: CYP2C19	6/7/2016													
2		Nucleotide chang	-2030C>T	-2020C>A	-1439T>C	-1041G>A	-806C>T	-13G>A	1A>G	7C>T	10T>C	50T>C	55A>C	83A>T	151A
3		Effect on protein	5' region	5' region	5' region	5' region	5' region	5' region	M1V	P3S	F4L	L17P	I19L	K28I	S51C
4		Position at NC_0	g.94760676C>T	g.94760686C>A	g.94761267T>C	g.94761665G>A	g.94761900C>T	g.94762693G>A	g.94762706A>G	g.94762712C>T	g.94762715T>C	g.94762755T>C	g.94762760A>C	g.94762788A>T	g.947
5		Position at NG_0	g.2971C>T	g.2981C>A	g.3562T>C	g.3960G>A	g.4195C>T	g.4988G>A	g.5001A>G	g.5007C>T	g.5010T>C	g.5050T>C	g.5055A>C	g.5083A>T	g.515
6		rsID	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs367543001	rs28399504	rs367543002	rs367543003	rs55752064	rs17882687		
7	Allele	Allele Functional Status													
8	*1	Normal function	C	C	T	G	C	G	A	C	T	T	A	A	A
9	*2	No function													
10	*3	No function													
11	*4A	No function							G						
12	*4B	No function					T		G						
13	*5	No function													
14	*6	No function													
15	*7	No function													
16	*8	No function													
17	*9	Decreased function													
18	*10	Decreased function													
19	*11	Normal function													
20	*12	Unknown function													
21	*13	Normal function													
22	*14	Unknown function										C			
23	*15	Normal function											C		
24	*16	Decreased function													
25	*17	Increased function					T								
26	*18	Normal function													
27	*19	Decreased function													G
28	*22	No function													
29	*23	Unknown function													
30	*24	No function													
31	*25	Decreased function													

https://www.pharmgkb.org/page/pgxGeneRef

https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

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Translating CYP genotypes to allelic functional status

Term/gene category	Final term[a]	Functional definition	Genetic definition	Example diplotypes/alleles
Allele functional status: all genes	Increased function	Function greater than normal function	N/A	*CYP2C19*17*
	Normal function	Fully functional/wild-type	N/A	*CYP2C19*1*
	Decreased function	Function less than normal function	N/A	*CYP2C19*9*
	No function	Nonfunctional	N/A	*CYP2C19*2*
	Unknown function	No literature describing function or the allele is novel	N/A	*CYP2C19*29*
	Uncertain function	Literature supporting function is conflicting or weak	N/A	*CYP2C19*12*

Genet Med. 2017 Feb;19(2):215-223.

Allele functionality table: alleles to function

The referenced substrates and cited articles are examples and may not represent all information that may be available for an allele.

GENE: CYP2C19	6/20/2017			Drug substrate	
Allele	Allele Functional Status	References	PMID	in vitro	in vivo
*1	Normal function	Romkes 1991	2009263		
		Richardson 1995	7487078	S-mephenytoin, tolbutamide	
		Blaisdell 2002	12464799	S-mephenytoin	
		Hanioka 2007	17455109	S-mephenytoin	
		Hanioka 2008	18312490	omeprazole	
		Wang 2011	21325430	S-mephenytoin, omeprazole	
		Takahashi 2015	25001882	clopidogrel, S-mephenytoin	
*2	No function	de Morais 1994	8195181	S-mephenytoin	
		Ibeanu 1998	9732415		S-mephenytoin
		Lee 2009	19661214		S-mephenytoin, omeprazole
		Xiao 1997	9103550		S-mephenytoin
*3	No function	de Morais 1994	7969038		S-mephenytoin
		Xiao 1997	9103550		S-mephenytoin
*4A	No function	Ferguson 1998	9435198		S-mephenytoin
*4B	No function	Scott 2012	21358751		clopidogrel
*5	No function	Xiao 1997	9103550		S-mephenytoin
		Ibeanu 1998	10022751	S-mephenytoin, tolbutamide	S-mephenytoin
		Wang 2011	21325430	S-mephenytoin, omeprazole	
		Takahashi 2015	25001882	clopidogrel, S-mephenytoin	
*6	No function	Ibeanu 1998	9732415		S-mephenytoin
		Wang 2011	21325430	S-mephenytoin, omeprazole	
		Takahashi 2015	25001882	clopidogrel, S-mephenytoin	
*7	No function	Ibeanu 1999	10411572		S-mephenytoin
*8	No function	Ibeanu 1999	10411572	S-mephenytoin, tolbutamide	S-mephenytoin
		Wang 2011	21325430	S-mephenytoin, omeprazole	
		Takahashi 2015	25001882	clopidogrel, S-mephenytoin	
*9	Decreased function	Blaisdell 2002	12464799	S-mephenytoin	
		Wang 2011	21325430	S-mephenytoin, omeprazole	
		Takahashi 2015	25001882	clopidogrel, S-mephenytoin	
*10	Decreased function	Blaisdell 2002	12464799	S-mephenytoin	

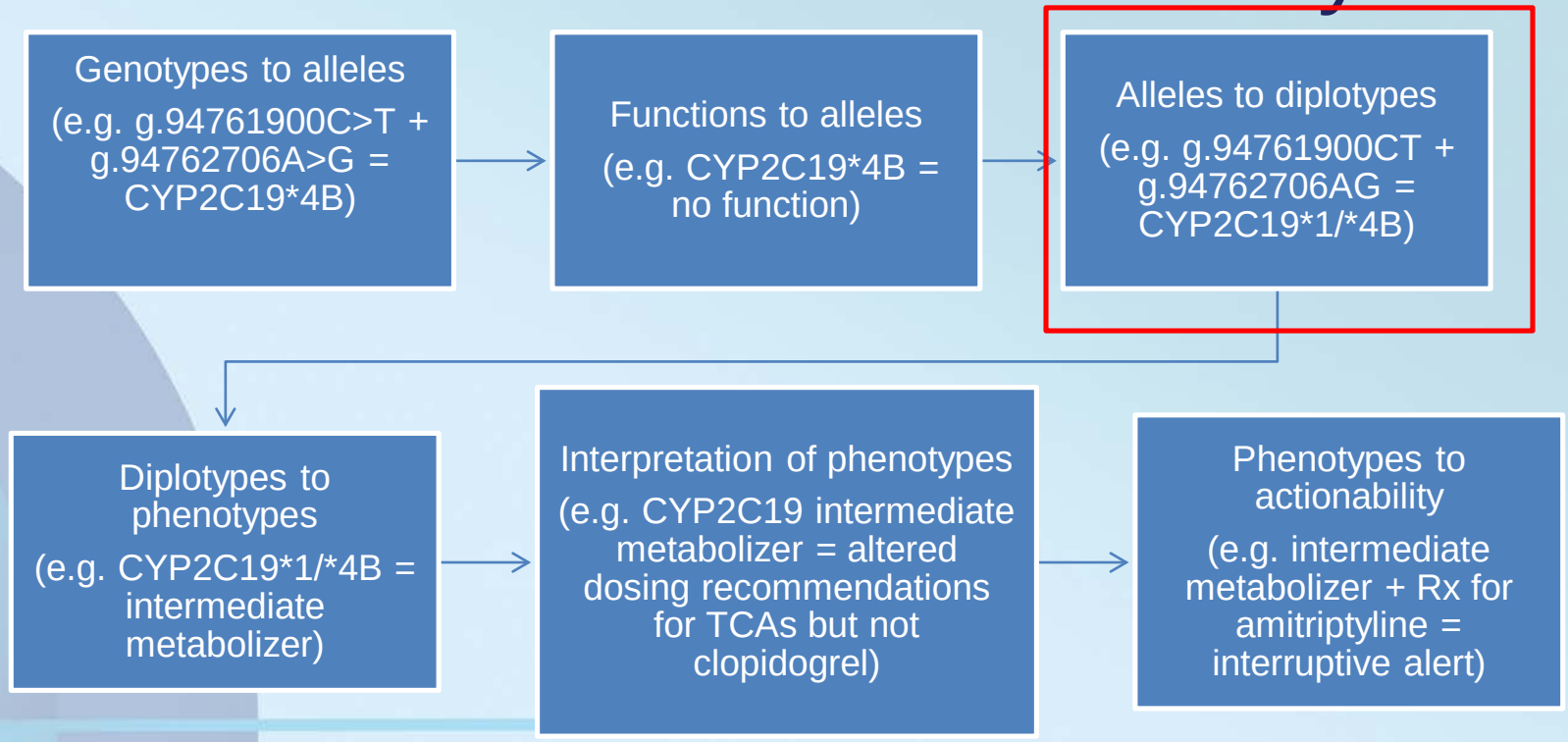
https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

Supplemental Table S2. Association between allelic variants and CYP2C9 function

Functional Status[a, b]	Alleles	In Vitro Activity	
		Substrate	Percent reduction of in vitro metabolism vs CYP2C9*1
Normal Activity	*1		
	*9	S-warfarin Tolbutamide Tolbutamide	82% of Cl_{int} [34] 96% of wild-type activity [34] 93% of Cl_{int} [35]
Decreased Activity	*2	S-warfarin Tolbutamide Phenytoin	32% of Cl_{int} [34] 42% of wild-type activity [34] 71% of Cl_{int} [36]
	*3	S-warfarin Tolbutamide Tolbutamide Phenytoin Phenytoin	21% of wild-type activity [34] 28% of wild-type activity [34] 26% of Cl_{int} [37] 5% of Cl_{int} [36] 7% of Cl_{int} [38]
No Activity	*6	N/A	Frameshift mutation [34]
	*15	N/A Tolbutamide	Nonsense mutation No expression [39]
	*25	N/A	Frameshift mutation [34]
Possible Decreased Activity (no available phenytoin in vitro activity studies)	*4	S-warfarin Tolbutamide	16% of wild-type activity [34] 22% of wild-type activity [34]
	*5	S-warfarin Tolbutamide S-warfarin	19% of wild-type activity [34] 24% of wild-type activity [34] 8% of Cl_{int} [40]

https://cpicpgx.org/guidelines/guideline-for-phenytoin-and-cyp2c9-and-hla-b/

CPIC tables allow translation of genetic test results to actionability



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https://www.pharmgkb.org/page/cyp2c19RefMaterials

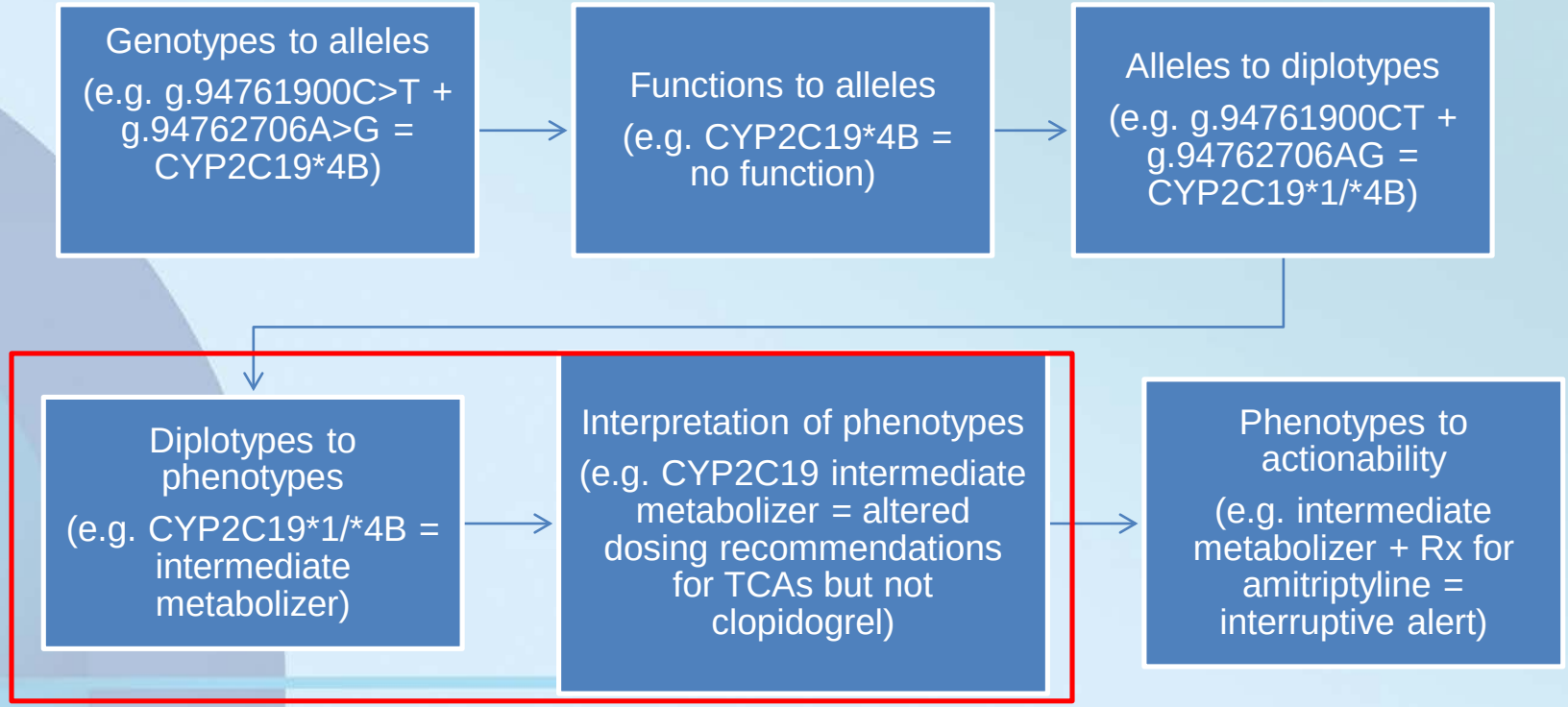
Variants must be phased to assign diplotypes for pharmacogenes

CPIC Gene	Var/var different than var/wt?
TPMT	Yes
CYP2C19	Yes
CYP2D6	Yes
DPYD	Yes
CYP2C9	Yes
SLCO1B1	Yes
HLA-B	No
VKORC1	Yes
IL28-B	Yes
CFTR	No
G6PD	Yes
UGT1A1	Yes
CYP3A5	Yes

CYP2D6: 207 diplotypes observed in first 4046 pts on PG4KDS

TPMT is much simpler

CPIC tables allow translation of genetic test results to actionability



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Genotype to phenotype assignment based on allele function

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes[a]	Examples of *CYP2C19* diplotypes
CYP2C19 ultrarapid metabolizer (~2–5% of patients)[b]	An individual carrying two increased function alleles	*17/*17
CYP2C19 rapid metabolizer (~2–30% of patients)[b]	An individual carrying one normal function allele and one increased function allele	*1/*17
CYP2C19 normal metabolizer[c] (~35–50% of patients)[b]	An individual carrying two normal function alleles	*1/*1
CYP2C19 intermediate metabolizer (~18–45% of patients)[b]	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	*1/*2, *1/*3, *2/*17[d]
CYP2C19 poor metabolizer (~2–15% of patients)[b]	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3

Clin Pharmacol Ther. 2017 Jul: 102 (1):45-51.

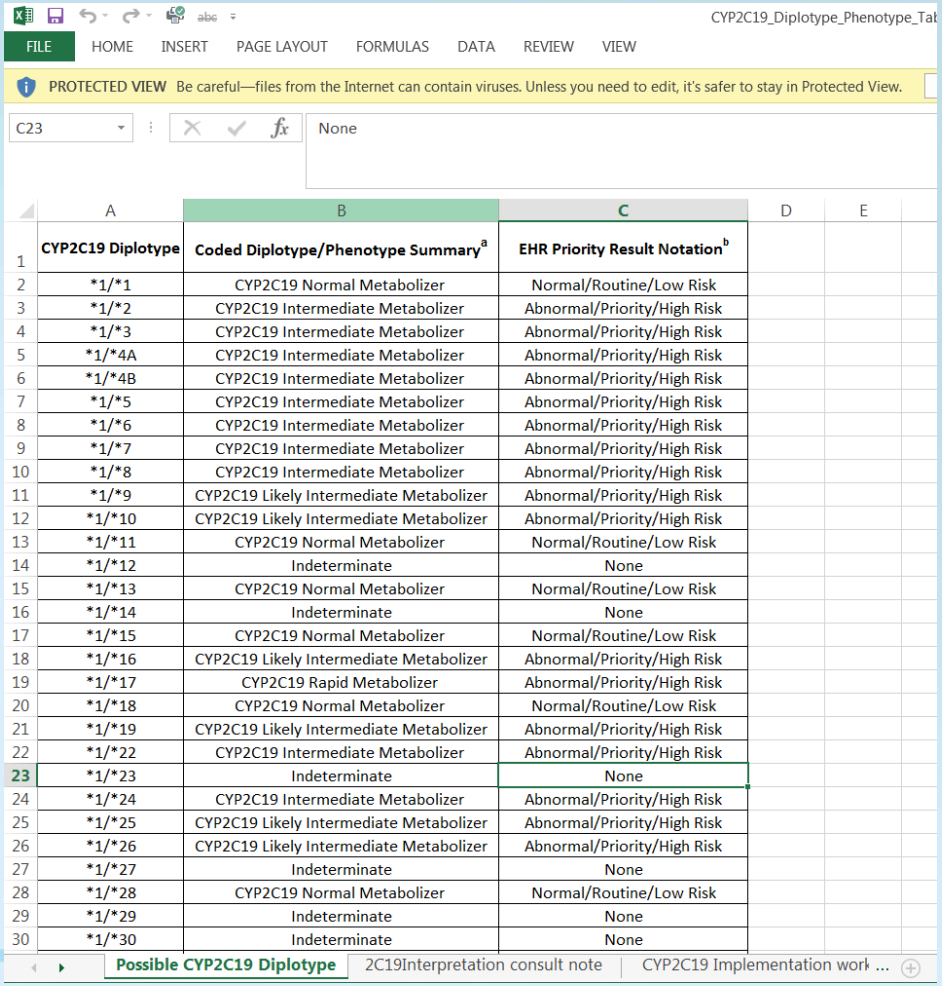
https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

Genotype to phenotype assignment based on allele function

Table 1 Assignment of likely CYP2D6 phenotypes based on diplotypes

Likely phenotyp	lotypes
CYP2D6 Ultrara (~1–2% of pati	2xN[c]
CYP2D6 Norma (~77–92% of p	/*5, 41/*41
CYP2D6 Interm (~2–11% of pa	
CYP2D6 Poor M (~5–10% of pa	/*6

There are differences in genotype to phenotype assignment between the CPIC and the DPWG guidelines. We are in the process of working together to resolve these discordances.



CYP2C19_Diplotype_Phenotype_Tab

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C23 | None

	A	B	C	D	E
1	**CYP2C19 Diplotype**	**Coded Diplotype/Phenotype Summary[a]**	**EHR Priority Result Notation[b]**		
2	*1/*1	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
3	*1/*2	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
4	*1/*3	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
5	*1/*4A	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
6	*1/*4B	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
7	*1/*5	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
8	*1/*6	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
9	*1/*7	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
10	*1/*8	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
11	*1/*9	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
12	*1/*10	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
13	*1/*11	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
14	*1/*12	Indeterminate	None		
15	*1/*13	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
16	*1/*14	Indeterminate	None		
17	*1/*15	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
18	*1/*16	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
19	*1/*17	CYP2C19 Rapid Metabolizer	Abnormal/Priority/High Risk		
20	*1/*18	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
21	*1/*19	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
22	*1/*22	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
23	*1/*23	Indeterminate	None		
24	*1/*24	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
25	*1/*25	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
26	*1/*26	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
27	*1/*27	Indeterminate	None		
28	*1/*28	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
29	*1/*29	Indeterminate	None		
30	*1/*30	Indeterminate	None		

Possible CYP2C19 Diplotype | 2C19Interpretation consult note | CYP2C19 Implementation work ...

https://www.pharmgkb.org/page/cyp2c19RefMaterials
https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

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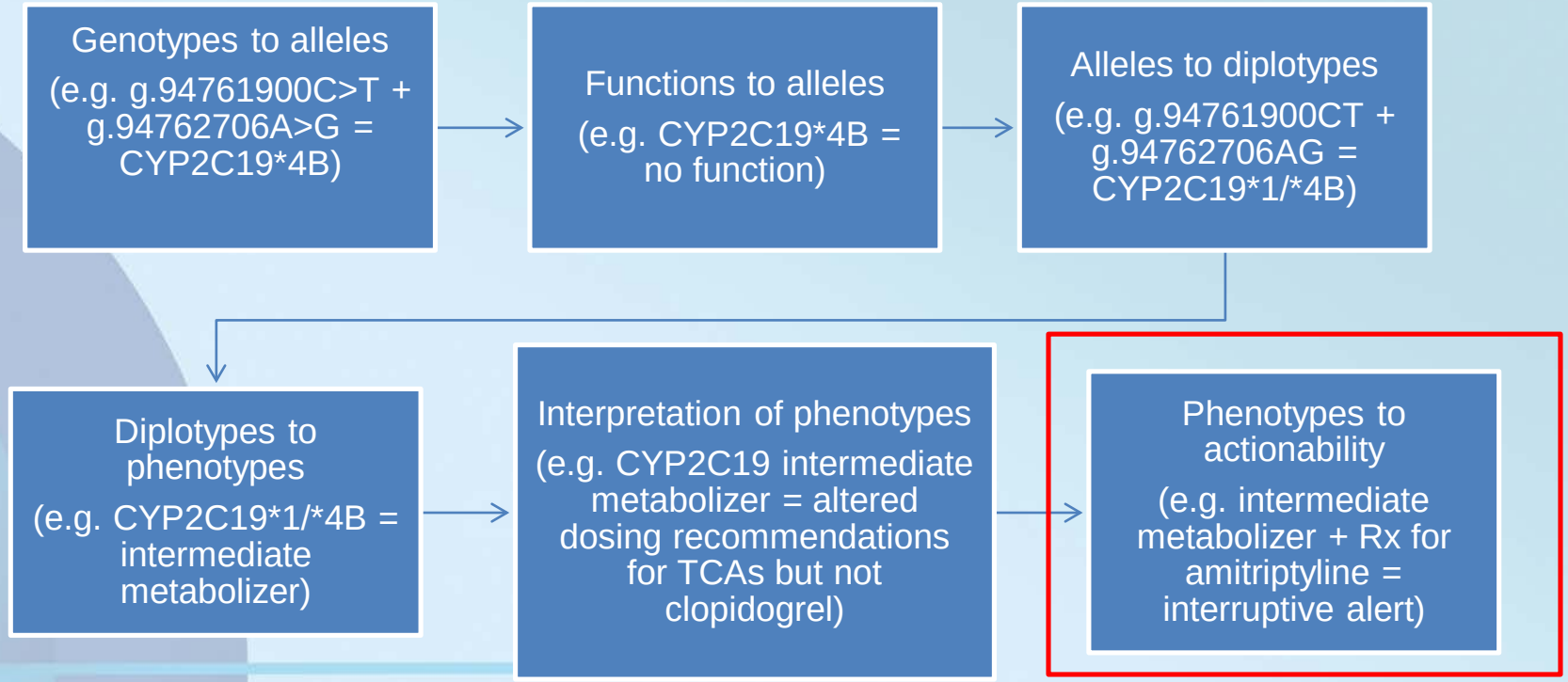
CPIC tables allow translation of genetic test results to actionability



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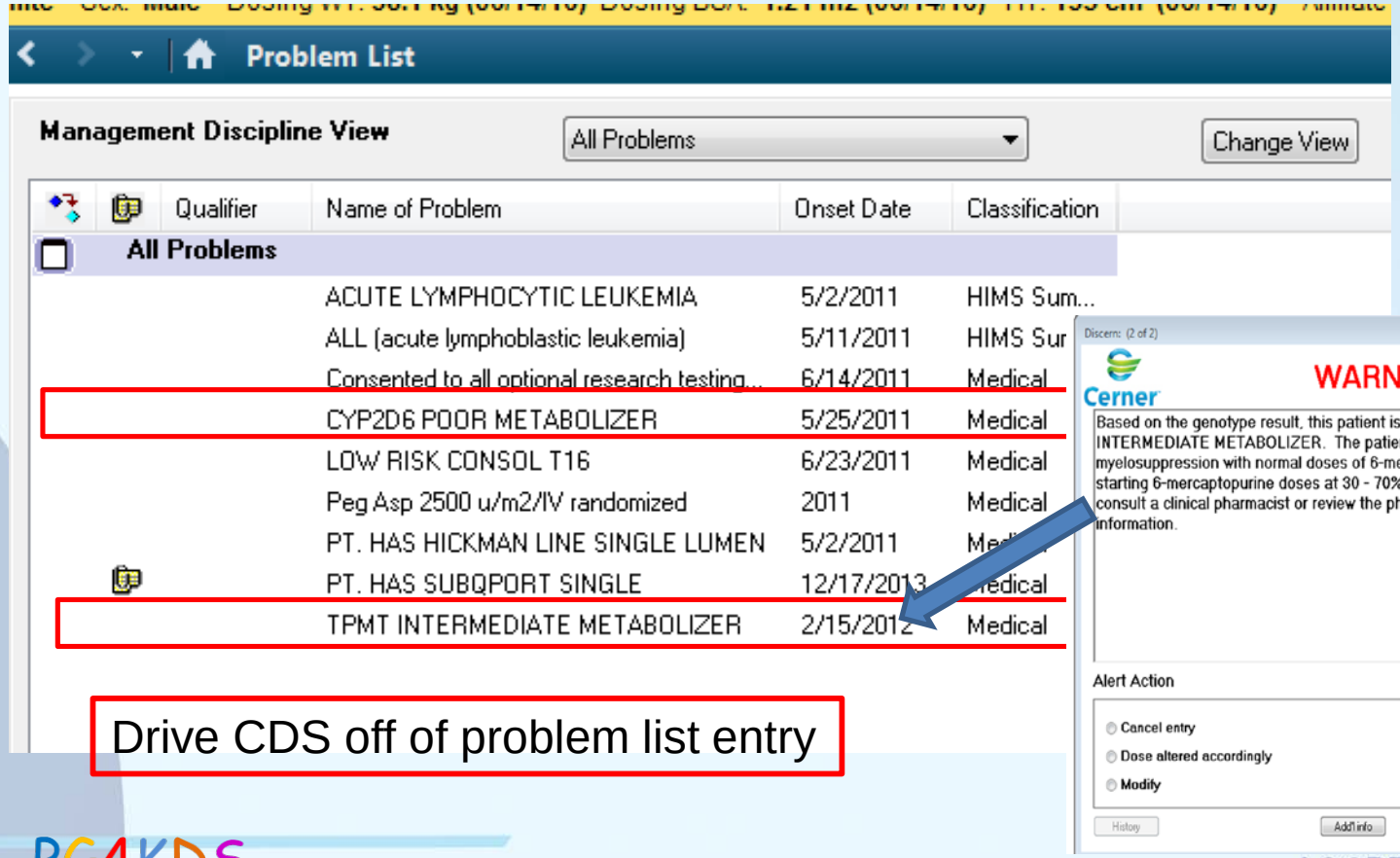

Drive CDS off of problem list entry

PG4KDS

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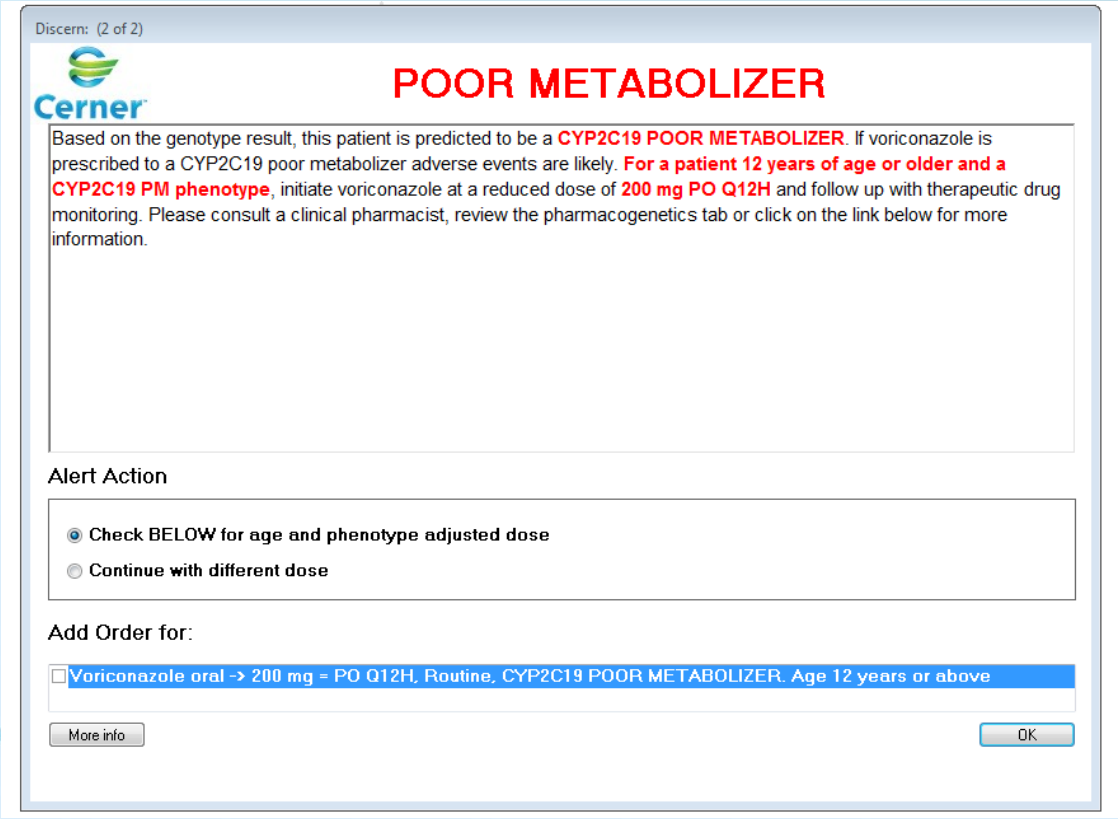
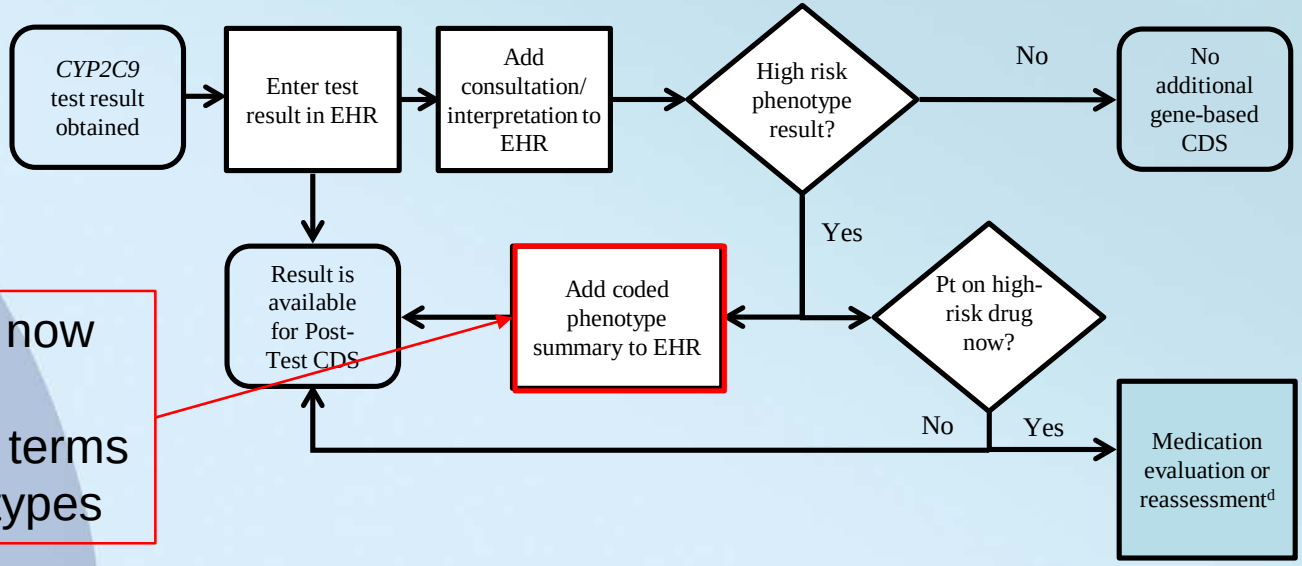
Post-test alert can incorporate non-genetic info too: based on CYP2C19 phenotype, route of administration, age



PG4KDS

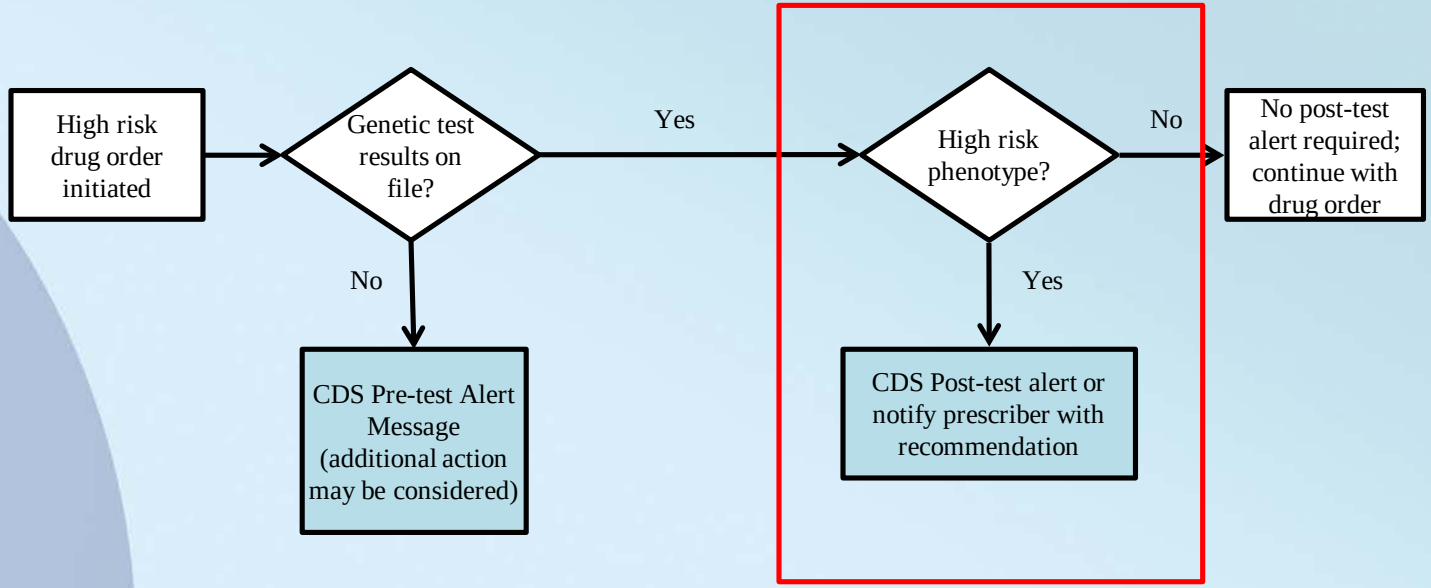
Integrating substrate-dependence into genotype-to-phenotype translation



There are now available SNOMED terms for phenotypes

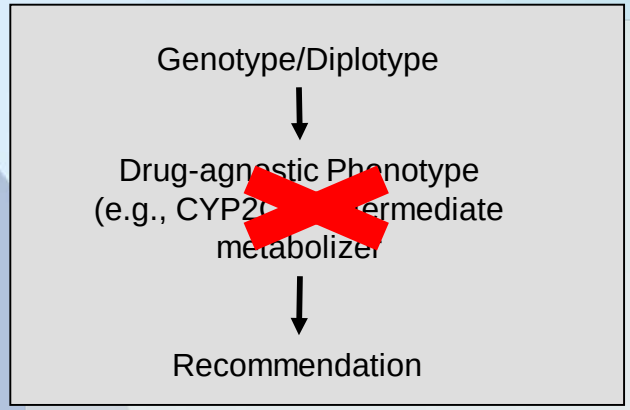
Blue shading indicates interaction with provider

Integrating substrate-dependence into genotype-to-phenotype translation

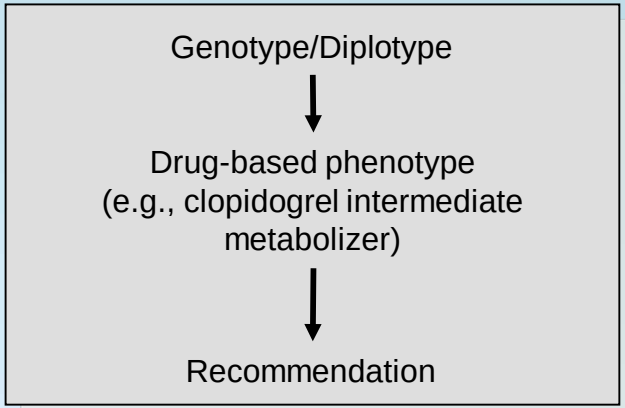


Integrating substrate-dependence into genotype-to-phenotype translation

Option 1:



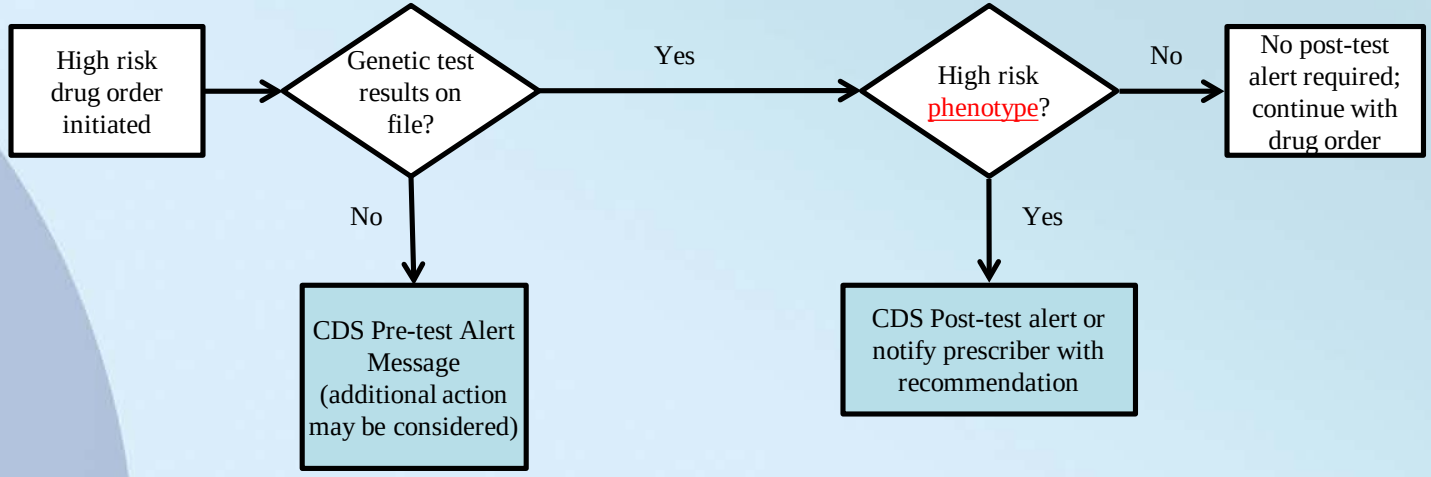
Option 2:



- Is there enough clinical evidence to allow for clinical recommendations based on genotype/diplotype?
- How would this affect current system/implementation?

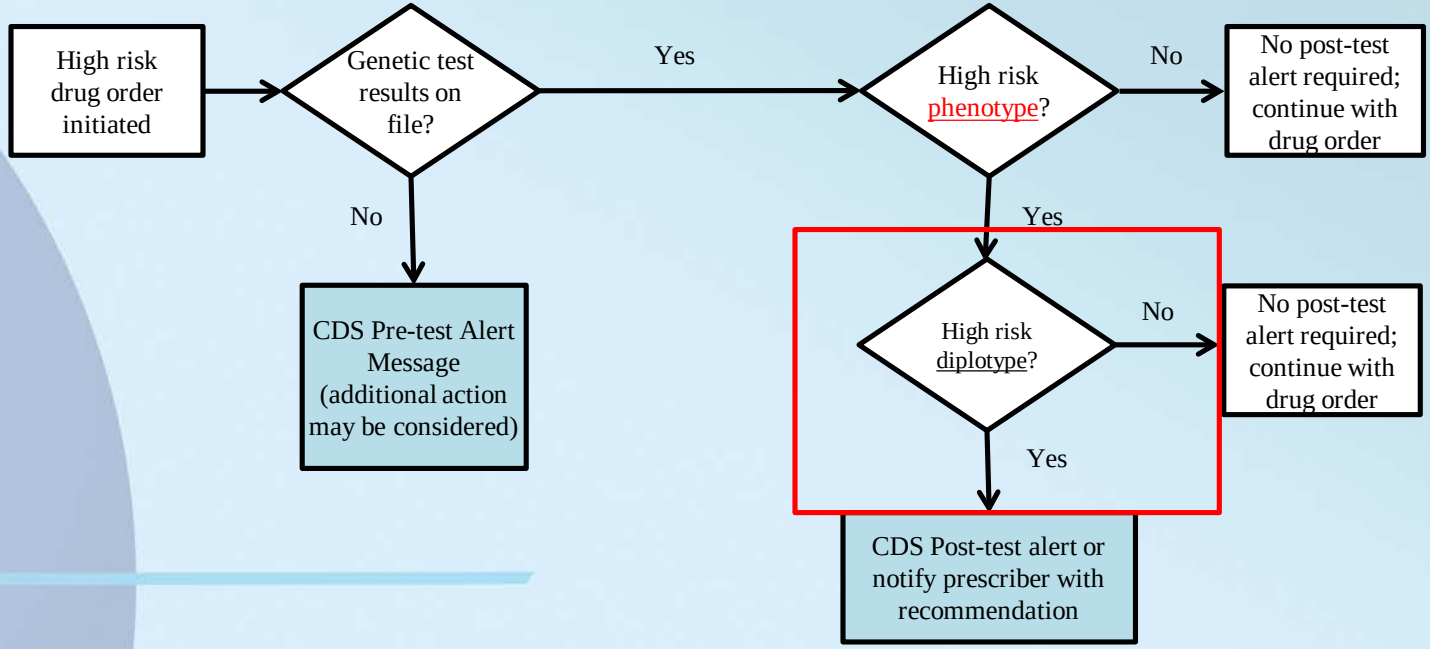
Integrating substrate-dependence into genotype-to-phenotype translation

Change to diplotype or drug-based phenotype?



How would this impact problem list entry or use of standardized terminology such SNOMED?

Integrating substrate-dependence into genotype-to-phenotype translation



Integrating substrate-dependence into genotype-to-phenotype translation

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Ultrarapid metabolizer: normal or increased activity (~5–30% of patients)	An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased-activity allele (*17)	*1/*17, *17/*17
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)	*1/*2, *1/*3, *2/*17
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

Some rare genotype combinations have unclear predicted metabolic phenotypes; see **Supplementary Table S5** online.

Clin Pharmacol Ther. 2013 Sep;94(3):317-23

Integrating substrate-dependence into genotype-to-phenotype translation

Table 2 Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[a]
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[b]	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

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Integrating substrate-dependence into genotype-to-phenotype translation

Table 3 Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

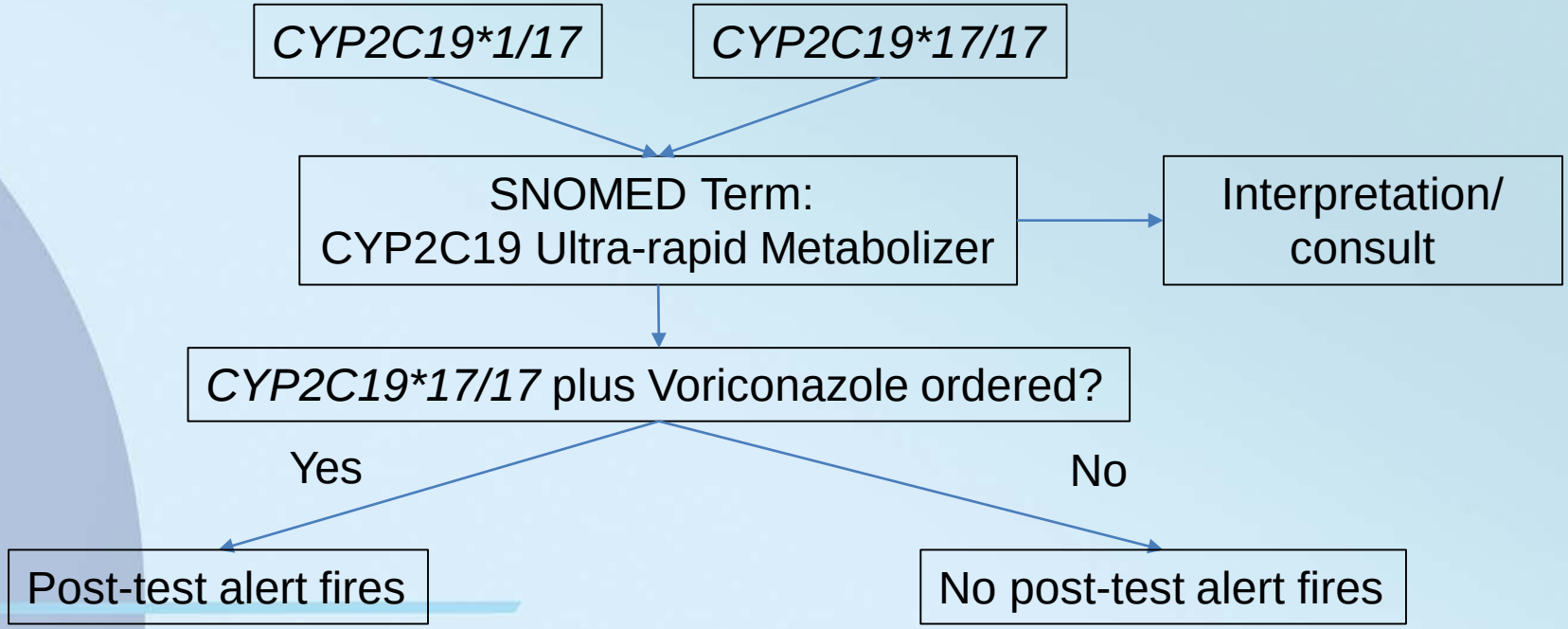
CYP2C19 phenotype	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Classification of recommendations[a]
CYP2C19 ultrarapid metabolizer (*17/*17)	In patients for whom an ultrarapid metabolizer genotype (*17/*17) is	Choose an alternative agent that is not dependent on CYP2C19 metabo-	Moderate
	trations of voriconazole and may increase probability of adverse events	not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include liposomal amphotericin B and posaconazole.[b,e] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	

BUT BEFORE THIS CHANGE….

https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

Clin Pharmacol Ther. 2017 Jul: 102 (1):45-51.

Integrating substrate-dependence into genotype-to-phenotype translation

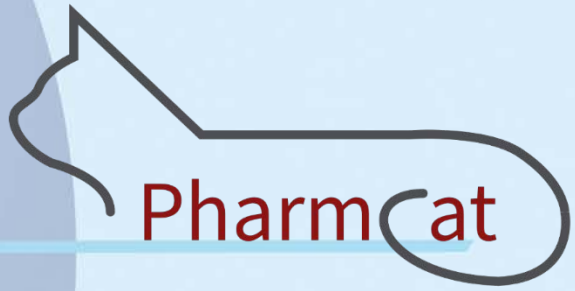


Why not so straightforward?

- SNOMED CT terms
- Clinical evidence
- Scalability/Shareable
- Diplotype not always a discrete field in EHR

PharmCAT

To automate the annotation of .vcf files with the appropriate haplotypes or diplotypes from the CPIC guideline genes, and generate a report with the corresponding CPIC guideline prescribing recommendations



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