Clinical Pharmacogenetics Implementation Consortium (CPIC®) tables for EHR implementation

Mary V. Relling, Pharm.D.

PGRN

CPIC™ Clinical Pharmacogenetics Implementation Consortium

PharmGKB

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

2009/2010 Survey of pgen "experts" (PGRN and ASCPT): 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 assign phenotype)
  - Providing recommendations for selecting the drug/gene pairs to implement

Clin Pharmacol Ther. 2011 89:464-7.
Similar in 2014

Since 2009, working to facilitate the process of preemptive clinical pharmacogenetic testing

CPIC
Clinical Pharmacogenetics Implementation Consortium

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

St. Jude Children's Research Hospital
PG4KDS Protocol

STANFORD UNIVERSITY

Long-term goal: preemptive pharmacogenetic testing as the standard of care… for everyone
All CPIC guidelines.

The most clinically important part of a CPIC guideline is “Table 2”: Linking phenotypes to prescribing actions

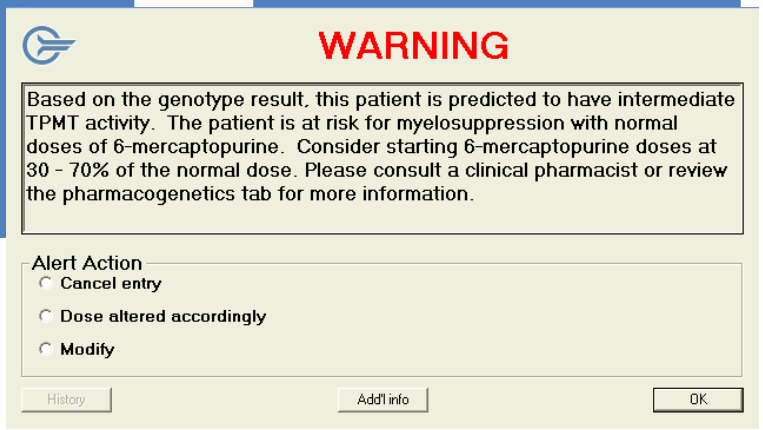
Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

CPIC™
Clinical Pharmacogenetics Implementation Consortium

How do we get from genotype to interruptive CDS for prescribing?

g.94761900C>T +
g.94762706A>G

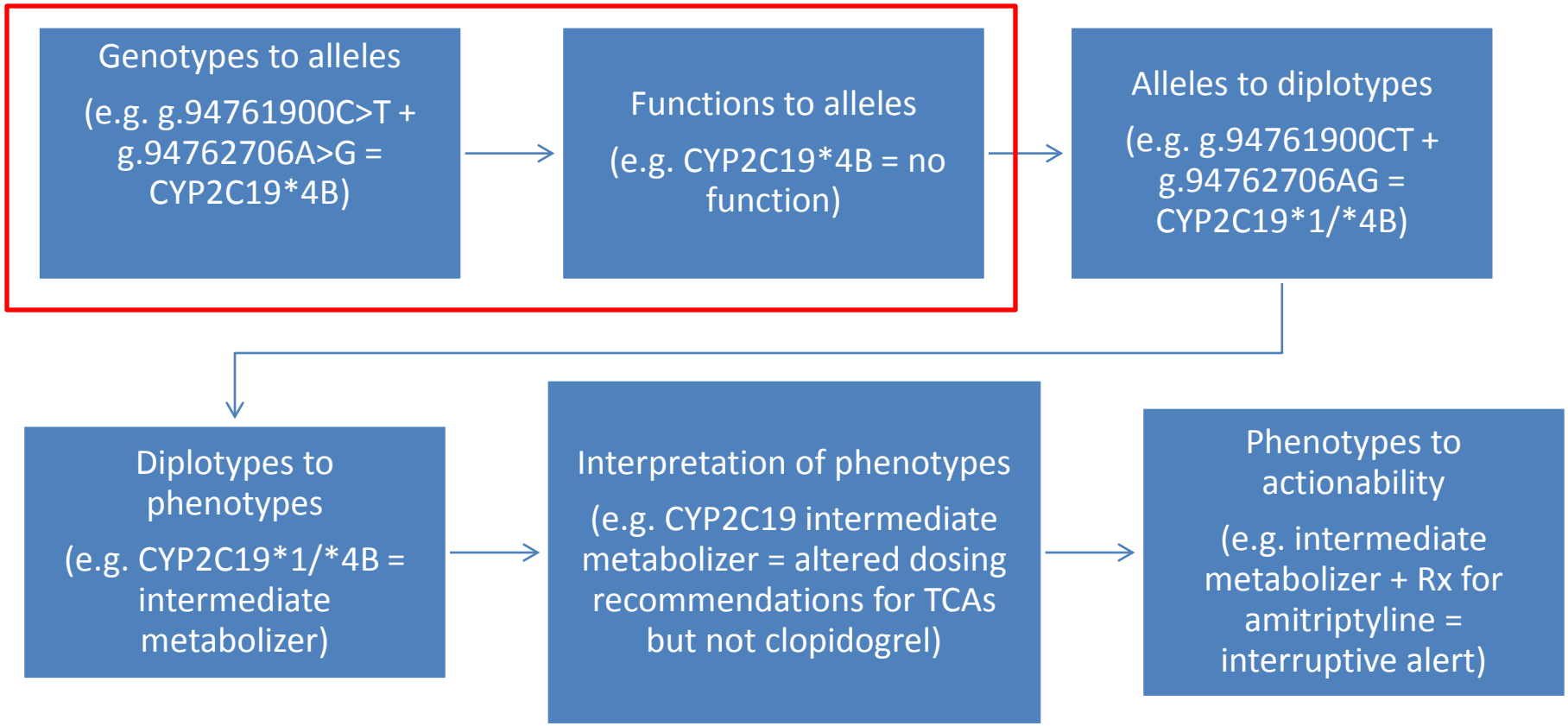


Improvements to facilitate implementation

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- Web versions of tables; links in guideline and supplement
- More comprehensive listing of alleles
- CPIC standardized terms for allele function and phenotype
- More unambiguous ID of alleles
- Citations for assigning function to alleles
- More comprehensive listing of diplotypes and assignments of phenotypes
- More emphasis on CDS language for prescribing

CPIC tables allow translation of genetic test results to actionability



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

https://cpicpgx.org

WhatsApp Imported From IE (1) PGx Gene Reference

CPIC Guidelines Genes-Drugs Alleles Publications Meetings Resources Informatics Members Contact

CPIC®
Clinical Pharmacogenetics Implementation Consortium

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

Background

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

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.

Search:

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*

CPIC® Guideline for Voriconazole and CYP2C19

Most Recent Guideline Publication

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Updates since publication: No updates on dosing recommendations since publication.

Tables provided in the main manuscript of the guideline

Table 1. Assignment of likely CYP2C29 phenotype based on genotypes
Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients
Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Tables provided in the guideline publication supplement or referenced in the guideline[a]

Levels of Evidence Linking Genotype to Phenotype
CYP2C19 Allele Definition Table
CYP2C19 Allele Functionality Table
CYP2C19 Frequency Table
CYP2C19 Diplotype-Phenotype Table
Gene Resource Mapping *CYP2C19* Gene Resource Mappings

PharmGKB
Pharmacogenomics. Knowledge. Implementation.

HOME | PUBLICATIONS | FEEDBACK | SIGN IN | Search PharmGKB Search

About Us | News & Events | CPIC | Collaborators | Search | Download | H

Gene-specific; footnotes indicate drug-specific concerns

Gene-specific Information Tables for CYP2C19

This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C19.

- **CYP2C19 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP219 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C19 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C19 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

CYP2C19_allele_definition_table (8).xlsx - Excel

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

Paste Cut Copy Format Painter | Arial 10 | Wrap Text | General | Conditional Formatting | Format as Table | Normal Bad Good Neutral | Insert Delete Format | AutoSum Fill Clear | Sort & Filter Find & Select

Clipboard Font Alignment Number Styles Cells Editing

A1 GENE: CYP2C19

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	GENE: CYP2C19	1/23/2017											
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
3		Effect on protein	5' region	5' region	5' region	5' region	5' region	5' region	M1V	P3S	F4L	L17P	I19L
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
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
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
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											

Alleles

READY

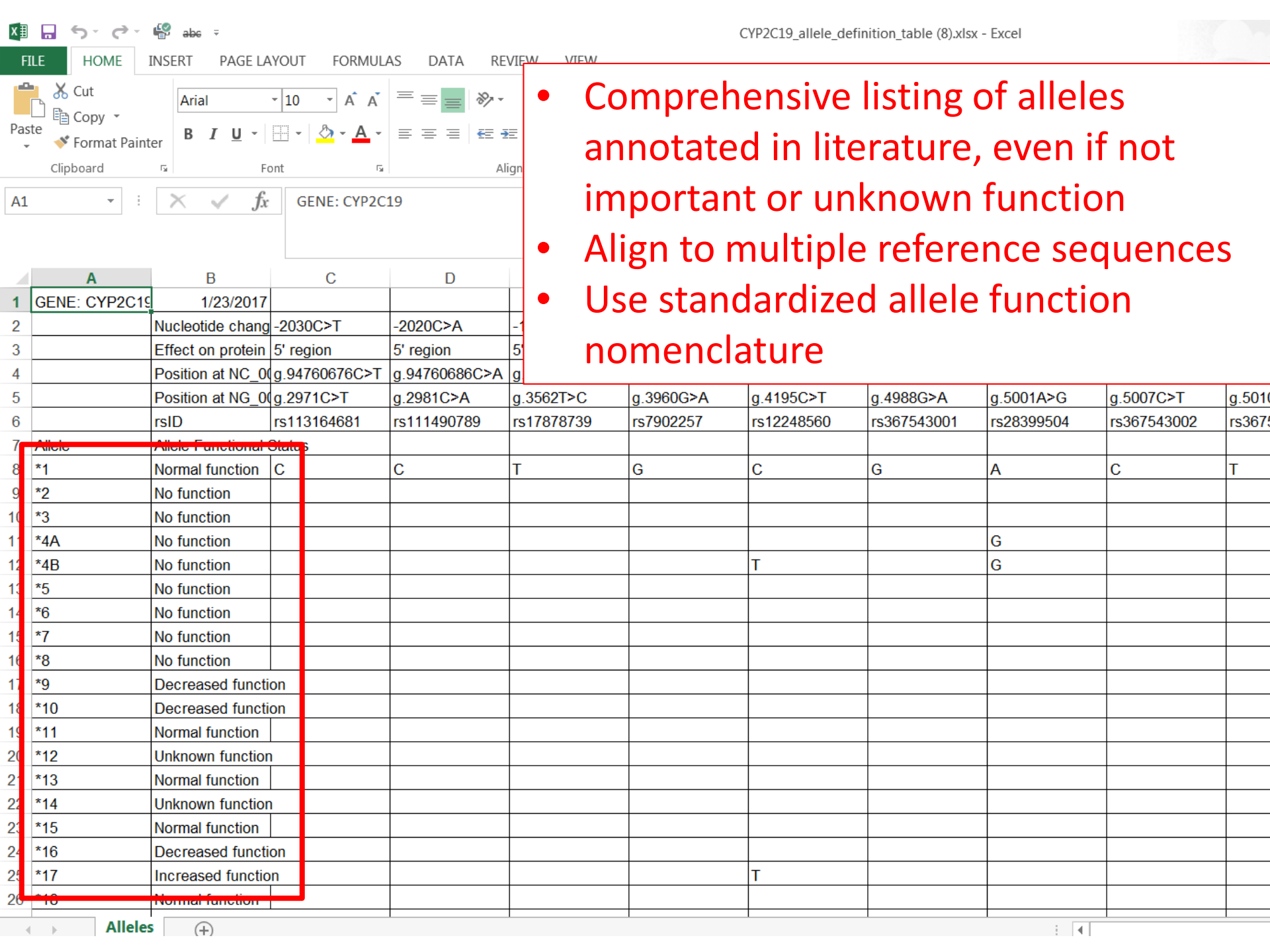
Table 1 from main manuscript: **Example** translation of diplotypes to phenotypes

Table 1 Assignment of likely thiopurine methyltransferase phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Homozygous wild-type or normal, high activity (constitutes ~86–97%[a] of patients)	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~3–14%[a] of patients)	An individual carrying one functional allele (*1) plus one nonfunctional allele (*2, *3A, *3B, *3C, or *4)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Homozygous variant, mutant, low, or deficient activity (~1 in 178 to 1 in 3,736 patients[a])	An individual carrying two nonfunctional alleles (*2, *3A, *3B, *3C, or *4)	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4

CPIC™
Clinical Pharmacogenetics Implementation Consortium

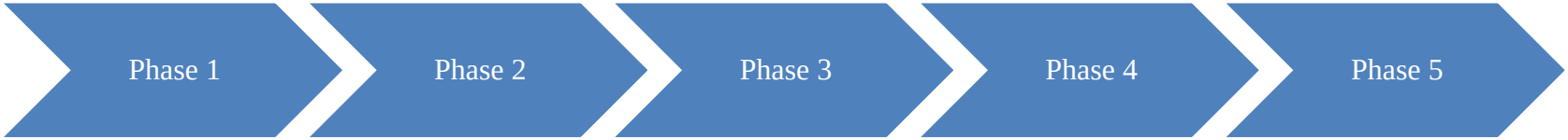
Clin Pharmacol Ther. 2011 Mar;89(3):387-91.



	A	B	C	D							
1	GENE: CYP2C19	1/23/2017									
2		Nucleotide chang	-2030C>T	-2020C>A							
3		Effect on protein	5' region	5' region							
4		Position at NC_0(	g.94760676C>T	g.94760686C>A							
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.501(
6		rsID	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs367543001	rs28399504	rs367543002	rs367
7	Allele	Allele Functional Status									
8	*1	Normal function	C	C	T	G	C	G	A	C	T
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									
23	*15	Normal function									
24	*16	Decreased function									
25	*17	Increased function					T				
26	*18	Normal function									

CPIC Phenotype Term Standardization Project

Goal: standardize terms for allele function and on phenotypes



- **Development**
  - Created a list of options for terms (literature review and survey to genetic testing labs)
- **Prioritization**
  - Survey 1: Experts specified their level of agreement or disagreement on a symmetric agree-disagree scale (1-4) for each set of gene terms. Experts can also list additional terms.
- **Refinement:**
  - Survey 2: For each gene, retained terms in which 70% of the experts agreed or strongly agreed in Survey 1.
  - Related terms were grouped together into value sets and experts specified their level of acceptance to sets of terms for each gene/gene group (acceptable/not acceptable).
- **Consensus**
  - Survey 3-5: For each gene/gene group, retained top terms selected by experts.
  - Repeat process until 70% consensus achieved.
- **Validation**
  - After 70% consensus reached, terms were circulated to the experts again for final review and feedback (as part of survey 5).

Caudle et al. *Genetics in Medicine* 2016

Group memberships for Delphi process to standardize pgen terms

- CPIC
- ClinVar
- PGRN
- CDC Pgx nomenclature WG
- GA4GH's Clinical WG
- ClinGen PG and data modeling WG
- IGNITE
- eMERGE
- IUPHAR
- ACMG Laboratory Standards and Guidelines Committee
- CAP Pharmacogenetics WG
- HL7 Clinical Genomics WG
- IOM's Roundtable on Translating Genomic-Based Research for Health
- AMIA genomics and translational bioinformatics WG
- European Medicines Agency
- G2MC Pharmacogenomics WG

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

Introduction: Reporting and sharing pharmacogenetic test results across clinical laboratories and electronic health records is a crucial step toward the implementation of clinical pharmacogenetics, but allele function and phenotype terms are not standardized. Our goal was to develop terms that can be broadly applied to characterize pharmacogenetic allele function and inferred phenotypes.

Materials and methods: Terms currently used by genetic testing laboratories and in the literature were identified. The Clinical Pharmacogenetics Implementation Consortium (CPIC) used the Delphi method to obtain a consensus and agree on uniform terms among pharmacogenetic experts.

Results: Experts with diverse involvement in at least one area of pharmacogenetics (clinicians, researchers, genetic testing laboratorians, pharmacogenetics implementers, and clinical informaticians; $n = 58$) participated. After completion of five surveys, a consensus (>70%) was reached with 90% of experts agreeing to the final sets of pharmacogenetic terms.

Discussion: The proposed standardized pharmacogenetic terms will improve the understanding and interpretation of pharmacogenetic tests and reduce confusion by maintaining consistent nomenclature. These standard terms can also facilitate pharmacogenetic data sharing across diverse electronic health care record systems with clinical decision support.

Genet Med advance online publication 21 July 2016

Key Words: CPIC; nomenclature; pharmacogenetics; pharmacogenomics; terminology

Final Standardized Terms: Allele function

Term/Gene Category	Final Term	Functional Definition	Example diplotypes/alleles
Allele Functional Status-all genes	Increased Function	Function greater than normal function	*CYP2C19*17*
	Normal Function	Fully functional/wild-type	*CYP2C19*1*
	Decreased Function	Function less than normal function	*CYP2C19*9*
	No Function	Non-functional	*CYP2C19*2*
	Unknown Function	No literature describing function or the allele is novel	*CYP2C19*29*
	Uncertain Function	Literature supporting function is conflicting or weak	*CYP2C19*12*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

CPIC™ Clinical Pharmacogenetics Implementation Consortium

Result History

Value	Valid From	Valid Until
Priority	5/25/2016 18:04	Current
Priority	5/25/2016 17:58	5/25/2016 18:04

Result | Specimen | **Comments** | Action List

1.) (Medium Importance) Result Comment by PASTERNAK, AMY on May 25, 2016 18:04

PHARMACOGENETICS CONSULT FOR
CYP2C19 GENOTYPE

Sample for CYP2C19 Genotype Obtained: 04/12/2016 07:54:00
PG4KDS CYP2C19 Genotype Result: *15/*17
CYP2C19 Phenotype Assignment: CYP2C19 Rapid Metabolizer

This result signifies that the patient has one copy of a normal function allele (*15) and one copy of an increased function allele (*17). Based on the genotype result, this patient is predicted to be a rapid metabolizer of CYP2C19 substrates. This means that the patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19 (such as amitriptyline). To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. For more information about specific medications metabolized by CYP2C19, please go to www.stjude.org/pg4kds.

Kristine Crews, Pharm.D., pager 2256.

2C19 RM 4-20160518

Gene-specific Information Tables for CYP2C19

This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C19.

- **CYP2C19 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP219 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C19 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C19 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

Paste Cut Copy Format Painter Clipboard

Arial 12 Font

Wrap Text Merge & Center General

Conditional Formatting Format as Table

Normal Bad Good Neutral

Insert Delete Format

Provide citations for assignment of function to alleles

E1

	A	B	C	D	E	F
1	GENE: CYP2C19	5/25/2016			Drug substrate	
2	Allele	Allele Functional Status	References	PMID	in vitro	in vivo
3	*1	Normal function	Romkes 1991	2009263		
4			Richardson 1995	7487078	mephenytoin, tolbutamide	
5			Blaisdell 2002	12464799	mephenytoin	
6			Hanioka 2007	17455109	mephenytoin	
7			Hanioka 2008	18312490	omeprazole	
8			Wang 2011	21325430	mephenytoin, omeprazole	
9			Takahashi 2015	25001882	clopidogrel, mephenytoin	
10	*2	No function	de Morais 1994	8195181	mephenytoin	
11			Ibeanu 1998	9732415		mephenytoin
12			Lee 2009	19661214		mephenytoin, omeprazole
13			Xiao 1997	9103550		mephenytoin
14	*3	No function	de Morais 1994	7969038		mephenytoin
15			Xiao 1997	9103550		mephenytoin
16	*4A	No function	Ferguson 1998	9435198		mephenytoin
17	*4B	No function	Scott 2012	21358751		clopidogrel
18	*5	No function	Xiao 1997	9103550		mephenytoin
19			Ibeanu 1998	10022751	mephenytoin, tolbutamide	mephenytoin
20			Wang 2011	21325430	mephenytoin, omeprazole	
21			Takahashi 2015	25001882	clopidogrel, mephenytoin	
22	*6	No function	Ibeanu 1998	9732415		mephenytoin
23			Wang 2011	21325430	mephenytoin, omeprazole	
24			Takahashi 2015	25001882	clopidogrel, mephenytoin	
25	*7	No function	Ibeanu 1999	10411572		mephenytoin
26	*8	No function	Ibeanu 1999	10411572	mephenytoin, tolbutamide	mephenytoin

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

ClinGen — The Clinical Genome Resource

Heidi L. Rehm, Ph.D., Jonathan S. Berg, M.D., Ph.D., Lisa D. Brooks, Ph.D., Carlos D. Bustamante, Ph.D., James P. Evans, M.D., Ph.D., Melissa J. Landrum, Ph.D., David H. Ledbetter, Ph.D., Donna R. Maglott, Ph.D., Christa Lese Martin, Ph.D., Robert L. Nussbaum, M.D., Sharon E. Plon, M.D., Ph.D., Erin M. Ramos, Ph.D., Stephen T. Sherry, Ph.D., and Michael S. Watson, Ph.D., fo

CPIC™
Clinical Pharmacogenetics Implementation Consortium

is a 4-star submitter to CliinVar

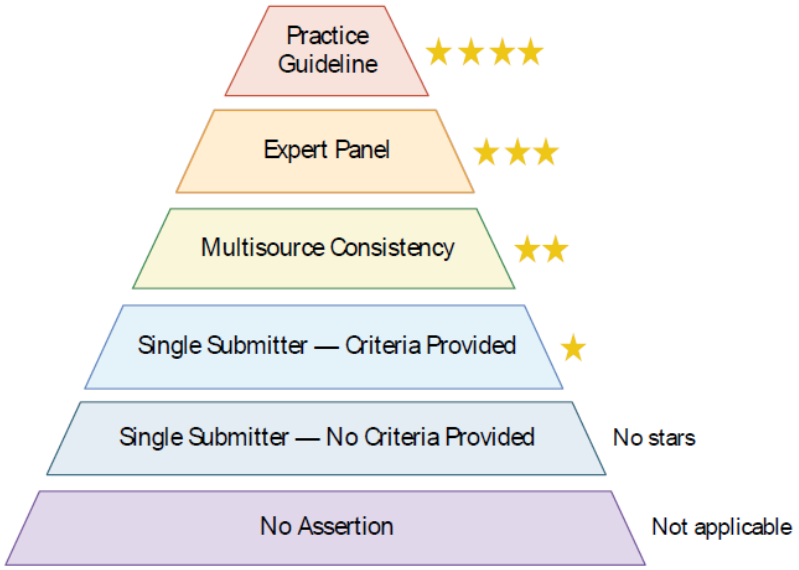


Figure 4. Review Levels Annotated in ClinVar.

Variants with assertions are rated according to the source and level of review for each submitted variant assertion. Submitters must comply with requirements (www.ncbi.nlm.nih.gov/clinvar/docs/assertion_criteria) for a submission to be assigned one, three, or four stars. Two stars are automatically assigned when multiple one-star submitted assertions are consistent. The distinction between submitters that have provided criteria and those

Gene-specific Information Tables for CYP2C19

This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C19.

- **CYP2C19 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP219 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C19 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C19 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

Allele frequencies in major race/ethnic groups

Frequencies[a] of *CYP2C19* alleles in major race/ethnic groups[b]								
CYP2C19 allele[c]	African Allele Frequency	African American Allele Frequency	Caucasian (European + North American) Allele Frequency	Middle Eastern Allele Frequency	East Asian Allele Frequency	South/Central Asian Allele Frequency	Americas Allele Frequency	Oceanian Allele Frequency
*1[d]	33.10	57.00	62.10	64.80	57.60	48.50	67.00	28.60
*2	14.20	18.30	14.60	13.10	29.30	33.10	13.10	54.90
*3	0.80	0.30	0.60	2.60	8.60	1.60	0.30	13.90
*4A	0.00	0.00	0.30		0.10	0.00	0.03	
*4B		0.00						
*5	0.00	0.00	0.00		0.00	0.00	0.00	
*6	0.00	0.00	0.10		0.00	0.00	0.00	
*7	0.00	0.00	0.00		0.00	0.00	0.00	
*8	0.00	0.20	0.30		0.00	0.00	0.10	
*9	4.20	1.10	0.00		0.00		0.10	
*10	0.00	0.40	0.00		0.00		0.10	
*11				0.00	0.00			
*12	0.00	0.20	0.00		0.00		0.00	
*13	0.00	1.20	0.10		0.00		0.40	
*14	0.00	0.00	0.00		0.00		0.00	
*15	5.70	1.40	0.20		0.20		0.40	
*16		0.00	0.00		0.00		0.00	
*17	15.10	20.10	21.30	19.50	1.60	16.90	16.30	2.50
*18					0.10			

Allele frequency by race | Diplotype frequency by race | Phenotype frequency by race | References | change log

READY

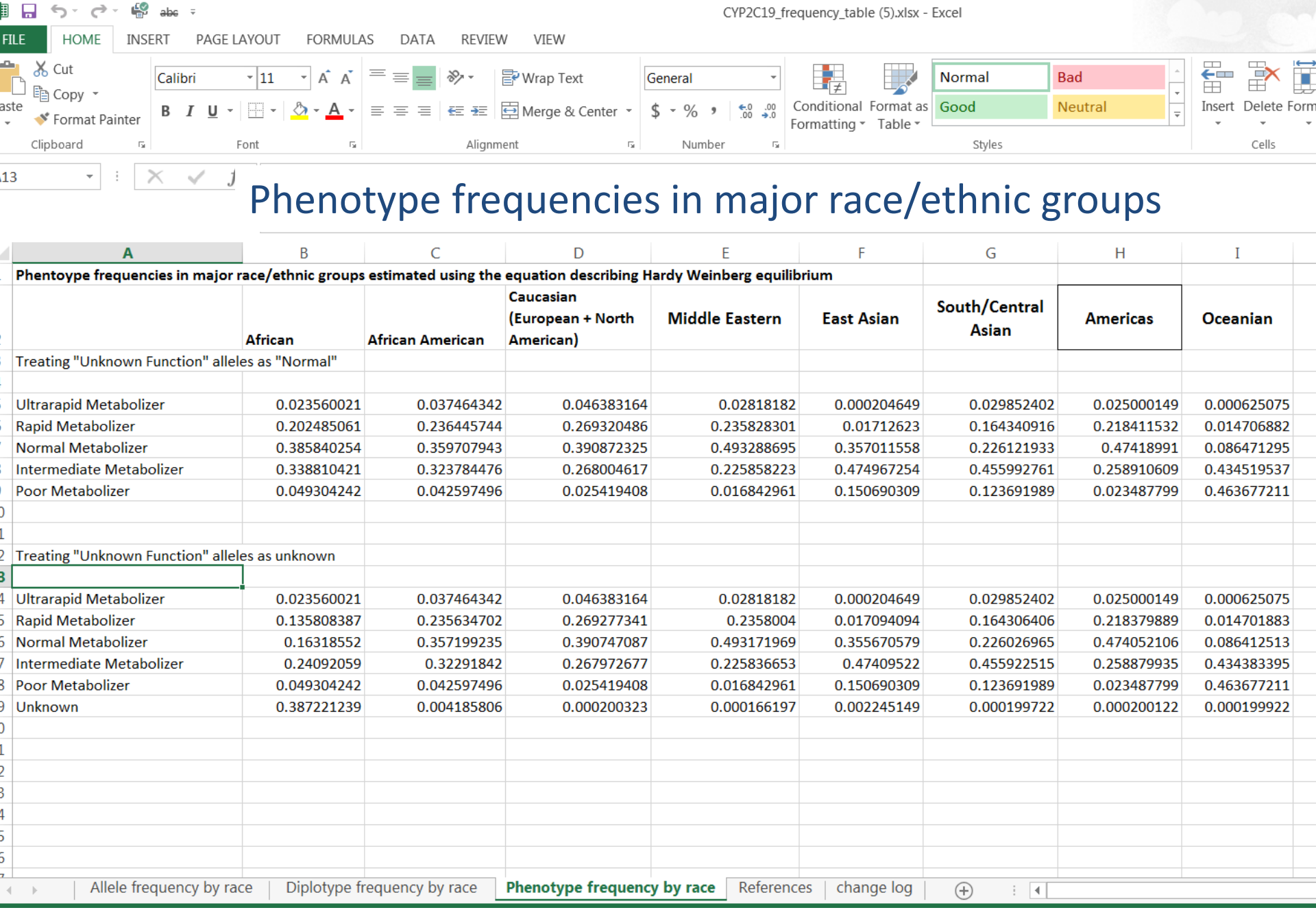
A1 | Diplotypye frequencies in major race/ethnic groups estimated using the equation describing Hardy Weinberg equilibrium

Diplotype frequencies in major race/ethnic groups

	A	B	C	D	E	F	G	H	I
1	Diplotypye frequencies in major race/ethnic groups estimated using the equation describing Hardy Weinberg equilibrium								
2	Diplotype	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
3	*1/*1	0.118567	0.326809	0.386937	0.493114	0.351966	0.225979	0.463025	0.086383
4	*1/*10	3.48E-06	0.002287	6.23E-06	5.84E-06	6.06E-06	4.75E-06	0.000688	2.94E-06
5	*1/*11	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
6	*1/*12	3.48E-06	0.001146	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
7	*1/*13	3.48E-06	0.00685	0.000629	5.84E-06	6.06E-06	4.75E-06	0.00273	2.94E-06
8	*1/*14	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
9	*1/*15	0.018779	0.00799	0.001252	5.84E-06	0.001218	4.75E-06	0.00273	2.94E-06
10	*1/*16	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
11	*1/*17	0.052853	0.110651	0.133968	0.117885	0.008487	0.082134	0.10759	0.007348
12	*1/*18	3.48E-06	5.70E-06	6.23E-06	5.84E-06	0.000612	4.75E-06	6.81E-06	2.94E-06
13	*1/*19	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
14	*1/*2	0.050767	0.104378	0.090975	0.076452	0.176895	0.159991	0.085801	0.159248
15	*1/*22	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
16	*1/*23	3.48E-06	5.70E-06	6.23E-06	5.84E-06	0.000612	4.75E-06	6.81E-06	2.94E-06
17	*1/*24	3.48E-06	5.70E-06	6.23E-06	5.84E-06	0.000612	4.75E-06	6.81E-06	2.94E-06
18	*1/*25	3.48E-06	5.70E-06	6.23E-06	5.84E-06	0.000612	4.75E-06	6.81E-06	2.94E-06
19	*1/*26	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
20	*1/*27	0.074758	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
21	*1/*28	0.001742	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
22	*1/*29	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
23	*1/*3	0.002785	0.001717	0.003745	0.014595	0.051498	0.007126	0.00205	0.040843
24	*1/*30	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
25	*1/*31	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
26	*1/*32	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06
27	*1/*33	3.48E-06	5.70E-06	6.23E-06	5.84E-06	6.06E-06	4.75E-06	6.81E-06	2.94E-06

Allele frequency by race | **Diplotype frequency by race** | Phenotype frequency by race | References | change log

READY



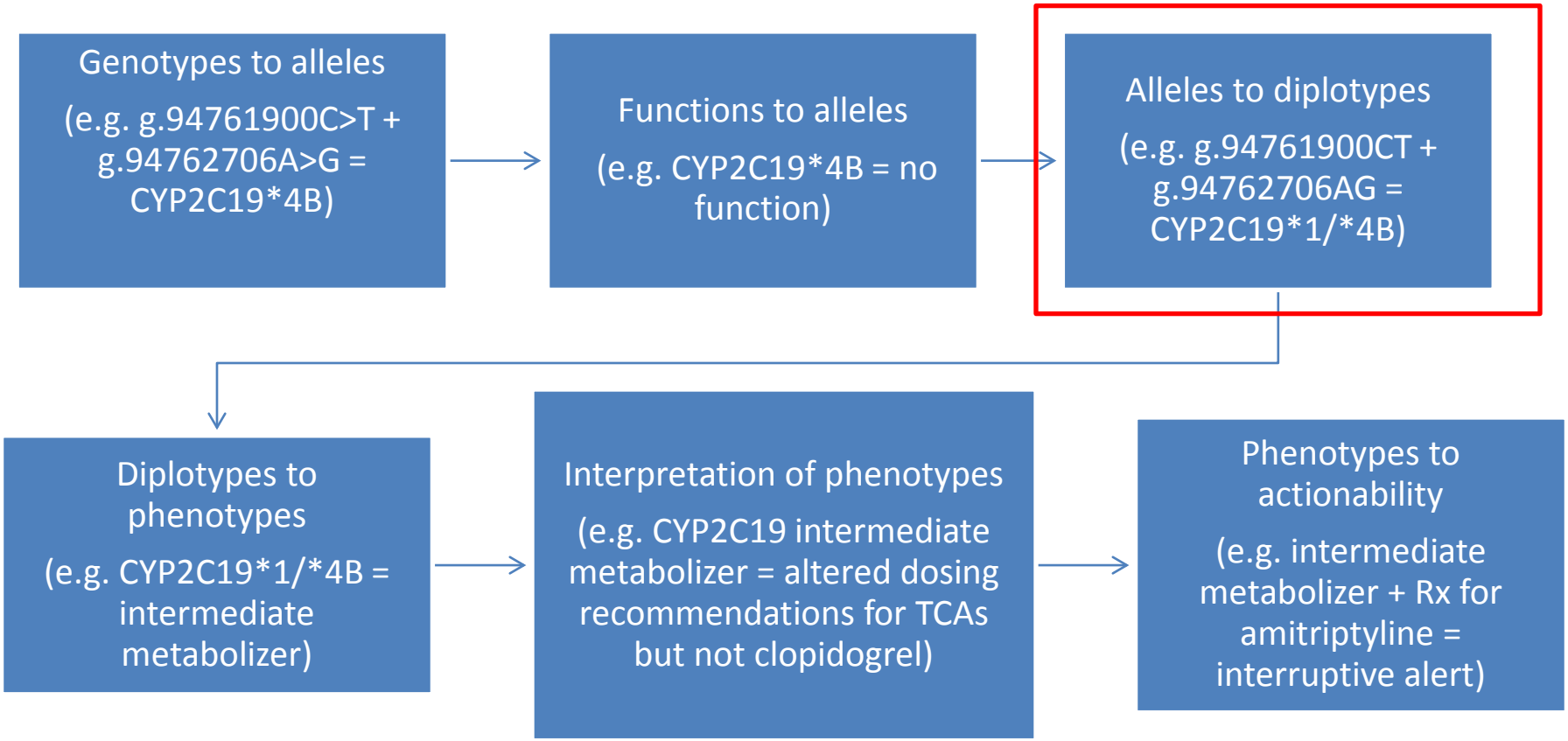
Phentoype frequencies in major race/ethnic groups estimated using the equation describing Hardy Weinberg equilibrium								
	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
Treating "Unknown Function" alleles as "Normal"								
Ultrarapid Metabolizer	0.023560021	0.037464342	0.046383164	0.02818182	0.000204649	0.029852402	0.025000149	0.000625075
Rapid Metabolizer	0.202485061	0.236445744	0.269320486	0.235828301	0.01712623	0.164340916	0.218411532	0.014706882
Normal Metabolizer	0.385840254	0.359707943	0.390872325	0.493288695	0.357011558	0.226121933	0.47418991	0.086471295
Intermediate Metabolizer	0.338810421	0.323784476	0.268004617	0.225858223	0.474967254	0.455992761	0.258910609	0.434519537
Poor Metabolizer	0.049304242	0.042597496	0.025419408	0.016842961	0.150690309	0.123691989	0.023487799	0.463677211
Treating "Unknown Function" alleles as unknown								
Ultrarapid Metabolizer	0.023560021	0.037464342	0.046383164	0.02818182	0.000204649	0.029852402	0.025000149	0.000625075
Rapid Metabolizer	0.135808387	0.235634702	0.269277341	0.2358004	0.017094094	0.164306406	0.218379889	0.014701883
Normal Metabolizer	0.16318552	0.357199235	0.390747087	0.493171969	0.355670579	0.226026965	0.474052106	0.086412513
Intermediate Metabolizer	0.24092059	0.32291842	0.267972677	0.225836653	0.47409522	0.455922515	0.258879935	0.434383395
Poor Metabolizer	0.049304242	0.042597496	0.025419408	0.016842961	0.150690309	0.123691989	0.023487799	0.463677211
Unknown	0.387221239	0.004185806	0.000200323	0.000166197	0.002245149	0.000199722	0.000200122	0.000199922

Citations for frequencies in major race/ethnic groups

EN	Authors	Year	PMID	Major ethnicity	Population	Add'l population info	Subject type	N Subjects genotyped	*1	sum of variants
14	Edeki et al.	1996	8873222	Africa	African-American	Tennessee	healthy	76		
15	Marinac et al.	1996	8823231	Africa	African-American	Kansas City	healthy subjects	100		
13	Goldstein et al.	1997	9110363	Africa	African-American	Durham and Chapel Hill	healthy	108		
1	Luo et al.	2006	16815315	Africa	African American	Los Angeles		236		
21	de Leon et al.	2009	19169185	Africa	African-American	Kentucky	mentally ill patients	478		
240	Kearns et al	2010	20223877	Africa	African-American	Kansas City	sample repository	114		
278	Strom et al	2012	22237437	Africa	African-American	US	n/a	149		
239	Martis et al	2013	22491019	Africa	African-American	New York	healthy blood donors	250		
238	Langaee et al	2014	24945780	Africa	African-American		from PEAR and INVEST studies	181		
314	Cresci et al.	2014	24762860	Africa	African-American		from TRIUMPH study	670		
315	Chaudhry et al.	2015	26021325	Africa	African-American	Americans of African Ancestry in SW USA	1000 Genomes	61		
	Average								57.27	42.73
	Min									
	Max									
22	Masimirembwa et al.	1995	7781265	Africa	Zimbabwean	Shona	healthy	84		
42	Persson et al.	1996	9014201	Africa	Ethiopian		healthy	114		
12	Herrlin et al.	1998	9797796	Africa	Tanzanian	Dar es Salaam	healthy	251		
5	Bathum et al.	1999	10510152	Africa	Tanzanian			195		
7	Dandara et al.	2001	11372584	Africa	South African	Venda		76		
7	Dandara et al.	2001	11372584	Africa	Tanzanian		psychiatric patients and controls	192		
10	Hamdy et al.	2002	12047484	Africa	Egyptian	Cairo	healthy	247		
2	Aklillu et al.	2002	12142727	Africa	Ethiopian	Sweden	healthy	70		

Allele frequency by race | Diplotype frequency by race | Phenotype frequency by race | References | change log

Sorting variants into not only alleles but diplotypes: phasing is required



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

Variants must be phased to assign diplotypes for pharmacogenes

CPIC Gene	Prescribing different for Var/var than for 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

DMET_8170_CYP2D6_translation.txt - Notepad

File Edit Format View Help

From genotype or sequencing data, call gene-centric **haplotypes and diplotypes**—not just variants

```
#SJAccession=08-155-0435B
#PatientName=XXXXX
#DMETfile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAF
#AnnotationFile=DMET_Plus.v1.20090910.dc_annot.csv
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker list.txt
PharmGKB link    http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Independent Copy Number 2
Called Interpretation Code          UNIQ+UNK
Called Diplotypes Possible          *1/*41
Called Novel Diplotypes Possible          *2/UNK
Copy Number Corrected Alleles    NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12261        Y       Ch22:40853887   rs16947 C/T     Ref/Var *2,*8,*11,*12,*14A,*14B,*17,*19,*20,*21,*29,*40,*41,*4
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       Ch22:40858512   rs1080983       G/A     Ref/Var -       CYP2D6_-1770G>A
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        Y       Ch22:40852557   rs1135840       G/C     Ref/Var S486T   CYP2D6_4180G>C(S486T)
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

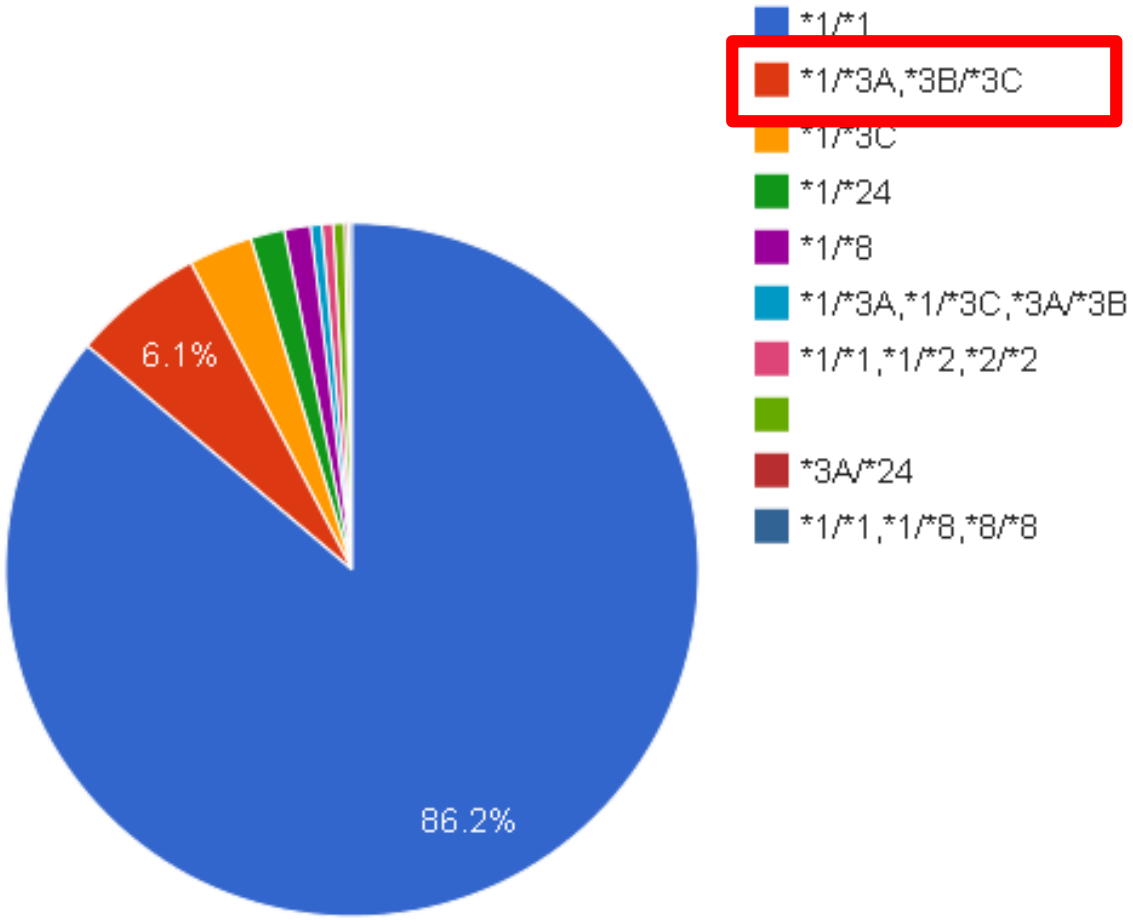
PharmCAT

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

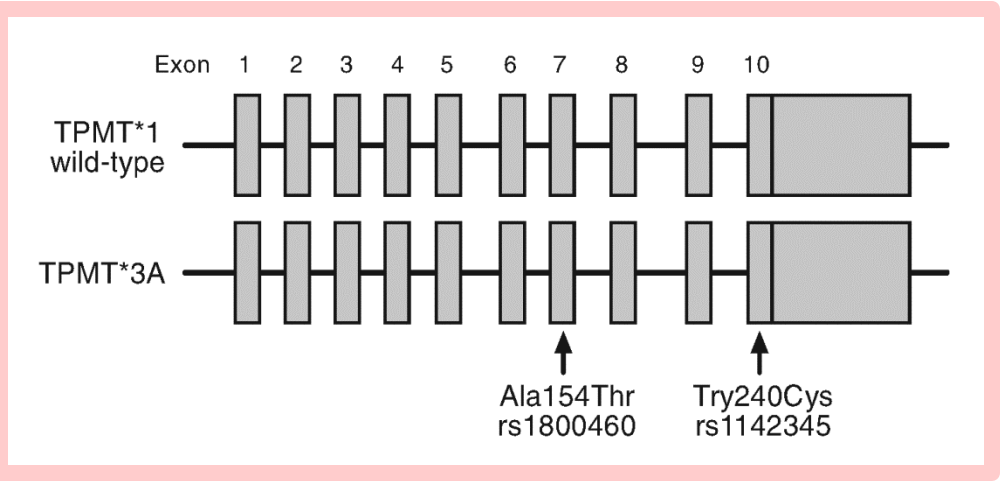
Geisinger

PharmGKB

For, the most commonly observed set of variants could be called TPMT *1/*3A vs *3B/*3C



Assigning/phasing SNPs into haplotypes makes a big difference clinically

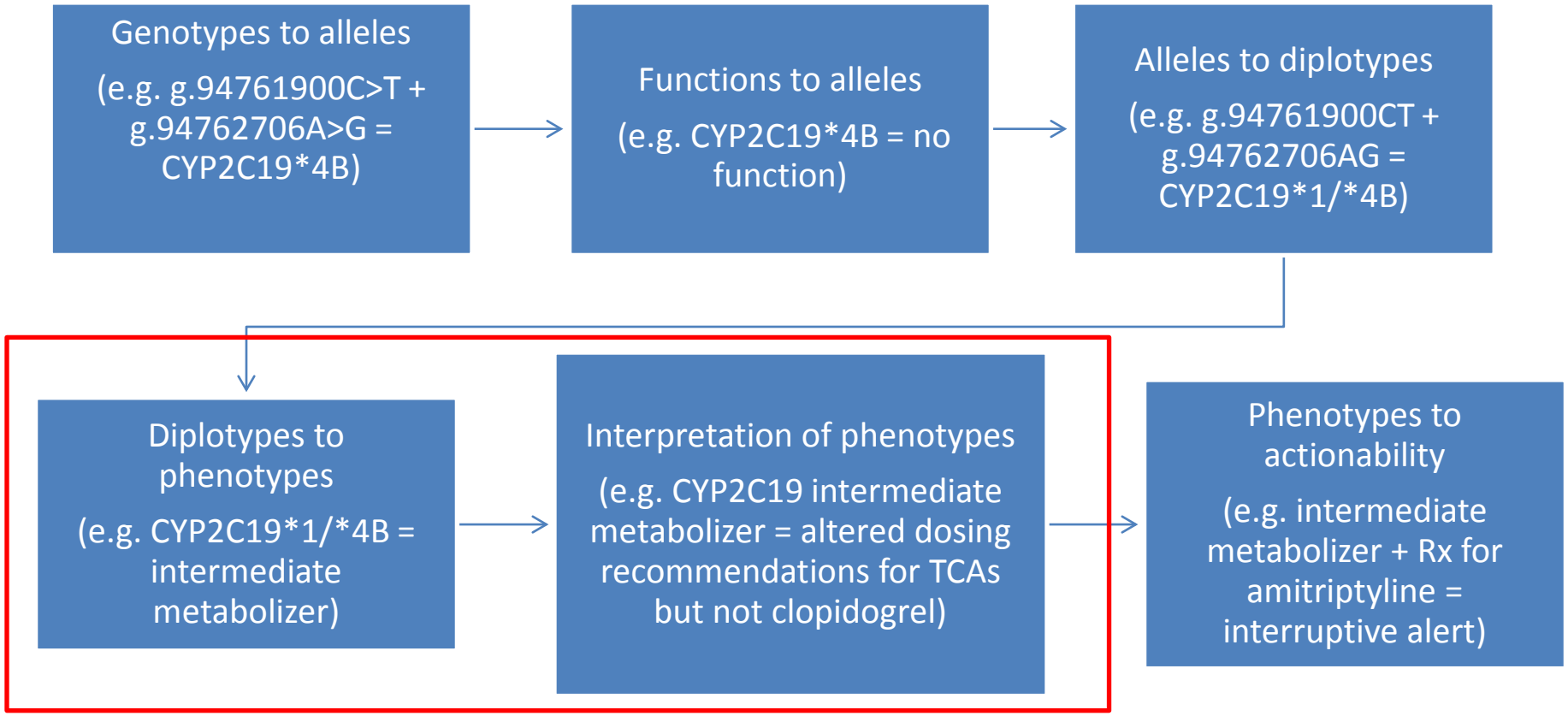


Gene-specific Information Tables for CYP2C19

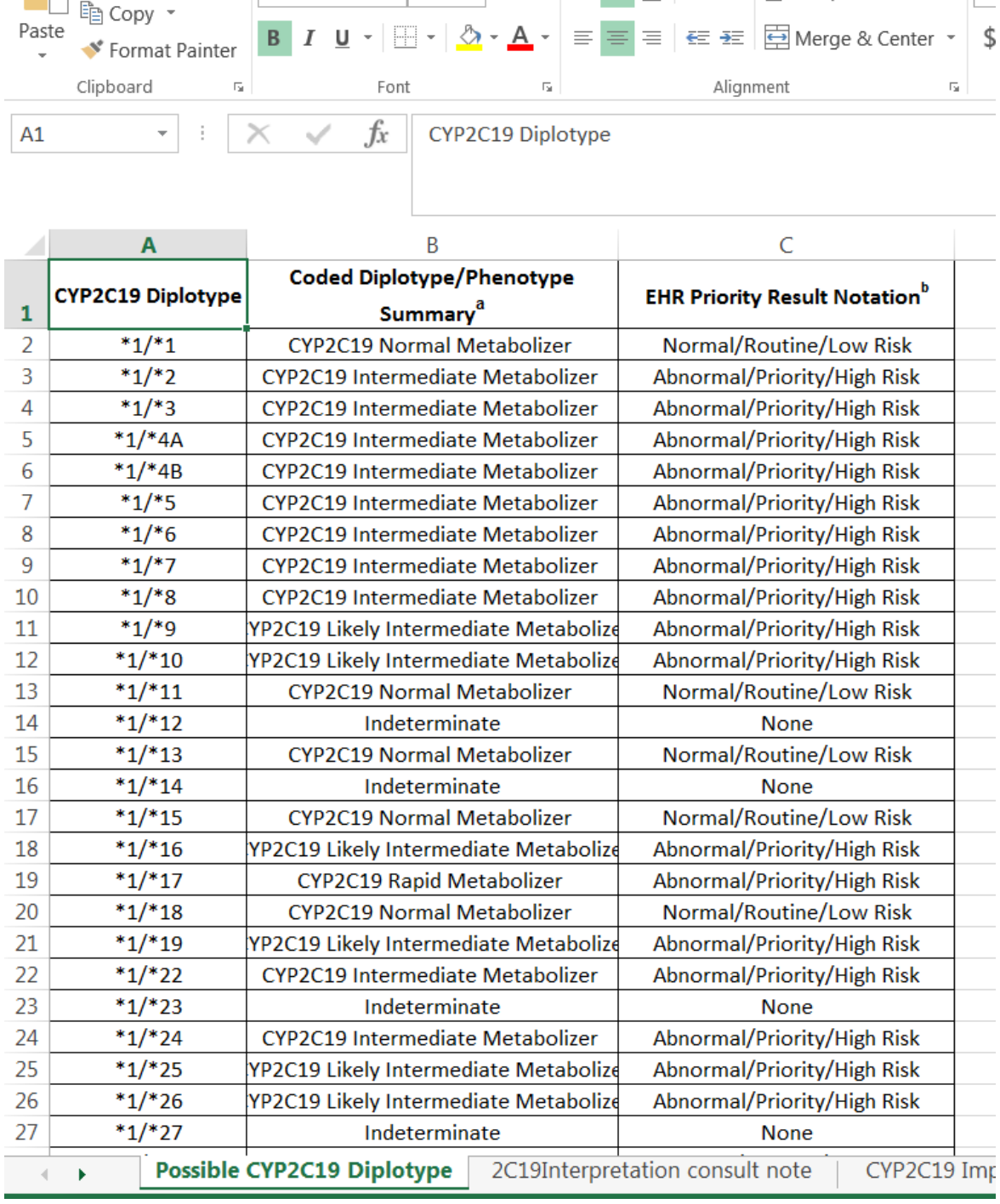
This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C19.

- **CYP2C19 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP219 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C19 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C19 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

CPIC tables allow translation of genetic test results to actionability



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



Paste
Copy
Format Painter
Clipboard
B I U
Font
Merge & Center
Alignment
A1
CYP2C19 Diplotype

	A	B	C
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	YP2C19 Likely Intermediate Metabolize	Abnormal/Priority/High Risk
12	*1/*10	YP2C19 Likely Intermediate Metabolize	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	YP2C19 Likely Intermediate Metabolize	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	YP2C19 Likely Intermediate Metabolize	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	YP2C19 Likely Intermediate Metabolize	Abnormal/Priority/High Risk
26	*1/*26	YP2C19 Likely Intermediate Metabolize	Abnormal/Priority/High Risk
27	*1/*27	Indeterminate	None

Possible CYP2C19 Diplotype | 2C19Interpretation consult note | CYP2C19 Imp

Use standardized terms for phenotypes

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

Introduction: Reporting and sharing pharmacogenetic test results across clinical laboratories and electronic health records is a crucial step toward the implementation of clinical pharmacogenetics, but allele function and phenotype terms are not standardized. Our goal was to develop terms that can be broadly applied to characterize pharmacogenetic allele function and inferred phenotypes.

Materials and methods: Terms currently used by genetic testing laboratories and in the literature were identified. The Clinical Pharmacogenetics Implementation Consortium (CPIC) used the Delphi method to obtain a consensus and agree on uniform terms among pharmacogenetic experts.

Results: Experts with diverse involvement in at least one area of pharmacogenetics (clinicians, researchers, genetic testing laboratorians, pharmacogenetics implementers, and clinical informaticians; $n = 58$) participated. After completion of five surveys, a consensus (>70%) was reached with 90% of experts agreeing to the final sets of pharmacogenetic terms.

Discussion: The proposed standardized pharmacogenetic terms will improve the understanding and interpretation of pharmacogenetic tests and reduce confusion by maintaining consistent nomenclature. These standard terms can also facilitate pharmacogenetic data sharing across diverse electronic health care record systems with clinical decision support.

Genet Med advance online publication 21 July 2016

Key Words: CPIC; nomenclature; pharmacogenetics; pharmacogenomics; terminology

Final Standardized Terms: Phenotype for Drug Metabolizing Enzymes

For example: CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Ultra-rapid Metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
Rapid Metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
Normal Metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
Intermediate Metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
Poor Metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

CPIC™
Clinical Pharmacogenetics Implementation Consortium

Final Standardized Terms: Phenotype for Drug Transporters

For example: SLCO1B1

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Increased Function	Increased transporter function compared to normal function	One or more increased function alleles	*SLCO1B1*1/*14*
Normal Function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
Decreased Function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
Poor Function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

CPIC™ Clinical Pharmacogenetics Implementation Consortium

Final Standardized Terms: (HLA-genes) Phenotype for High-Risk Genotype Status

For example: HLA-B*57:01

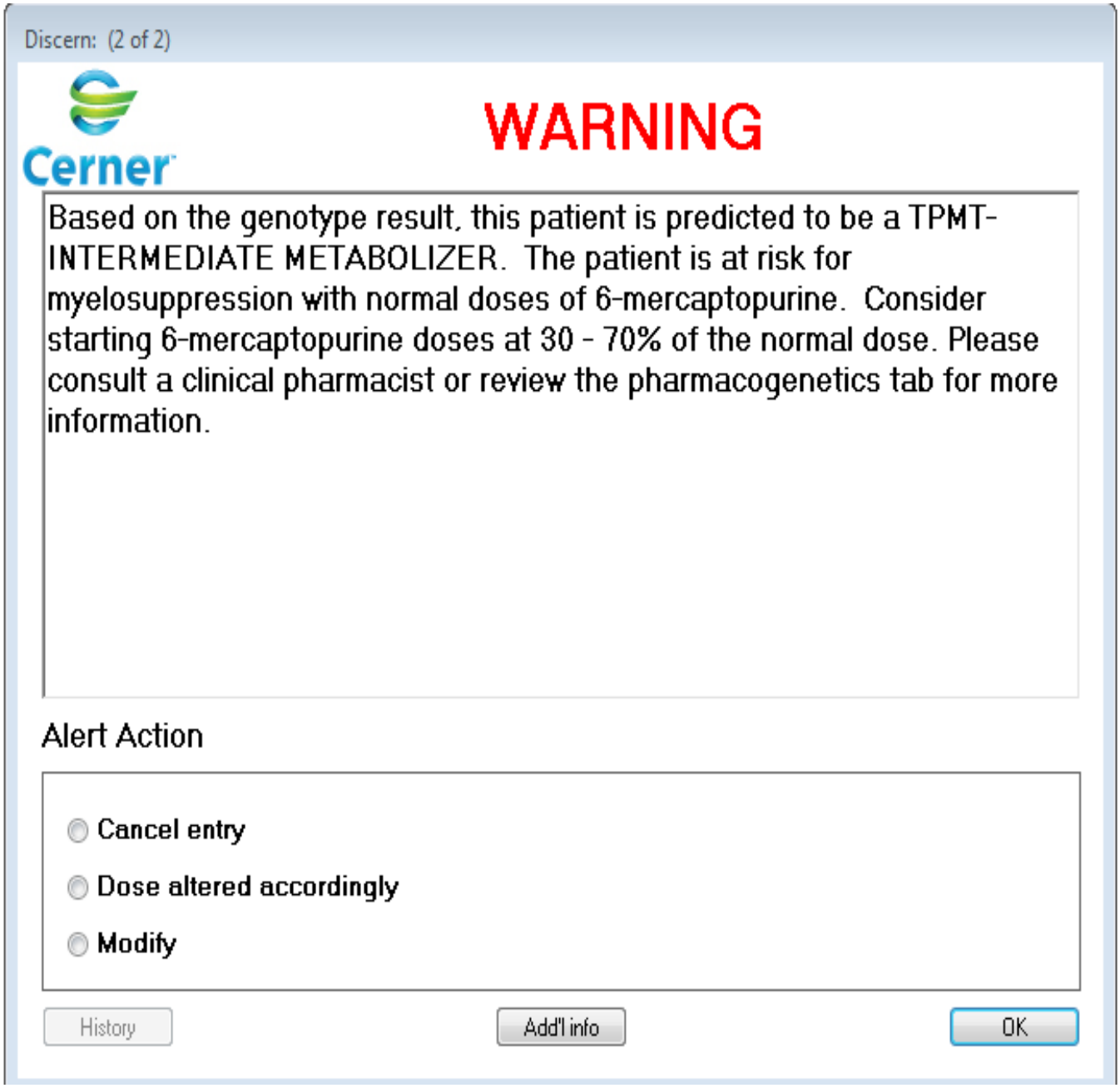
Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
Negative	High risk-allele not detected	No copies of high-risk allele	

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

CPIC™ Clinical Pharmacogenetics Implementation Consortium

TPMT post-test interruptive alert is driven off of the standardized term “TPMT intermediate metabolizer” plus the attempt to prescribe a thiopurine

Phenotype vs test result



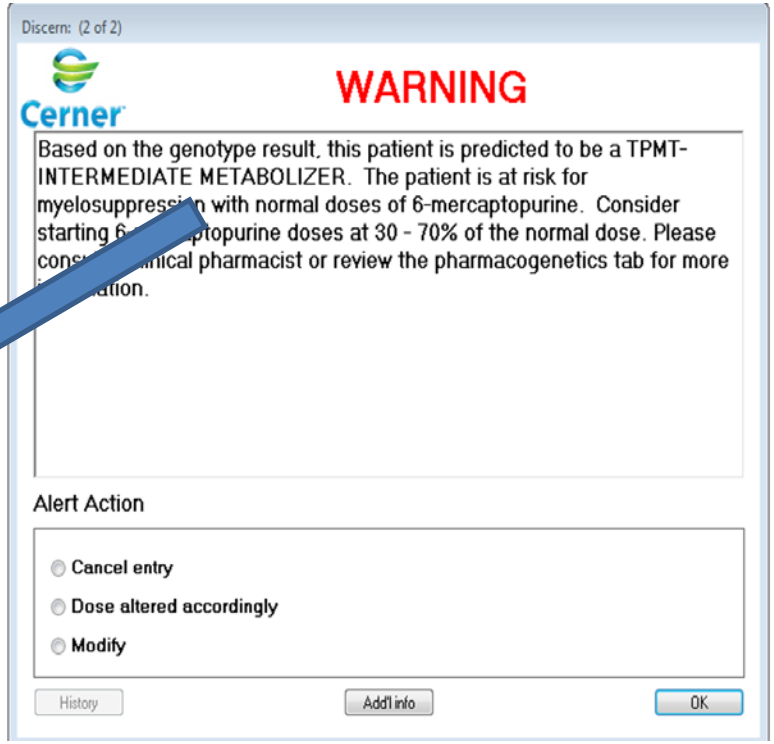
Problem List

Management Discipline View

All Problems

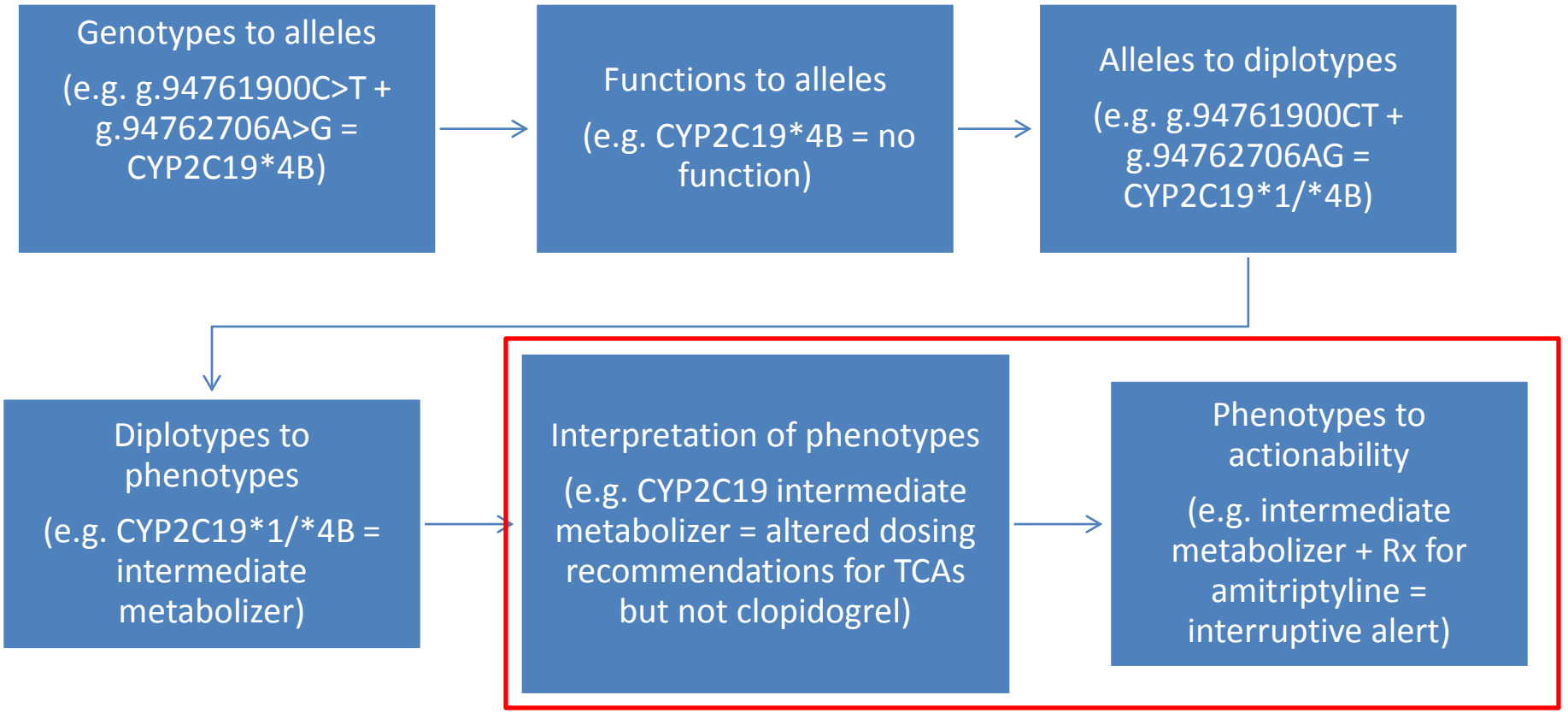
Change View

Qualifier	Name of Problem	Onset Date	Classification
All Problems			
	ACUTE LYMPHOCYTIC LEUKEMIA	5/2/2011	HIMS Sum...
	ALL (acute lymphoblastic leukemia)	5/11/2011	HIMS Sum...
	Consented to all optional research testing...		
	CYP2D6 POOR METABOLIZER		
	LOW RISK CONSOL T16		
	Peg Asp 2500 u/m2/IV randomized		
	PT. HAS HICKMAN LINE SINGLE LUMEN		
	PT. HAS SUBQPORT SINGLE		
	TPMT INTERMEDIATE METABOLIZER		



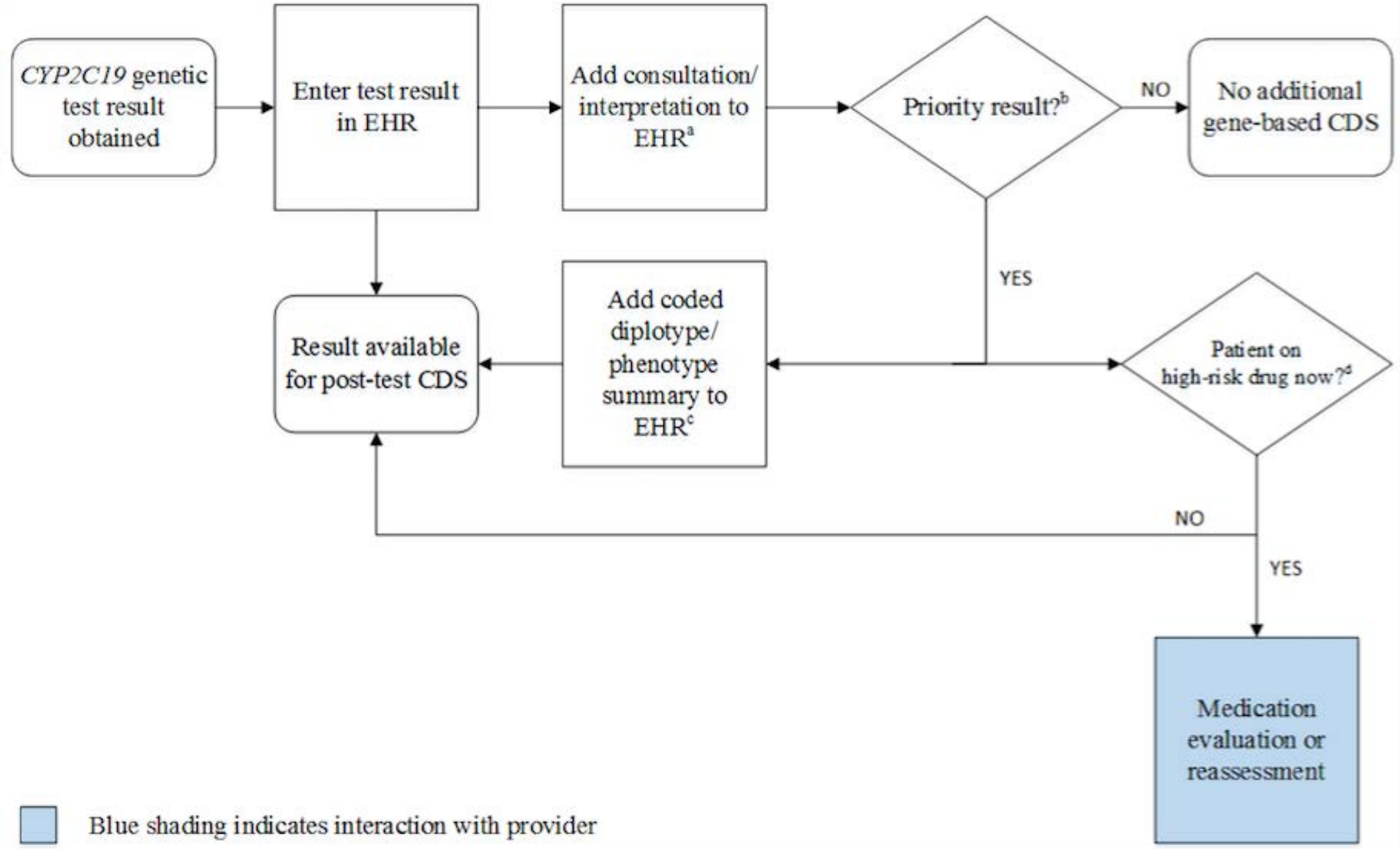
Advantage: can be a manual entry

CPIC tables allow translation of genetic test results to actionability



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

	A	B	C
1	**Coded Genotype/Phenotype Summary[a]**	**EHR Priority Result Notation[b]**	**Consultation (Interpretation) Text Provided with Test Result[c]**
2	CYP2C19 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of an increased function allele. Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
3	CYP2C19 Rapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of an increased function allele. Based on the genotype result this patient is predicted to be a rapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
4	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of a no function allele. Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
5	CYP2C19 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele. Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2C19 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or or alternative therapy may be necessary for medications metabolized by the CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.


CYP2C19 genetic test result obtained
Enter test result in EHR
Add consultation/ interpretation to EHR[a]
Priority result?[b]
NO
No additional gene-based CDS
YES
Add coded diplotype/ phenotype summary to EHR[c]
Result available for post-test CDS
Patient on high-risk drug now?[d]
NO
YES
Medication evaluation or reassessment
Blue shading indicates interaction with provider

Gene-specific Information Tables for CYP2C19

This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C19.

- **CYP2C19 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP219 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C19 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C19 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

	A	B	C	D	E
1	**Gene Symb**	**Source**	**Code Type**	**Code**	
2	*CYP2C19*	HGNC	Symbol	CYP2C19	
3	*CYP2C19*	HGNC	HGNC ID	HGNC:2621	
4	*CYP2C19*	NCBI	Gene ID	1557	
5	*CYP2C19*	Ensembl	Ensembl ID	ENSG00000165841	
6	*CYP2C19*	PharmGKB	PharmGKB ID	PA124	
7					
8					

CPIC® Guideline for Voriconazole and CYP2C19

Most Recent Guideline Publication

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Updates since publication: No updates on dosing recommendations since publication.

Tables provided in the main manuscript of the guideline

Table 1. Assignment of likely CYP2C29 phenotype based on genotypes
Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients
Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Tables provided in the guideline publication supplement or referenced in the guideline[a]

Levels of Evidence Linking Genotype to Phenotype
CYP2C19 Allele Definition Table
CYP2C19 Allele Functionality Table
CYP2C19 Frequency Table
CYP2C19 Diplotype-Phenotype Table
Gene Resource Mapping *CYP2C19* Gene Resource Mappings

CPIC® Guideline for Voriconazole and CYP2C19

Levels of Evidence Linking Genotype to 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

[a]Some of the tables included in the guideline may have been updated on-line, particularly to reflect newly described or newly characterized alleles. These include the gene-specific information tables (https://www.pharmgkb.org/page/pgxGeneRef) that support CPIC guidelines by providing information regarding star (*) allele definitions, allele function, allele frequency by major ethnic groups, translations of diplotype to phenotype, and gene resource mappings

	A	B	C	D	E
	Drug or ingredient	**Source**	**Code Type**	**Code**	
	Voriconazole	RxNorm	RxCUI	121243	
	Voriconazole	DrugBank	ccession Numb	DB00582	
	Voriconazole	ATC	ATC Code	J02AC03	
	Voriconazole	PharmGKB	PharmGKB ID	PA10233	

Current estimate: 17 genes, 87 drugs with pharmacogenetically-based prescribing

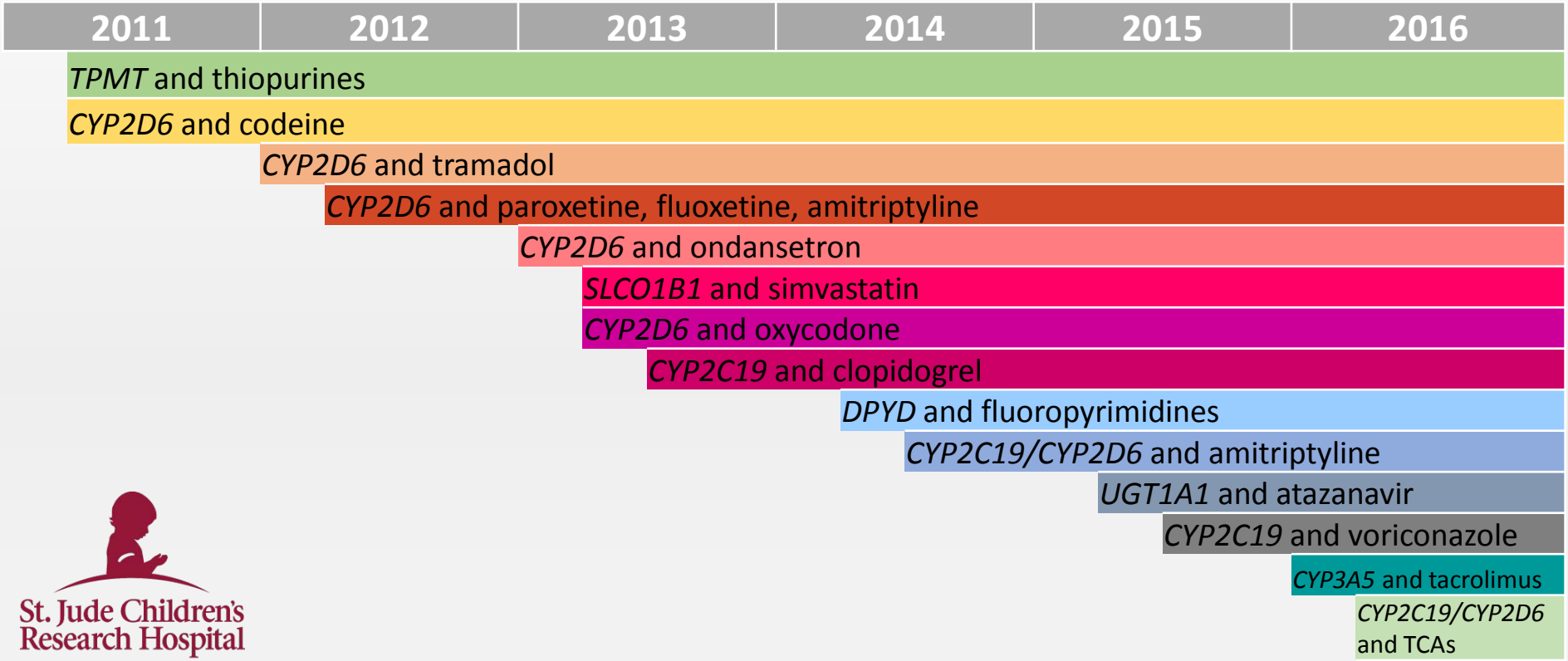
Number of current and planned CPIC genes, drugs and anticipated guidelines.	Genes	Drugs	Anticipated number of unique guidelines
Strong or Moderate prescribing action-CPIC level A	14	36	20 (17 published)
Optional prescribing actions-CPIC level B	7[a]	50	9
No prescribing actions-CPIC level C	16[b]	47	20

[a]Currently this is 3 unique genes (four are already subjects of CPIC level A guidelines). [b]Currently this is 13 unique genes (three are also subject to CPIC level A or B guidelines for other drugs).

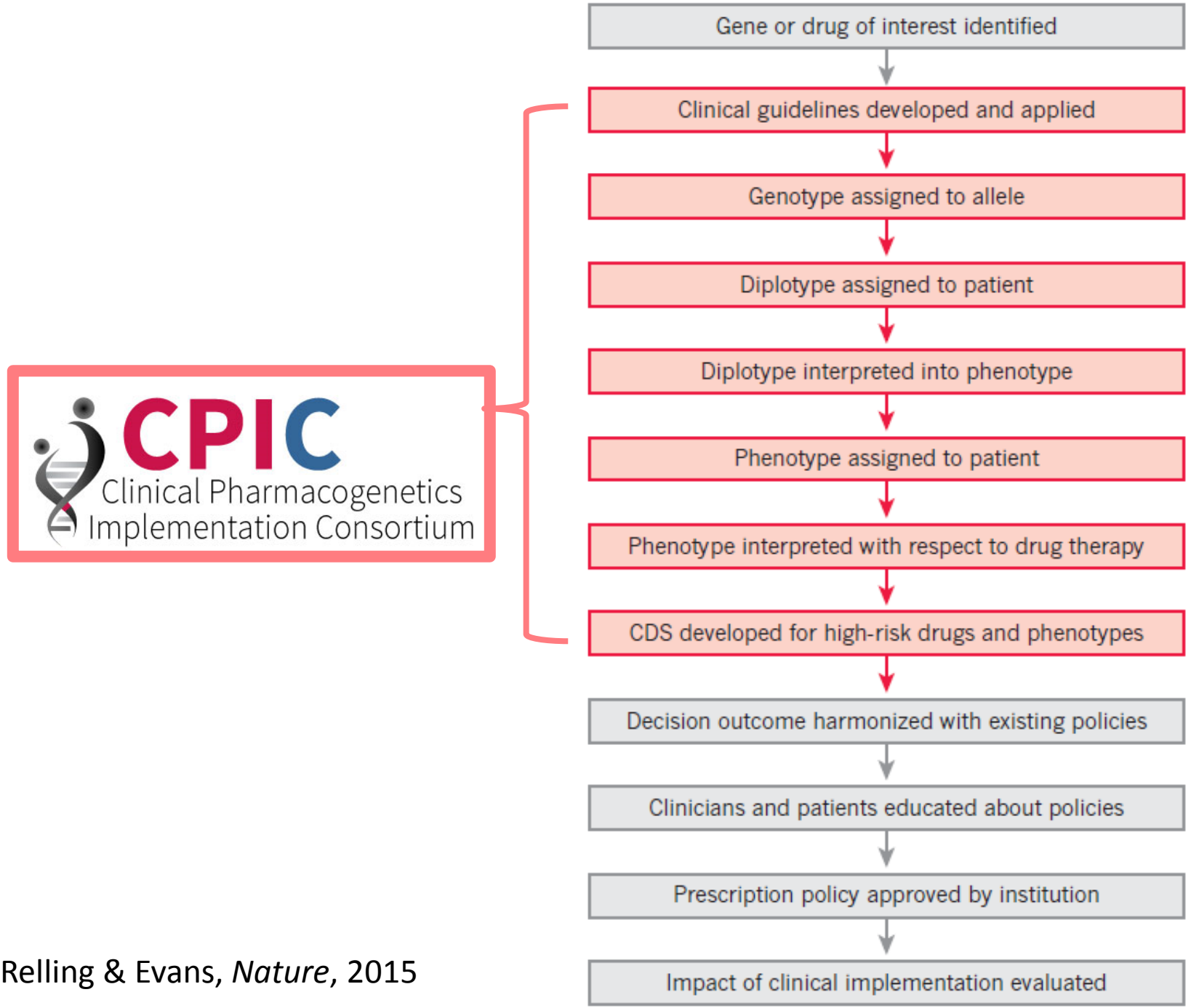
March 2017

PG4KDS Implementation Timeline

www.stjude.org/pg4kds/implement



St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.



Relling & Evans, *Nature*, 2015

Acknowledgements

- Stanford
  - Teri Klein
  - Russ B. Altman
  - Michelle Whirl-Carrillo
  - Li Gong
  - Katrin Sangkuhl
- St. Jude
  - Kelly Caudle
  - Rose Gammal
  - Cyrine E. Haidar
  - James M. Hoffman
  - Jennifer Hockings
  - Colton Smith

PharmGKB

R24 GM061374

- Stuart Scott, Mt. Sinai
- Marylyn Ritchie, Geisinger
- Sandy Aronson, Partners/Harvard
- Bob Freimuth, Mayo

- CPIC members and observers
- CPIC guideline authors

CPIC™ Clinical Pharmacogenetics Implementation Consortium

R24 GM115264

PG4KDS Protocol

Clinical Implementation of Pharmacogenetics

Cyrine Haidar
Kristine Crews
James Hoffman
Shane Cross
Jennifer Hockings
Don Baker & Clinical Informatics
Charles Mullighan
Aditya Gaur
Ulrike Reiss
Alicia Huettel
Cheng Cheng
Amar Gajjar
RNs: Sheri Ring, Lisa Walters, Paula Condy,
Terri Kuehner, Margaret Edwards, Shannon Gibbs, Melinda Wood
Austin Springer

Nancy Kornegay
Wenjian Yang
Colton Smith
Alejandro Molinelli
Alberto Pappo
Melissa Hudson
Ching-Hon Pui
Sima Jeha
Kim Nichols
William E. Evans

PG residents:

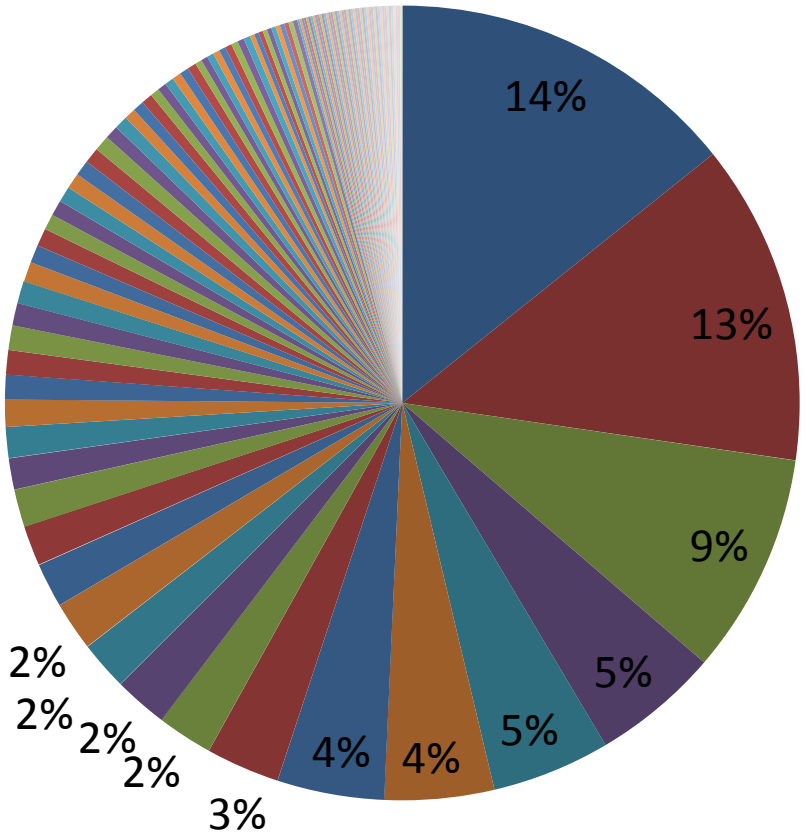
Kevin Hicks, Gillian Bell, Mark Dunnenberger
Rose Gammal, Amy Pasternak, Jennifer Hockings

Ulrich Broeckel, M.D.
Rachel Lorier
Amy Turner

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

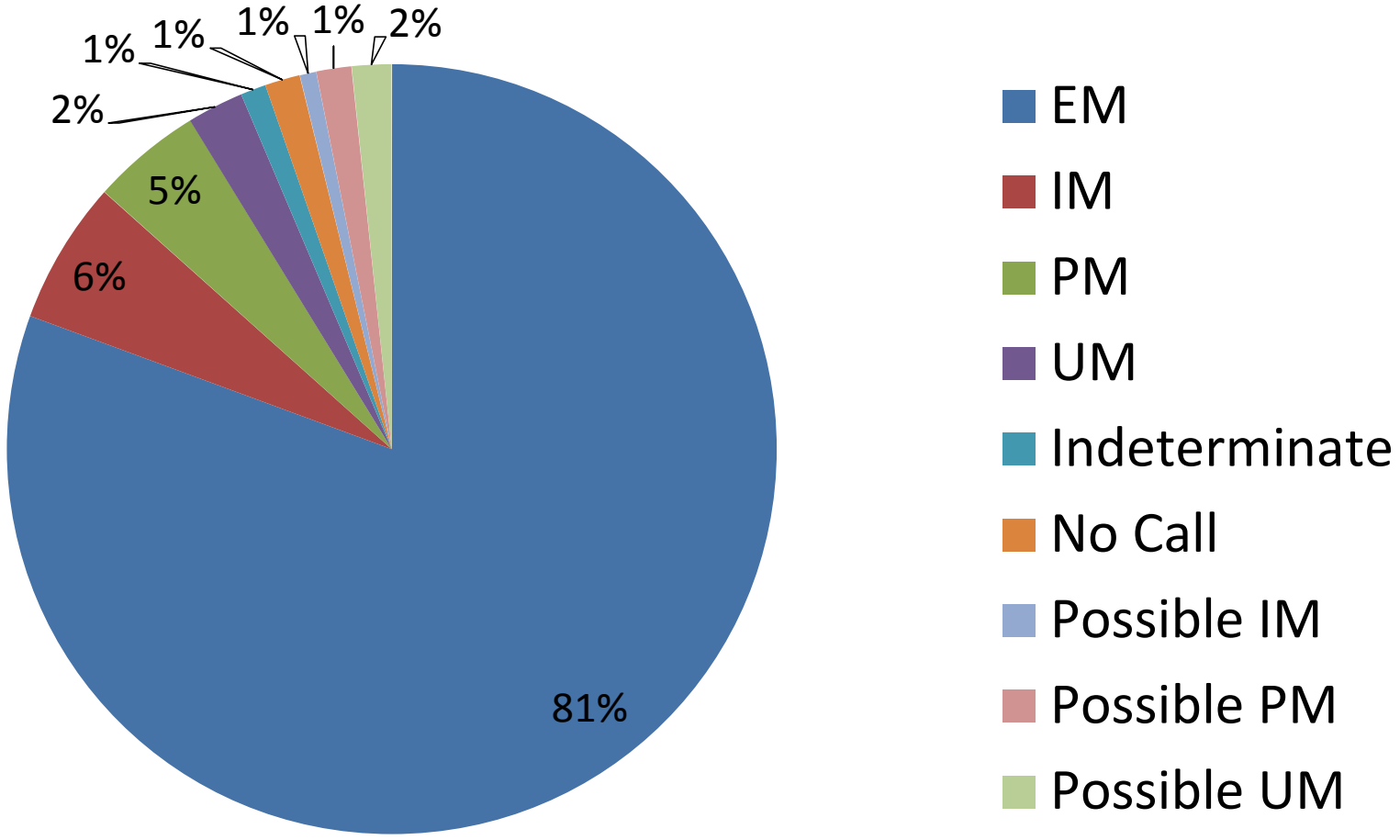
Medical College of Wisconsin

111 diplotypes observed for *CYP2D6*

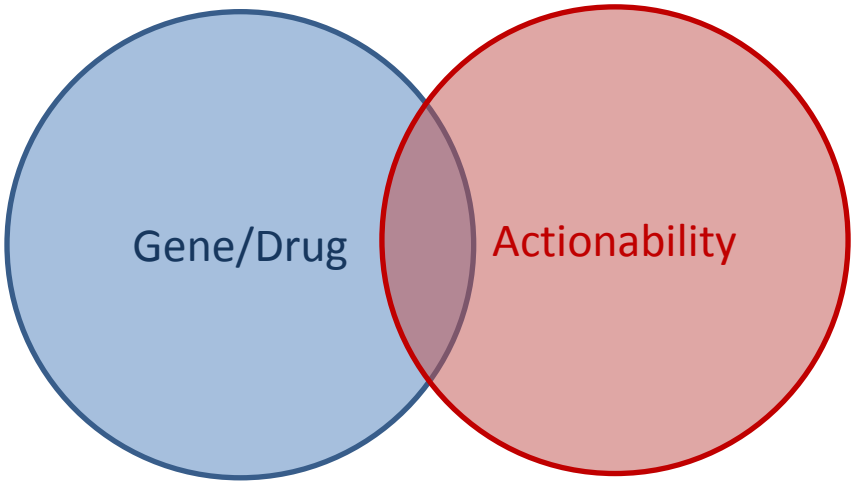


- (*1/*2)2N
- (*1/*4)2N
- (*2/*4)2N
- (*2/*2)2N
- (*4/*4)2N
- (*2/*17)2N
- (*1/*10)2N
- (*4/*41)2N
- (*17/*17)2N
- (*1/*2)3N
- (*4/*4)1N
- (*1/*4)3N
- (*17/*29)2N
- (*1/*3)2N
- (*1/*29)2N
- (*4/*10)2N
- (*2/*2)3N
- (*4/*9)2N
- (*9/*41)2N
- (*2/*6)2N
- (*2/*17,*17/*42)2N
- (*4/*6)2N
- (*5/*5)0N
- (*1/*17)3N
- (*1/*40)2N
- (*2/*41)3N
- (*9/*9)1N
- (*41/*41)1N
- (*10/*29)2N
- (*17/*40)2N
- (*4/*40,*10/*40)2N
- (*2/*2,*2/*42,*42/*42)2N
- (*9/*17)2N
- (*2/*10)2/3/2N
- (*4/*4)2/3/3N
- (*2/*2)2/3/3N
- (*2/*3,*3/*17)2N
- (*1/*2,*1/*41)2N
- (*1/*1)2N
- (*1/*17)2N
- (*1/*41)2N
- (*1/*1)1N
- (*2/*41)2N
- (*2/*29)2N
- (*2/*2)1N
- (-)2N
- (*1/*9)2N
- (*2/*9)2N
- (*2/*10)2N
- (*2/*4)3N
- (*41/*41)2N
- (*2/*3)2N
- (*17/*17)1N
- (*4/*17)2N
- (*29/*29)1N
- (*1/*1)3N
- (*6/*41)2N
- (*1/*4)2/3/3N
- (*29/*41)2N
- (*3/*4)2N
- (*2/*17)3N
- (*1/*10)2/3/3N
- (*4/*29)2N
- (*1/*6)2N
- (*2/*40)2N
- (*4/*29)3N
- (*2/*10)3N
- (*3/*17)2N
- (*29/*40)2N
- (*29/*29)2N
- (*18/*18)1N
- (*1/*4)2/2/1N
- (*1/*4)4N
- (*4/*41)3N
- (*1/*4)2/3/2N
- (*1/*6)1N

> 111 *CYP2D6* diplotypes have translated into 9 phenotype groups—a few of which are actionable



Evidence considered for pharmacogenetic-based clinical recommendations



<u>Gene/Drug Association</u>

- Observational studies
- Randomized clinical studies
- Pre-clinical and clinical studies
- Case reports
- *in vivo* PK
- *in vitro* functional studies
- *in vivo* functional studies

<u>Clinical Actionability</u>

- Therapeutic index
- Severity of disease
- Consequences of suboptimal prescribing
- Availability of genetic tests
- Availability of and evidence for alternative therapy

Evidence for CYP3A5 and tacrolimus prescribing recommendations

Clinical	In liver transplant patients, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Uesugi et al. (2014) [171] Xue et al. (2014) [33] Jalil et al. (2014) [172] Buendia et al. (2013) [173] Gómez-Bravo et al. (2013) [118] Shi et al. (2013) [39] Chen et al. (2013) [51] Chen et al. (2013) [54] Ji et al. (2012) [79] Muraki et al. (2011) [64] Uesugi et al. (2006) [70]	Moderate
Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of tacrolimus.	Rahsaz et al. (2012) [131] de Wildt et al. (2011) [150] Zhang et al. (2011) [41] Jun et al. (2009) [85] Provenzani et al. (2009) [109] Li et al. (2007) [46] Wei-lin et al. (2006) [49] Yu et al. (2006) [53]	
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Uesugi et al. (2014) [171] Xue et al. (2014) [33] Gómez-Bravo et al. (2013) [118] Buendia et al. (2013) [173] Rojas et al. (2013) [174] Durand et al. (2013) [175] Chen et al. (2013) [54] Chen et al. (2013) [51] Ji et al. (2012) [79] Provenzani et al. (2011) [106] Zhang et al. (2011) [41] Muraki et al. (2011) [64] Jun et al. (2009) [85] Provenzani et al. (2009) [109] Li et al. (2007) [46]	High

Informatics

Goal and Focus

A formal working group within CPIC was formed in 2013 to focus on informatics aspects of CPIC guidelines, especially as they relate to the application of the CPIC guidelines in electronic health records (EHRs) with clinical decision support (CDS). The goal of the CPIC Informatics Working Group is to support the adoption of the CPIC guidelines by identifying, and resolving where possible, potential technical barriers to the implementation of the guidelines within a clinical electronic environment.

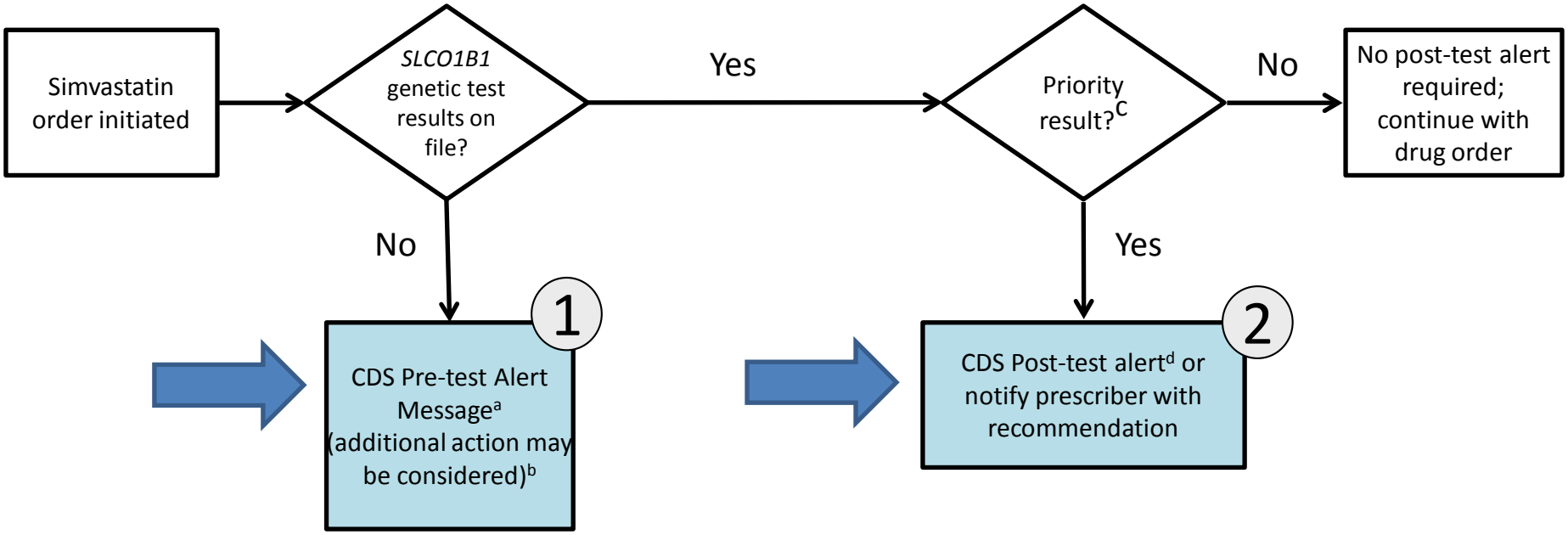
The primary initial focus for CPIC informatics is to:

- create comprehensive tables and other guidance to translate genotype information to phenotype to clinical recommendation for CPIC guidelines, using human readable and structured text with formal knowledge representation.
- develop recommendations for Clinical Decision Support (CDS) in Electronic Health Records (EHRs) based on the CPIC guidelines.

These resources are being incorporated into the supplement of each new and updated CPIC guideline.

The working group will maintain a relationship with groups (such as eMERGE and members of the PGRN) that are implementing pharmacogenetic testing with CDS. The working group works closely with the authors of CPIC guidelines, especially those implementing PGx rules.

SLCO1B1 Genotype and Simvastatin: Point of Care Clinical Decision Support



Note: Circled numerals refer to ***Supplementary Table 12***

[a,d] See **Supplementary Table S12** for diplotype/phenotype specific pre- and post-test alert example.
[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.
[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

Clinical Pharmacology & Therapeutics (2014); 96 4, 423–428

Supplemental Table S12. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S3)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[a]
1	Pre-Test	No *SLCO1B1* result on file	*SLCO1B1* diplotype may be important for simvastatin side effects. An *SLCO1B1* genotype does not appear to have been ordered for this patient. Use of an alternative statin or dose may be recommended. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 - Intermediate Function	Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function and may be at increased risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 – Low Function	Based on the genotype result, this patient is predicted to have low SLCO1B1 function and may be at high risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.

[a]The specific wording of the alert text may differ among sites.

[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

Clinical Pharmacology & Therapeutics (2014); 96 4, 423–428

In defense of * alleles….

- Don’t account for rare or untested variants
- Defined in terms of important variants: negative interrogations have meaning
- At least they force an attempt to phase the variants into haplotypes, and therefore assignment of diplotypes
- Patients have diplotypes, not an agglomeration of SNPs; if we can’t assign their allelic status, clinical utility is lessened