The Clinical Pharmacogenetics Implementation Consortium: Incorporating Pharmacogenetics into Clinical Practice and the EHR

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.

- As of May 2018:
  - 261 Members
    - Clinicians and scientists
    - 181 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 open meeting on 3/15/2017 in Washington DC – more details on the meetings page

What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB and the Pharmacogenomics

Background

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical

CPIC website: www.cpicpgx.org

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines were updated in June 2014.

Link to guideline page

Search:

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*
allopurinol	HLA-B	*guideline*
amitriptyline	CYP2C19 CYP2D6	*guideline*

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
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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)

...nacogenetics 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

Resources

CPIC slides

Overview Presentation

This presentation describes CPIC, the underlying assumptions of CPIC guidelines, the guideline development process and how the guidelines can be implemented in a clinical setting.

Overview Presentation (.pptx)

Implementation

View a list of current implementers

CPIC projects

Term Standardization for Clinical Pharmacogenetic Test Results

Learn about CPIC's Term Standardization Project

CPIC Logo Graphics

CPIC logo

Logo image files that you can use for referring to CPIC. The images are in PNG and SVG format.

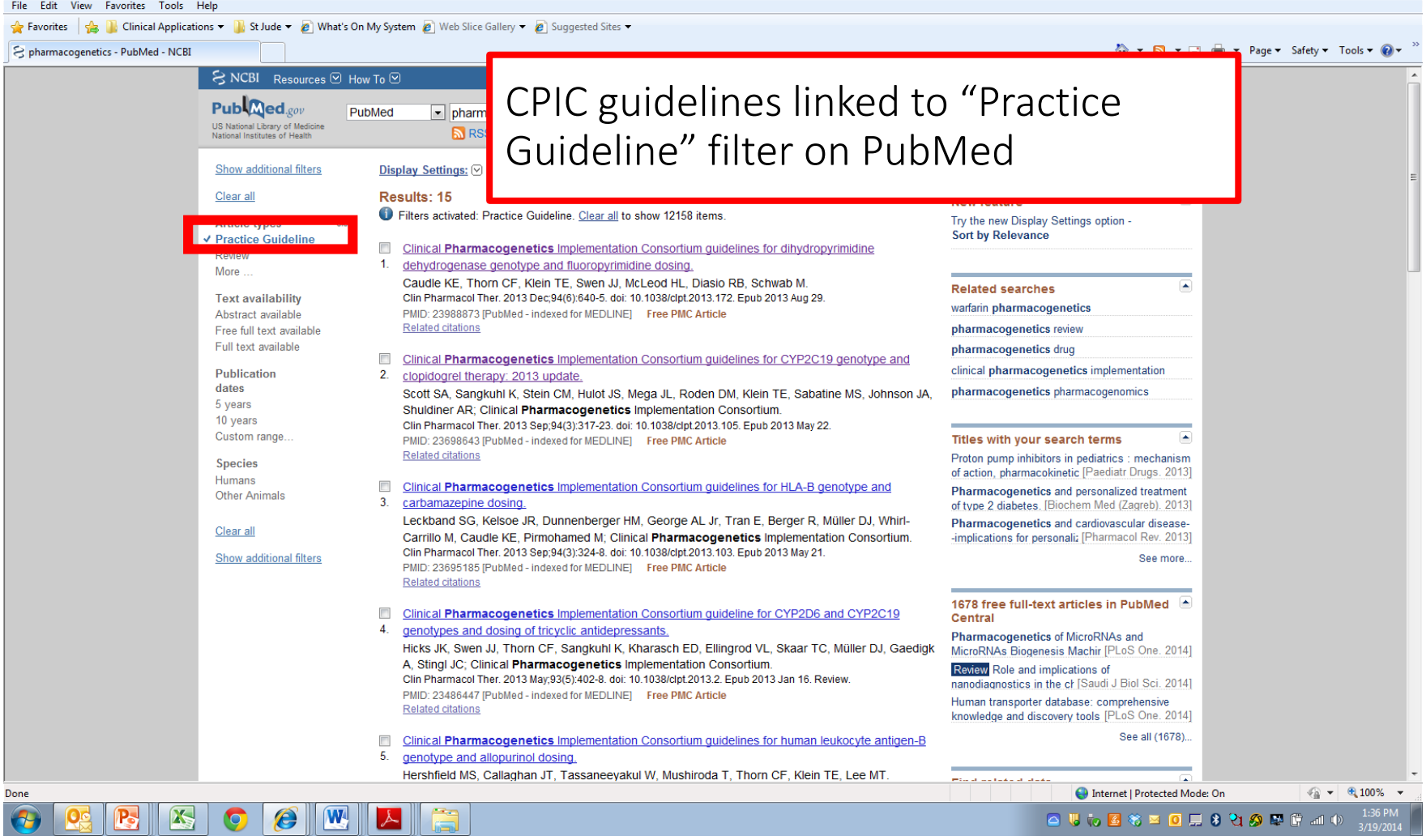
- logo without full name
  - 200px width PNG
  - 400px width PNG

Implementation

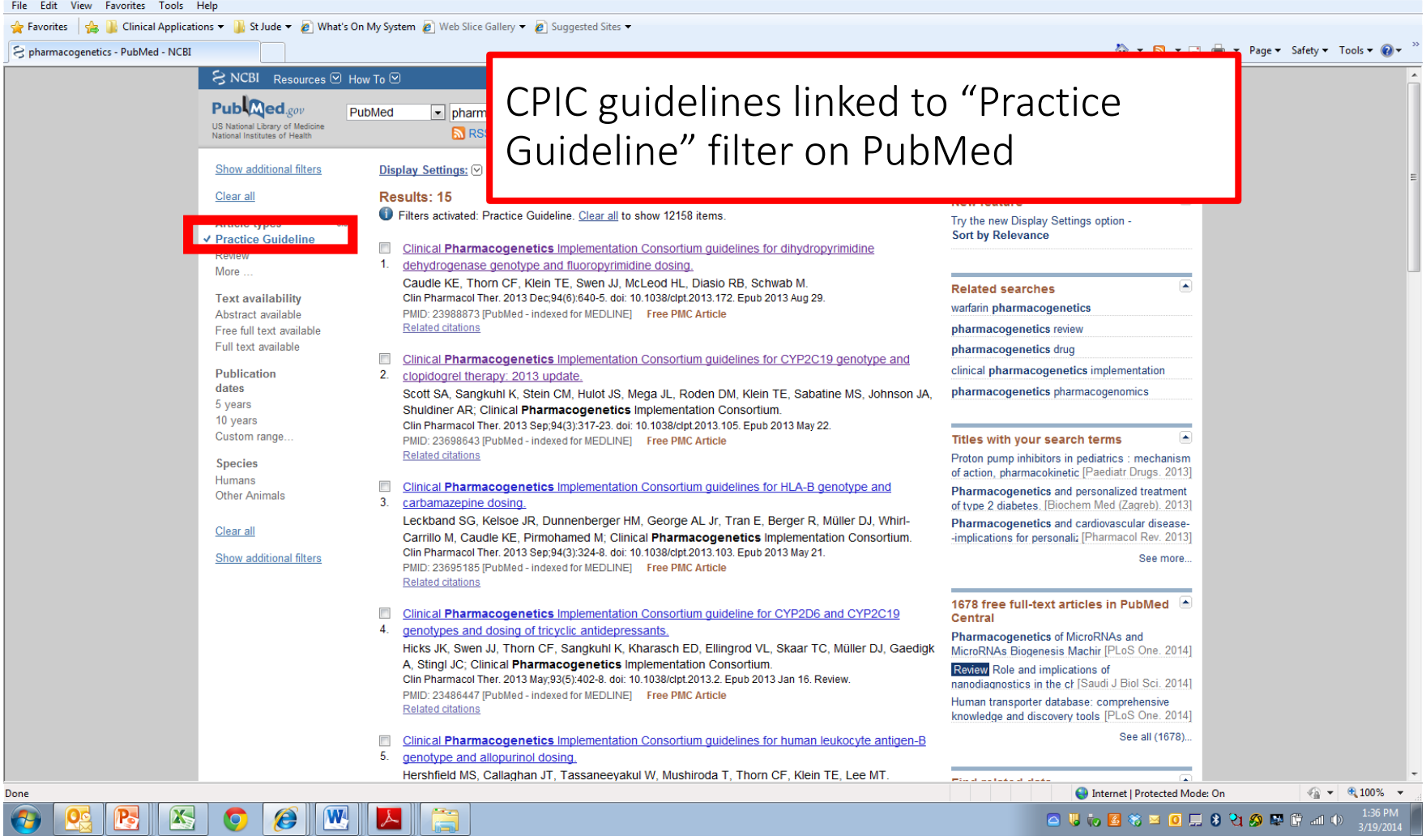
https://cpicpgx.org/implementation/

The following is a list of PGx implementers who are using CPIC guidelines as part of a program to facilitate use of genetic tests to guide prescribing for patients in clinical care settings:

Institution	Website and/or Contact (if available)
BJC Healthcare	
Boston Children's Hospital	Shannon Manzi; shannon.manzi@childrens.harvard.edu
Children's Minnesota	
Cincinnati Children's Hospital Medical Center	CCHMC Genetic Pharmacology Service
Clearview Cancer Institute	Emily K Pauli; emily.pauli@ccihsv.com
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology	Matthias Schwab; matthias.schwab@ikp-stuttgart.de
Erasmus MC	Ron van Schaik; r.vanschaik@erasmusmc.nl
Geisinger Health System	Geisinger Health System Genomic Medicine Institute
Icahn School of Medicine at Mount Sinai	Stuart Scott lab Aniwaa Owusu Obeng; aniwaa.owusu-obeng@mssm.edu

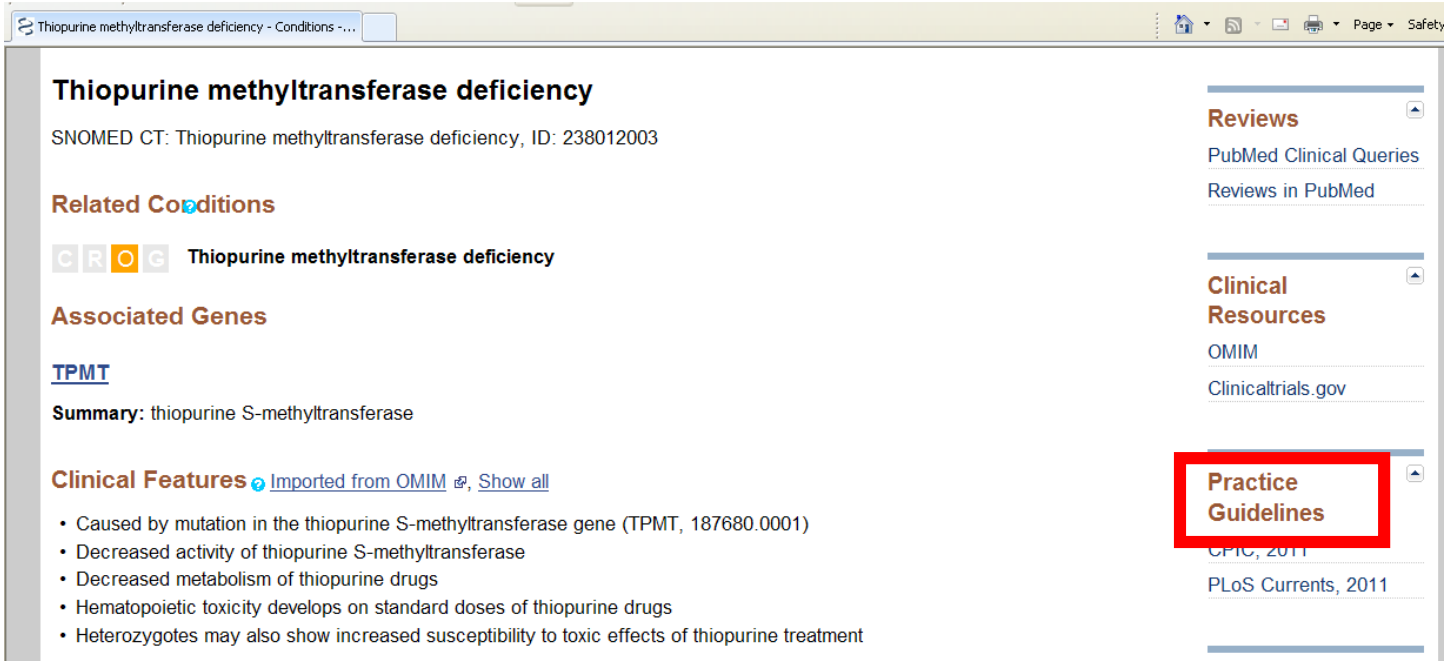


CPIC guidelines linked to “Practice Guideline” filter on PubMed

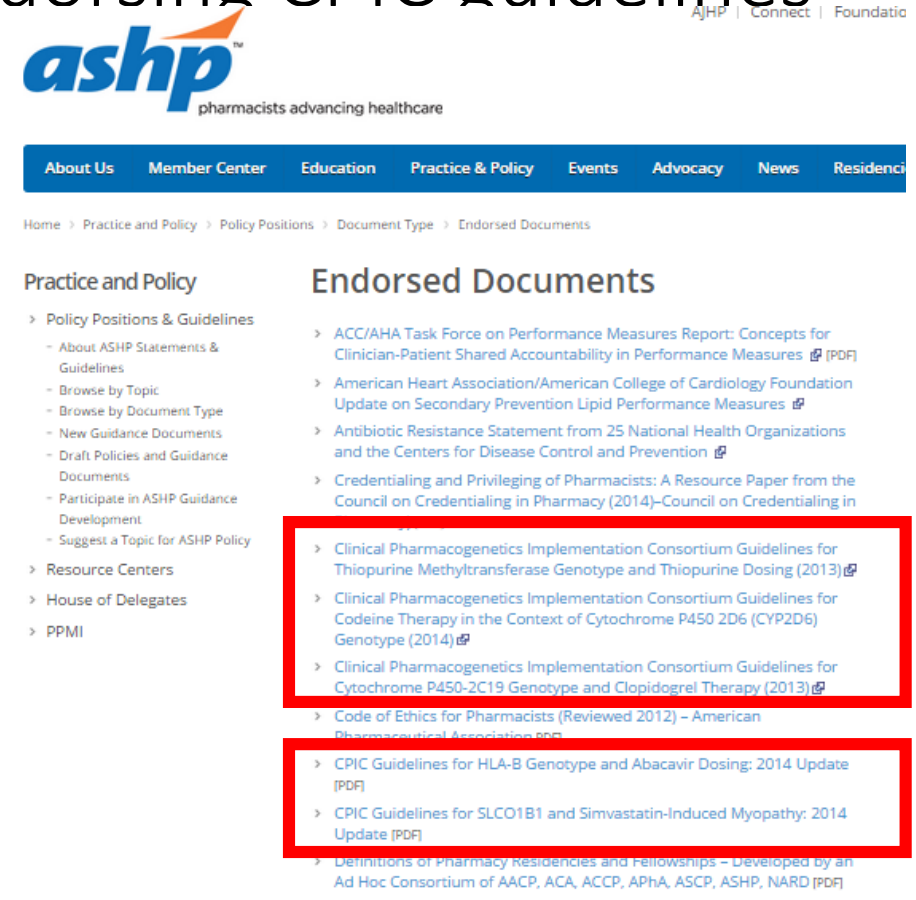


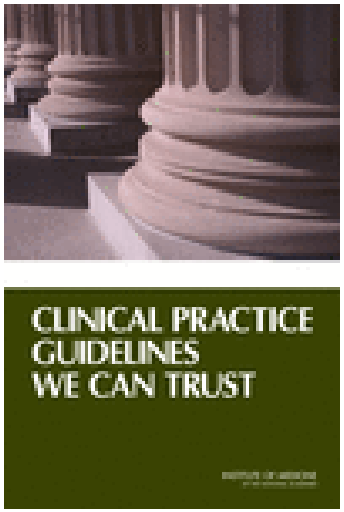
CPIC guidelines linked to “Practice Guideline” filter on PubMed

CPIC is cited in NIH's Genetic Test Registry (GTR) for clinical pharmacogenetic tests



ASHP is endorsing CPIC guidelines





Committee on Standards for Developing
Trustworthy Clinical Practice Guidelines

Board on Health Care Services

Robin Graham, Michelle Mancher, Dianne Miller Wolman,
Sheldon Greenfield, and Earl Steinberg, *Editors*

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OF THE NATIONAL ACADEMIES

Table 2. Comparison of CPIC guidelines to the IOM's Standards for Developing Trustworthy Clinical Practice Guidelines.

IOM Standard	CPIC Guidelines
Establishing transparency	
1.1 The process for developing a clinical practice guideline (CPG) – including funding – should be explicitly described and publicly accessible.	*In the initial article articulating the need for pharmacogenetics guidelines Relling and Klein outlined the CPIC process [1]. This article does not describe funding, but CPIC funding (currently via NIGMS) is fully and publicly disclosed in each guideline and on its webpage on PharmGKB (http://www.pharmgkb.org/page/cpic and http://www.pgrn.org/display/pgrnwebsite/PGRN+Home). The current publication provides additional transparency for the CPIC guideline development process.*

Caudle et al, *Current Drug Metab* 2014

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* and Voriconazole Therapy

B Moriyama[1], A Owusu Obeng[2,3,4], J Barbarino[5], SR Penzak[6], SA Henning[1], SA Scott[2,7], JAG Agúndez[8], JR Wingard[9], HL McLeod[10], TE Klein[5], SJ Cross[11,12], KE Caudle[11] and TJ Walsh[13]

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

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

[a]Assignment of allele function (CYP2C19 allele definition table) and citations for allele function (CYP2C19 allele functionality references) are posted to PharmGKB.org.[2] [b]See the CYP2C19 frequency table (link to PharmGKB) for race specific allele and phenotype frequencies. [c]Based on the Clinical Pharmacogenetics Implementation Consortium (CPIC) term standardization project (reference in press), the term "normal metabolizer" will be used instead of the term "extensive metabolizer" in all new and updated CPIC guidelines. [d]The predicted metabolizer phenotype for the*2/*17 genotypes is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP2C19*2* (5). See **Supplementary Materials** online for a more comprehensive list of predicted metabolizer phenotypes.

Table 2 Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for adult patients

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 identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate[c]
CYP2C19 rapid metabolizer (*1/*17)	In patients for whom a rapid metabolizer genotype (*1/*17) is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing[b]	Strong
CYP2C19 intermediate metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Initiate therapy with recommended standard of care dosing[b]	Moderate
CYP2C19 poor metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b] 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.	Moderate

[a]Rating scheme is described in **Supplementary Data** online. [b]Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, therapeutic drug monitoring, and comorbidities. [c]Recommendations based upon data extrapolated from patients with *CYP2C19*1/*17* genotype.

Supplemental Table S1. Evidence linking *CYP2C19* genotype to voriconazole phenotype
CYP2C19 allele definition table
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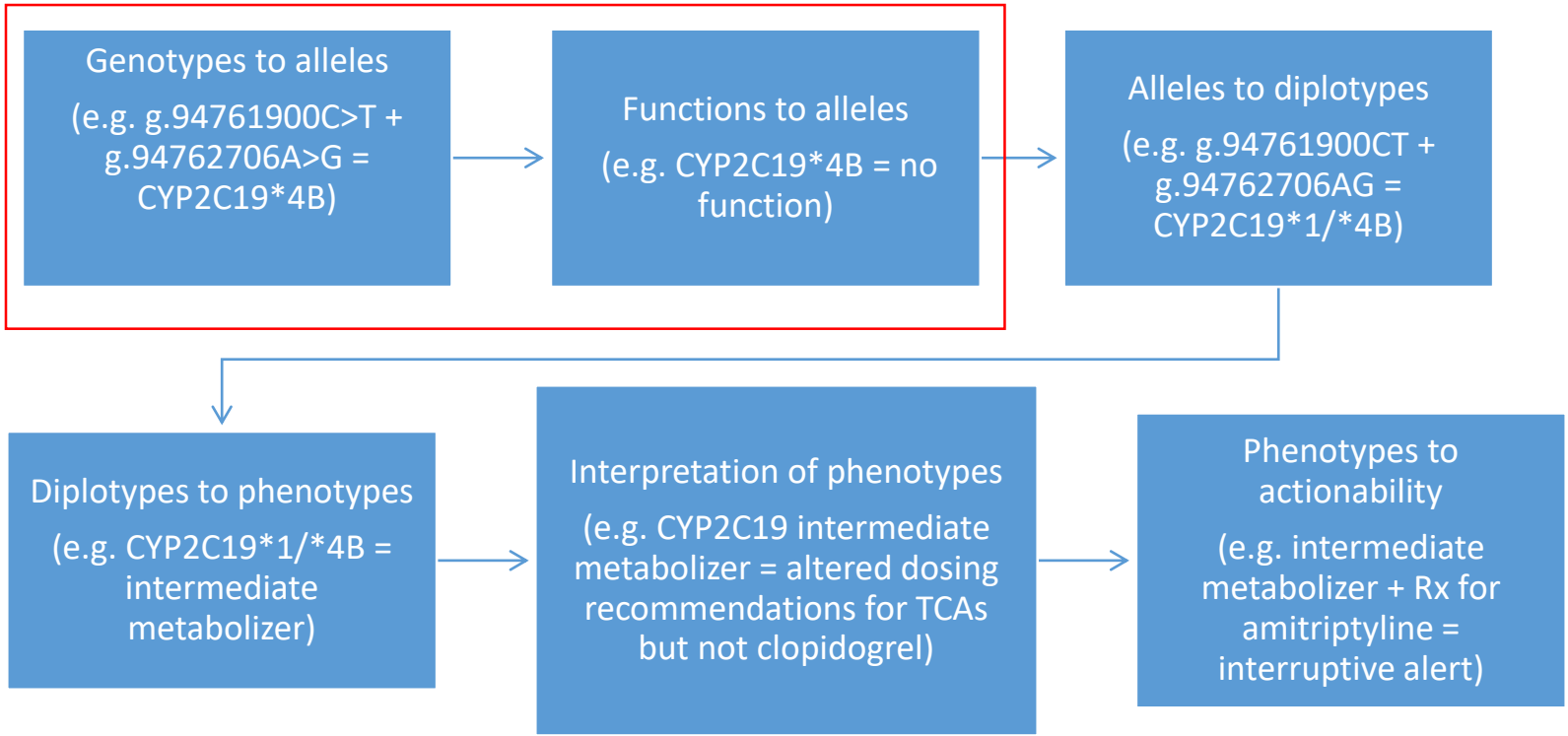
...the guideline publication supplement or referenced in the guideline[a]:

... *CYP2C19* genotype to voriconazole phenotype

Gene resource mapping

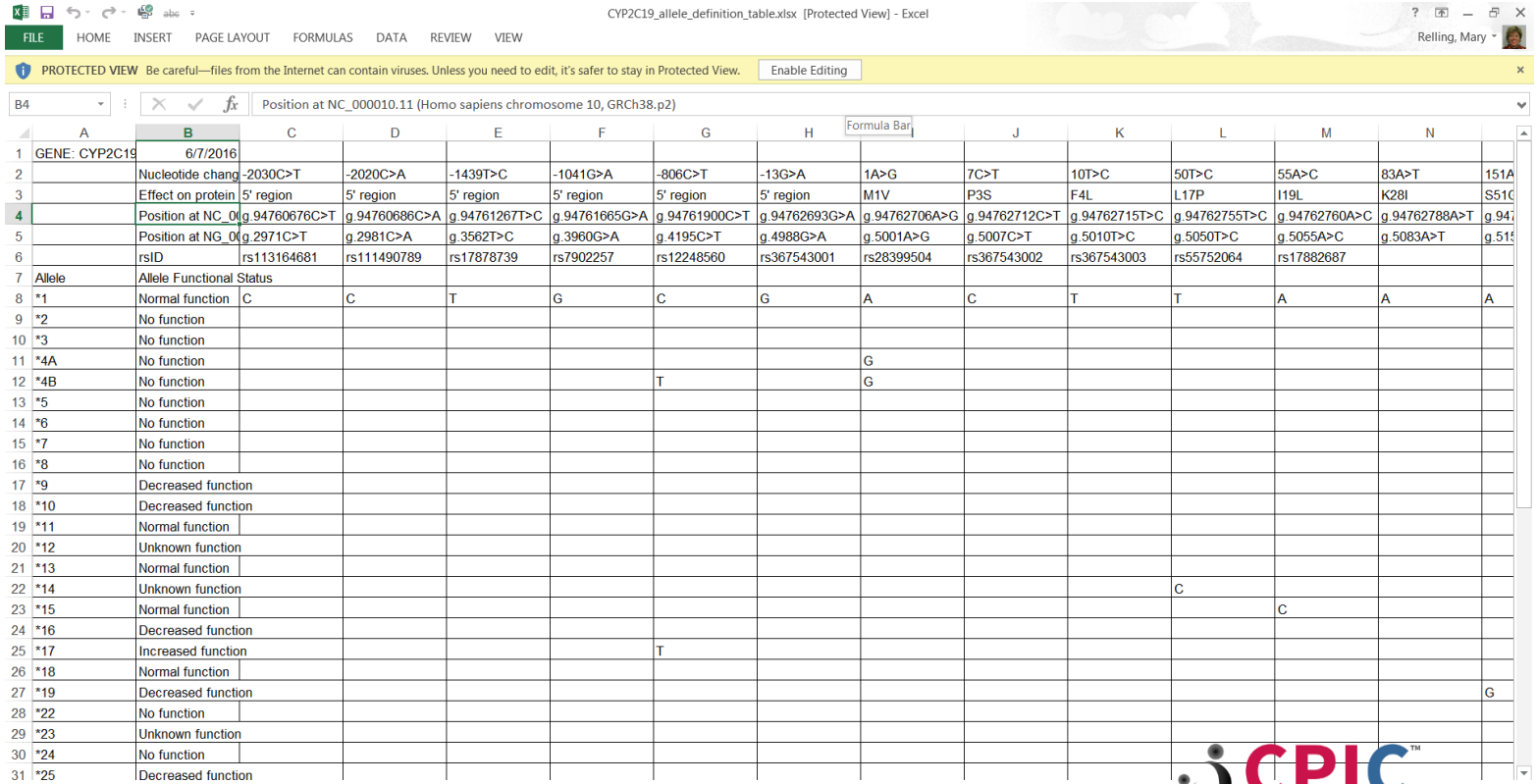
CYP2C19 gene resource mappings

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

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

Relling, Mary

PROTECTED VIEW Be careful—files from the Internet can contain viruses. Unless you need to edit, it's safer to stay in Protected View. Enable Editing

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*

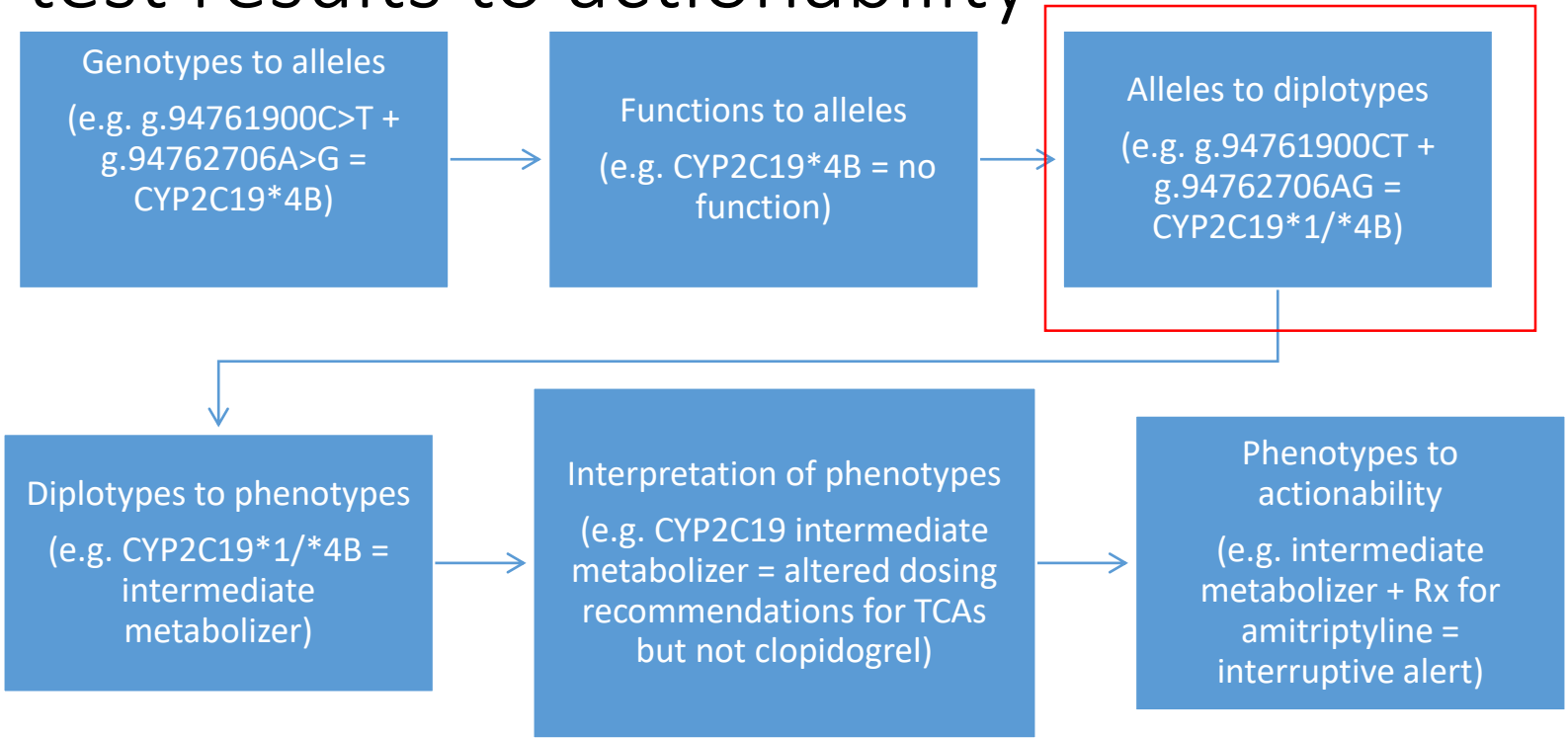
Allele functionality table: alleles to function

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/

CPIC tables allow translation of genetic test results to actionability

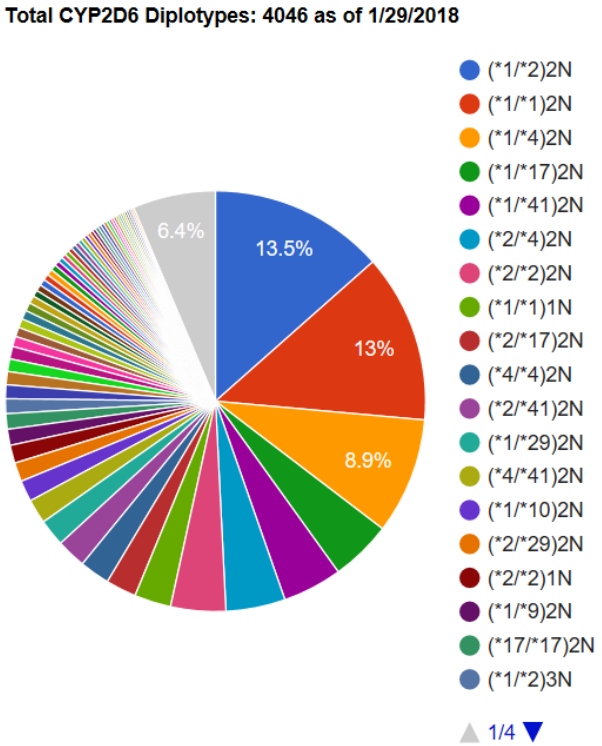


https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials

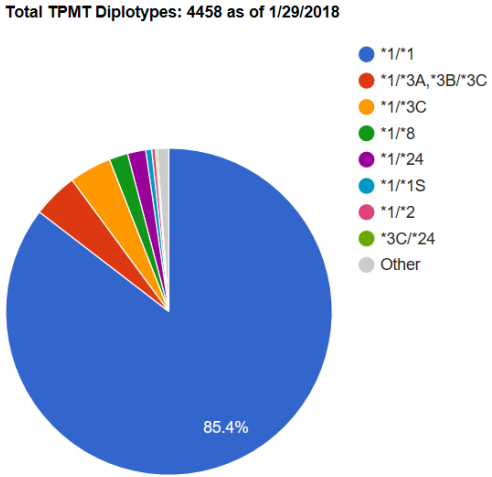
Variants must be phased to assign diplotypes for pharmacogenes

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

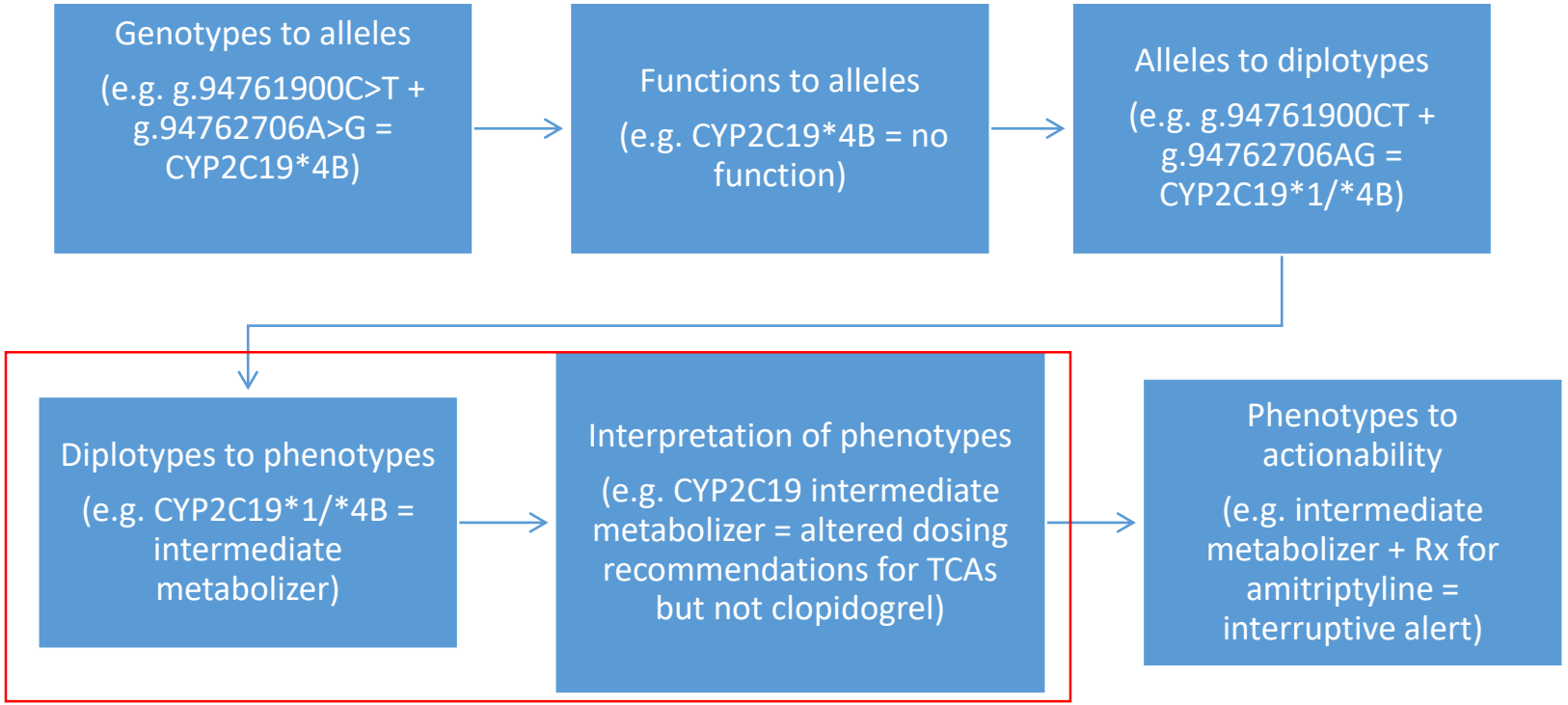
CYP2D6: 207 diplotypes observed in first 4046 pts on PG4KDS



TPMT is much simpler



CPIC tables allow translation of genetic test results to actionability



https://cpicpgx.org/guidelines/
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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.

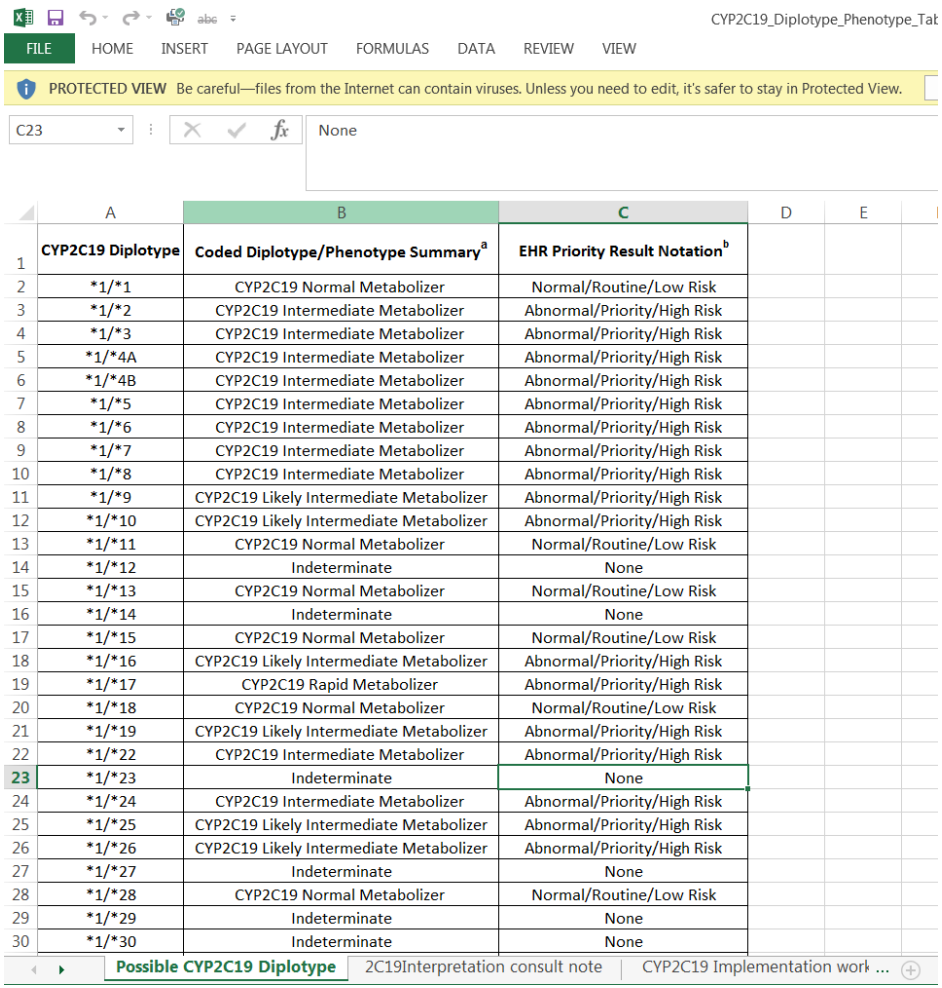
https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

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

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

PROTECTED VIEW Be careful—files from the Internet can contain viruses. Unless you need to edit, it's safer to stay in Protected View.

C23 | None

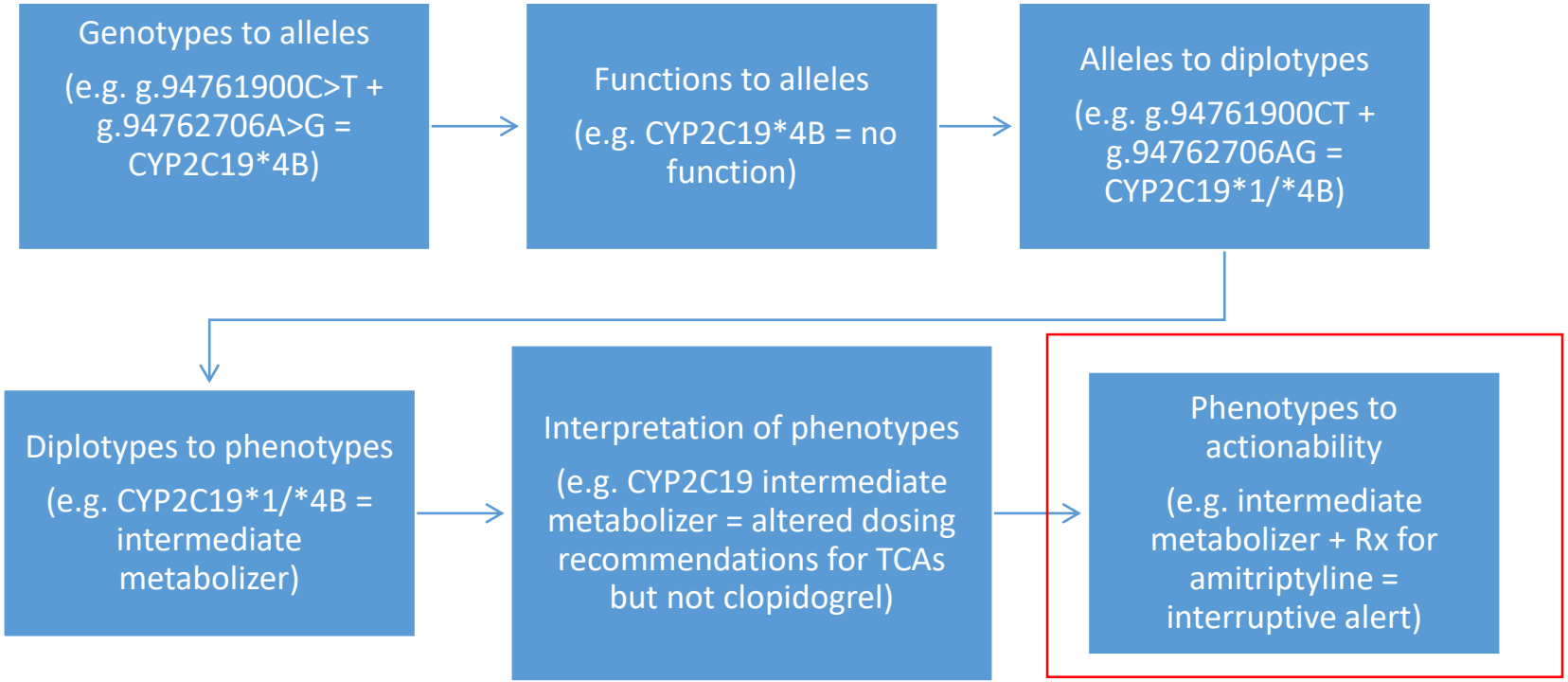
	A	B	C	D	E
1	**CYP2C19 Diplotype**	**Coded Diplotype/Phenotype Summary[a]**	**EHR Priority Result Notation[b]**		
2	*1/*1	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
3	*1/*2	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
4	*1/*3	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High 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 ...

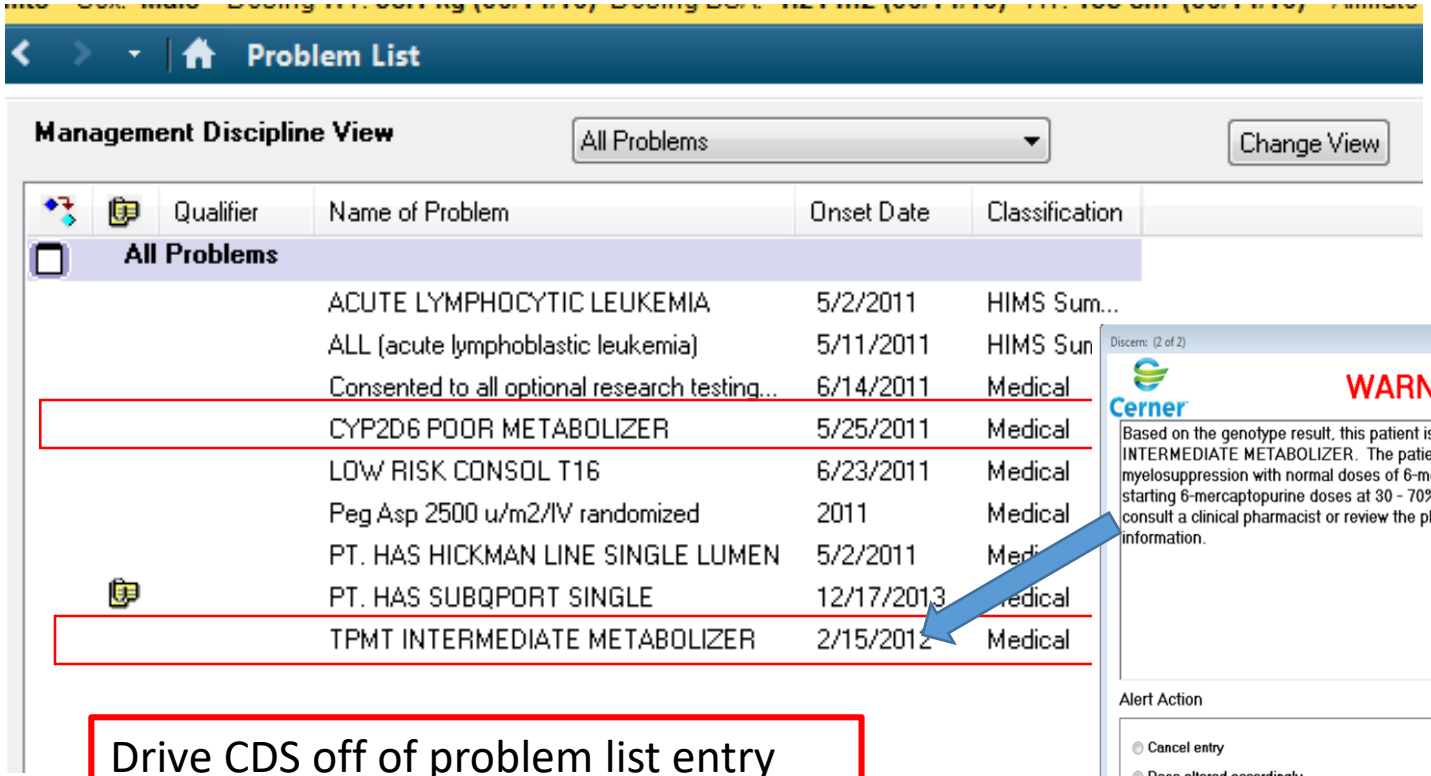
https://www.pharmgkb.org/page/cyp2c19RefMaterials
https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/

CPIC™ Clinical Pharmacogenetics Implementation Consortium

CPIC tables allow translation of genetic test results to actionability



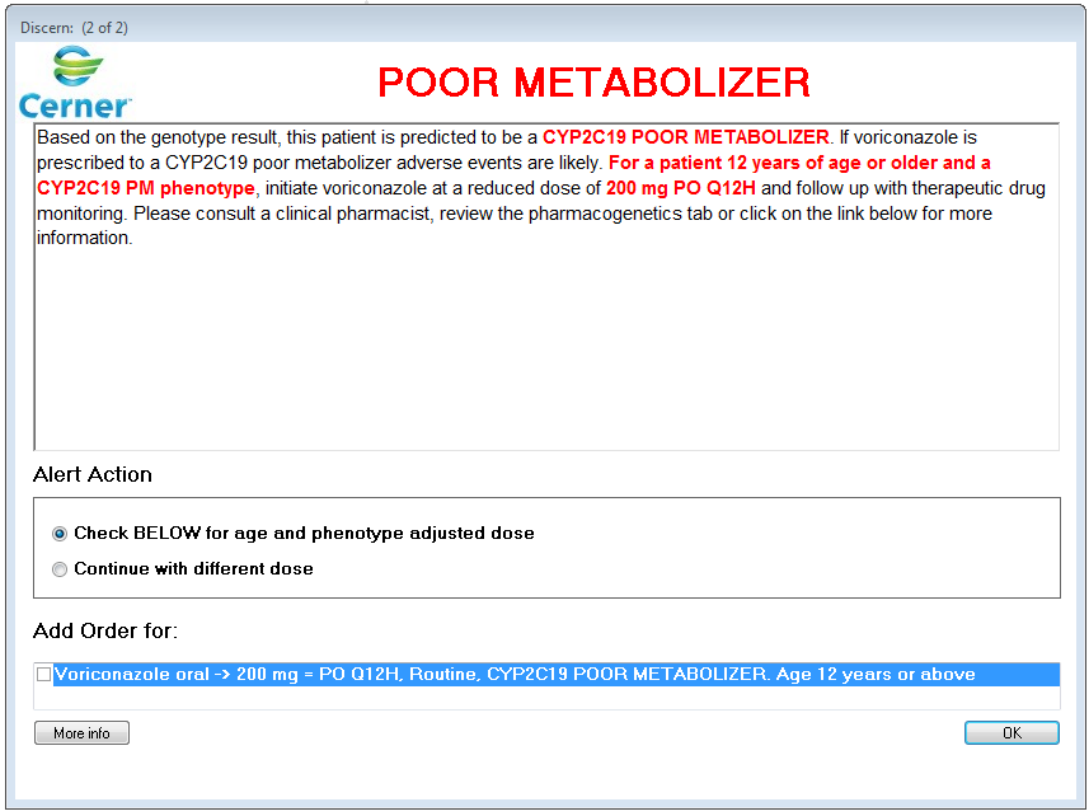
https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials



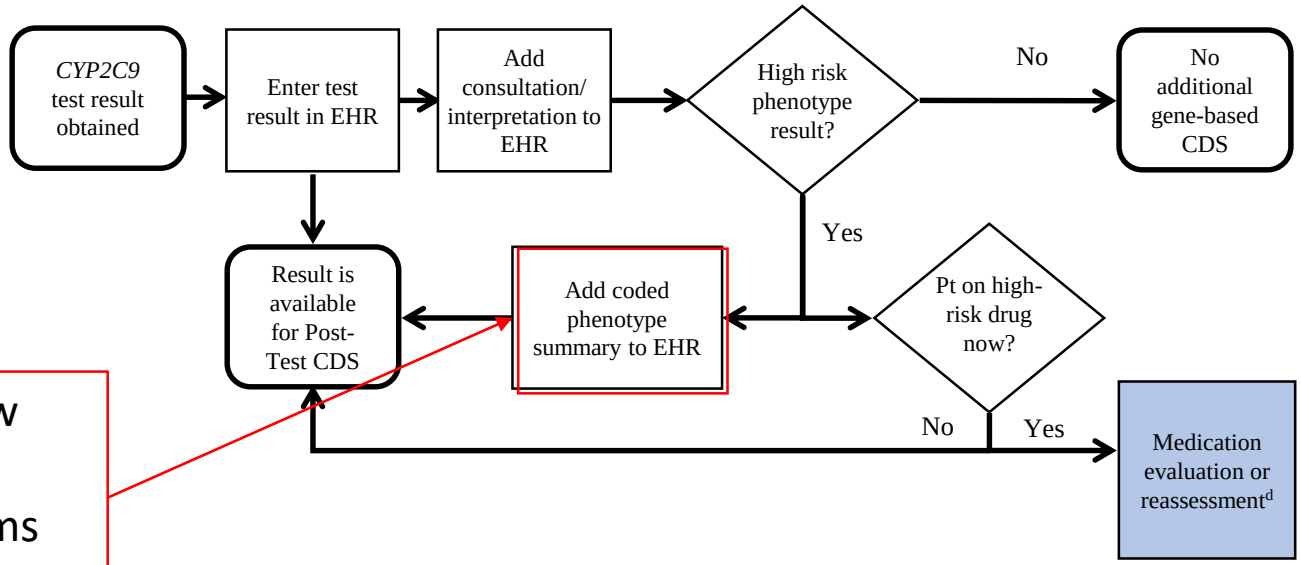
Drive CDS off of problem list entry

PG4KDS

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

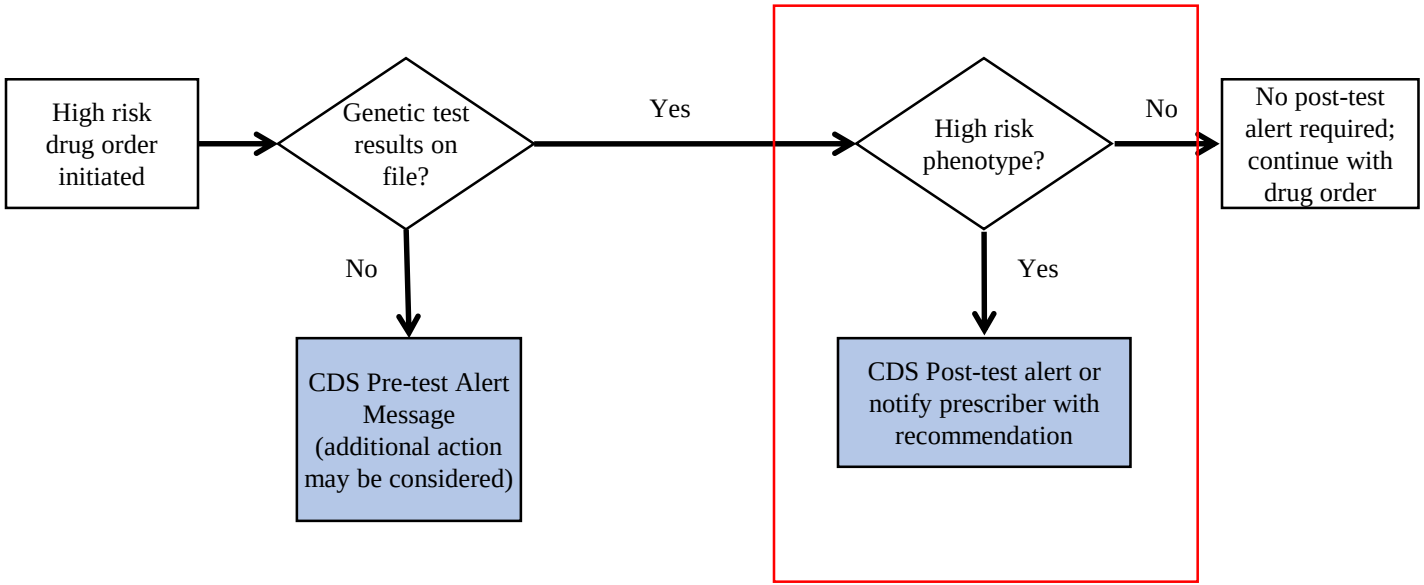


PG4KDS



There are now available SNOMED terms for phenotypes

Blue shading indicates interaction with provider


High risk drug order initiated
Genetic test results on file?
Yes
No
CDS Pre-test Alert Message (additional action may be considered)
High risk phenotype?
No
No post-test alert required; continue with drug order
Yes
CDS Post-test alert or notify prescriber with recommendation

CPIC® Guideline for Thiopurines and TPMT

Most recent guideline publication:

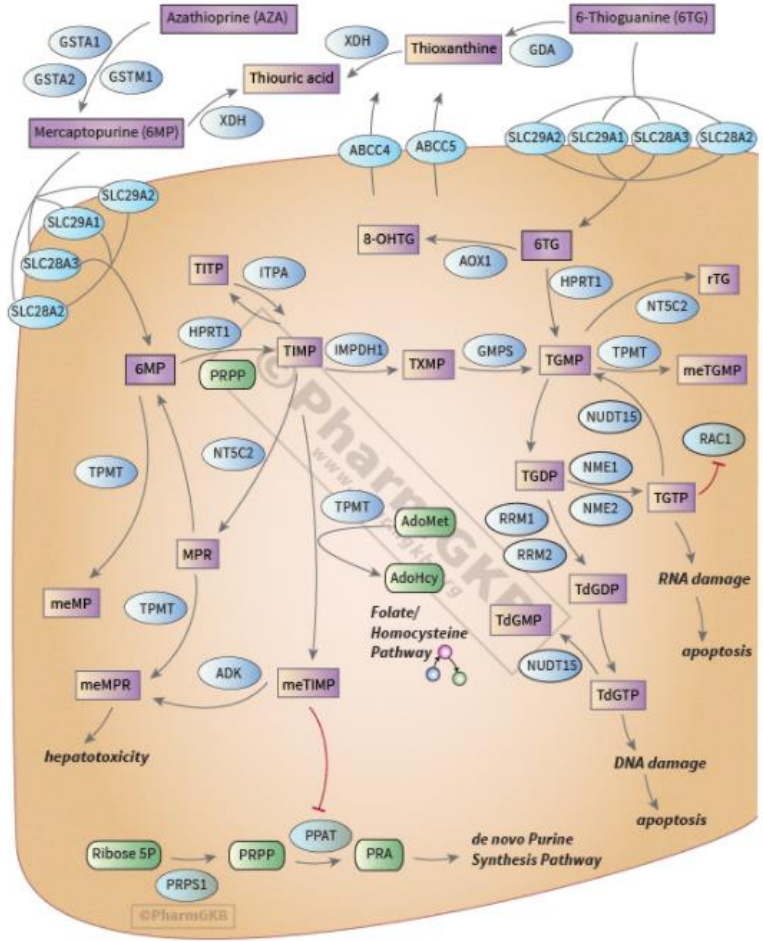
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing (March 2011)

Updates since publication:

May 2016: Several studies have reported that individuals who carry low-function alleles for *NUDT15* are unable to tolerate usual doses of thiopurines.[Yag SK et al. Nat Genet. 2014;46:1017, Yang JJ et al. J Clin Oncol. 2015;33:1235, Tanaka Y et al. Br J Haemtol. 2015;171:109, Kakuta Y et al. Pharmacogenomics J. 2015 doi: 10.1038/tpj.2015.43, Chiengthong K et al. Haematologica. 2016;101:e24, Liang DC et al. Pharmacogenomics J. 2015 doi: 10.1038/tpj.2015.75, Asada A et al. J Gastroenterol. 2016;51:22, Lee YJ et al. Eur J Gastroenterol Hepatol.2016;28:475, Moriyama T et al. Nat Genet. 2016;48:367] These alleles are more common among those of Asian ancestry and Hispanic ethnicity than others.[Yang JJ et al. J Clin Oncol. 2015;33:1235, Moriyama T et al. Nat Genet. 2016;48:367] The dose tolerated by those with two low-function alleles is only ~ 10% that tolerated by those with no low-function *NUDT15* or *TPMT* alleles.[Yang JJ et al. J Clin Oncol. 2015;33:1235, Moriyama T et al. Nat Genet. 2016;48:367] CPIC is planning a guideline to address *NUDT15* variants and possible dosing recommendations for thiopurines.

These studies have been annotated on PharmGKB – click for more information.

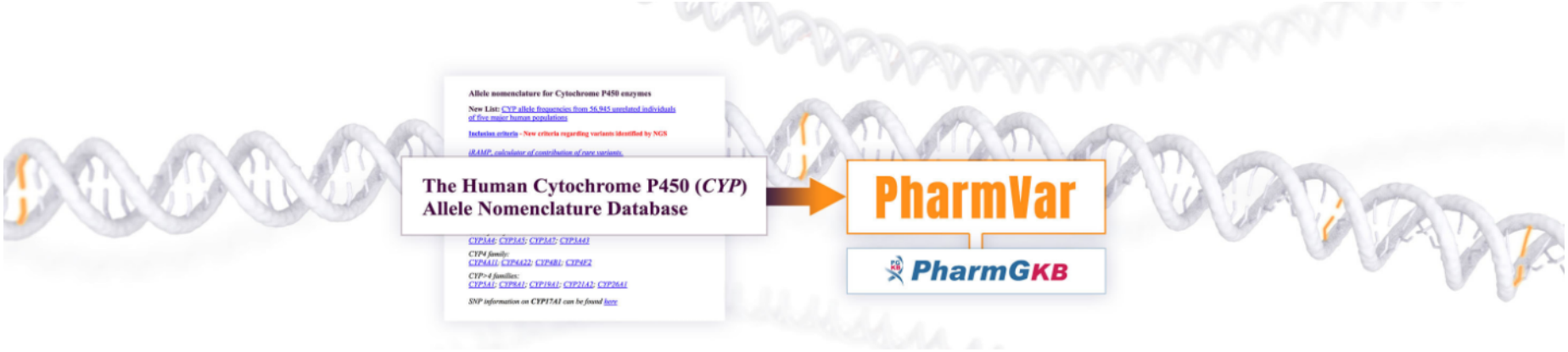
April 2013: Guideline authors reviewed additional literature and concluded that none of the evidence would change the therapeutic recommendations in the 2011 guideline; therefore, the 2011 guideline remains clinically current. The guideline supplement and evidence table were updated (see below).



- ↓ TPMT and/or NUDT15 activity =
- ↑ myelosuppression
- CPIC guideline update will include *NUDT15*

Defining alleles

	A	B	C	D	E	F	G	H	I
1	GENE: NUDT15	12/6/2017							
2		Nucleotide change on cDNA	37_42delGGAGTC	52G>A	55_56insGAGTCG	101G>C	103A>G	415C>T	416G>A
3		Effect on protein (NP_060753.1)	G17_V18del	V18I	V18_V19insGV	R34T	K35E	R139C	R139H
4		Position at NC_000013.11 (Homo sapiens chromosome 6, GRCh38.p7)	g.48037783_48037788delGGAGTC	g.48037798G>A	48037801_48037802insGAGTCG	g.48037847G>C	g.48037849A>G	g.48045719C>T	g.48045720G>A
5		Position at NG_047021.1 (NUDT15 RefSeqGene)	g.5217_5222delGGAGTC	g.5232G>A	g.5235_5326insGAGTCG	g.5281G>C	g.5283A>G	g.13153C>T	g.13154G>A
6		rsID	rs746071566	rs186364861	rs869320766	rs766023281	NA	rs116855232	rs147390019
7	NUDT15	Allele Functional Status							
8	*1	Normal function	GGAGTC	G	del	G	A	C	G
9	*2	No function			insGAGTCG			T	
10	*3	No function						T	
11	*4	Decreased Function							A
12	*5	Uncertain		A					
13	*6	Uncertain			insGAGTCG				
14	*7	Uncertain				C			
15	*8	Uncertain					G		
16	*9	Uncertain	del						
17									



The Pharmacogene Variation (PharmVar) Consortium is a central repository for pharmacogene (PGx) variation that focuses on haplotype structure and allelic variation. The information in this resource facilitates the interpretation of pharmacogenetic test results to guide precision medicine.

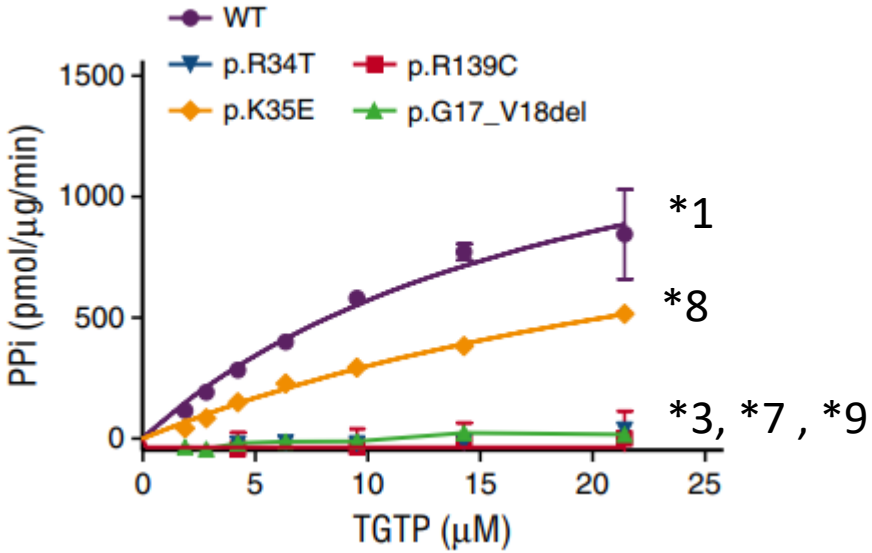
The **Pharm**acogene **Var**iation (PharmVar) Consortium is the new home for PGx gene nomenclature and serves as a centralized "Next-Generation" Pharmacogene Variation data repository. After more than 15 years, the Human Cytochrome P450 (CYP) Allele Nomenclature website has been transitioned from its original location at the Karolinska Institutet in Sweden to Children's Mercy in Kansas City, USA. The new interactive PharmVar database launched on March 21st, 2018 and contains the high-priority CYP2C9, CYP2C19 and CYP2D6 genes. Other P450 genes will be transferred to PharmVar within the first year of the project (once a gene is transferred into PharmVar, it will receive legacy status on the Nomenclature website). Other PGx genes including clinically actionable CPIC genes will be added in the future.

PharmVar Publication
An inaugural article on PharmVar has been published in Clinical Pharmacology & Therapeutics . Details available on the resources page.

Original content from the **cypalleles.ki.se** site is available through the archive

www.pharmvar.org

Determining function of NUDT15 novel variants



Nucleotide diphosphatase activity

Blood. 2017 Sep 7;130(10):1209-1212

Determining function of NUDT15 novel variants

Table 1. Patient characteristics and MP tolerance

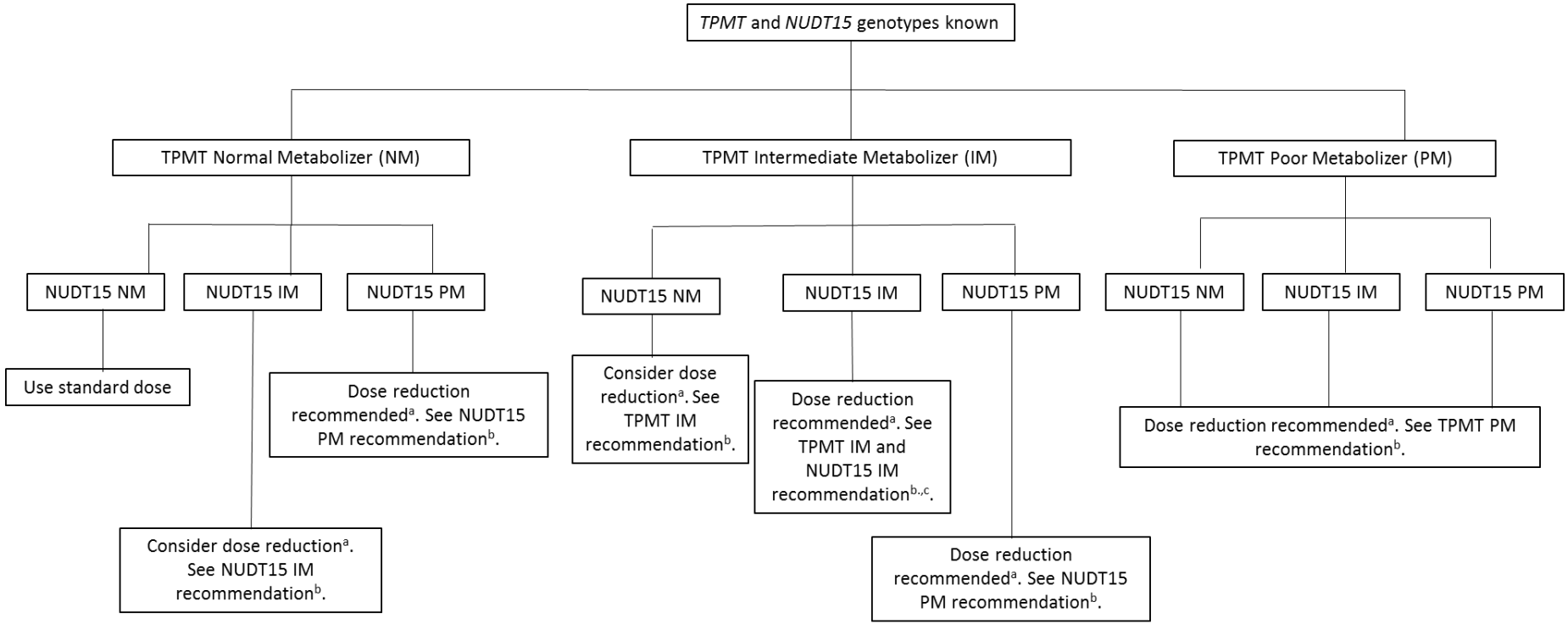
	NUDT15 novel variant				
	c.101G>C p.R34T (*7)		c.103A>G p.K35E (*8)	c.37_42delGGAGTC p.G17_V18del (*9)	
Position at chr13	48037847		48037849	48037783-48037788	
rsID	rs766023281		NA	rs746071566	
	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**	**Subject 5**
Sex	Male	Male	Male	Female	Male
Age, y	13.8	0.3	4.4	13.7	6.3
Race	East Asian	East Asian	East Asian	African	European
Diagnosis	B-ALL	B-ALL	B-ALL	T-ALL	B-ALL
Protocol	MaSpore 2003 SR	TPOG-2002-infantile ALL	MaSpore 2003 IR	TOT XIIIB HR	TOT XVI LR
NUDT15 diplotype*	*1/p.R34T	*1/p.R34T	*2/p.K35E	*1/p.G17_V18del	*1/p.G17_V18del
TPMT genotype	WT	WT	WT	WT	WT
4-wk tolerated MP dosage, mg/m^2 per day	17.9	16.4†	8.5	82.5 for a 1-wk period‡	43.5
Protocol MP dosage, mg/m^2 per day	50	25†	50	75 for a 1-wk period‡	75

Blood. 2017 Sep 7;130(10):1209-1212

Assigning allele function

GENE: NUDT15	12/6/2017		
Allele	**Allele Functional Status**	**References**	**PMID**
*1	Normal Function		
*2	No Function	Moriyama et al., 2016	26878724
*3	No Function	Moriyama et al., 2016	26878724
*4	Decreased Function	Moriyama et al., 2016	26878724
*5	Uncertain	Moriyama et al., 2016	26878724
*6	Uncertain	Moriyama et al., 2016	26878724
*7	Uncertain	Moriyama et al., 2017	28659275
*8	Uncertain	Moriyama et al., 2017	28659275
*9	Uncertain	Moriyama et al., 2017	28659275

Assignment of likely NUDT15 phenotypes based on genotypes		
Normal metabolizer	an individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	an individual carrying one normal function allele PLUS one no function allele OR one decreased function allele PLUS one no function allele	*1/*2; *1/*3 *3/*4
Possible Intermediate metabolizer	an individual carrying one uncertain function allele PLUS one no function allele	*2/*5, *3/*6
Poor metabolizer	an individual carrying two no function alleles	*2/*2; *2/*3, *3/*3
Indeterminate	an individual carrying two decreased function alleles OR one normal function allele PLUS one decreased function allele or one uncertain function allele OR one decreased function PLUS one uncertain function allele	*4/*4 *1/*4 *1/*5 *4/*5


TPMT and *NUDT15* genotypes known
TPMT Normal Metabolizer (NM)
TPMT Intermediate Metabolizer (IM)
TPMT Poor Metabolizer (PM)
NUDT15 NM
NUDT15 IM
NUDT15 PM
NUDT15 NM
NUDT15 IM
NUDT15 PM
NUDT15 NM
NUDT15 IM
NUDT15 PM
Use standard dose
Dose reduction recommended[a]. See NUDT15 PM recommendation[b].
Consider dose reduction[a]. See NUDT15 IM recommendation[b].
Consider dose reduction[a]. See TPMT IM recommendation[b].
Dose reduction recommended[a]. See TPMT IM and NUDT15 IM recommendation[b,c].
Dose reduction recommended[a]. See NUDT15 PM recommendation[b].
Dose reduction recommended[a]. See TPMT PM recommendation[b].

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