CPIC™

Clinical Pharmacogenetics Implementation Consortium

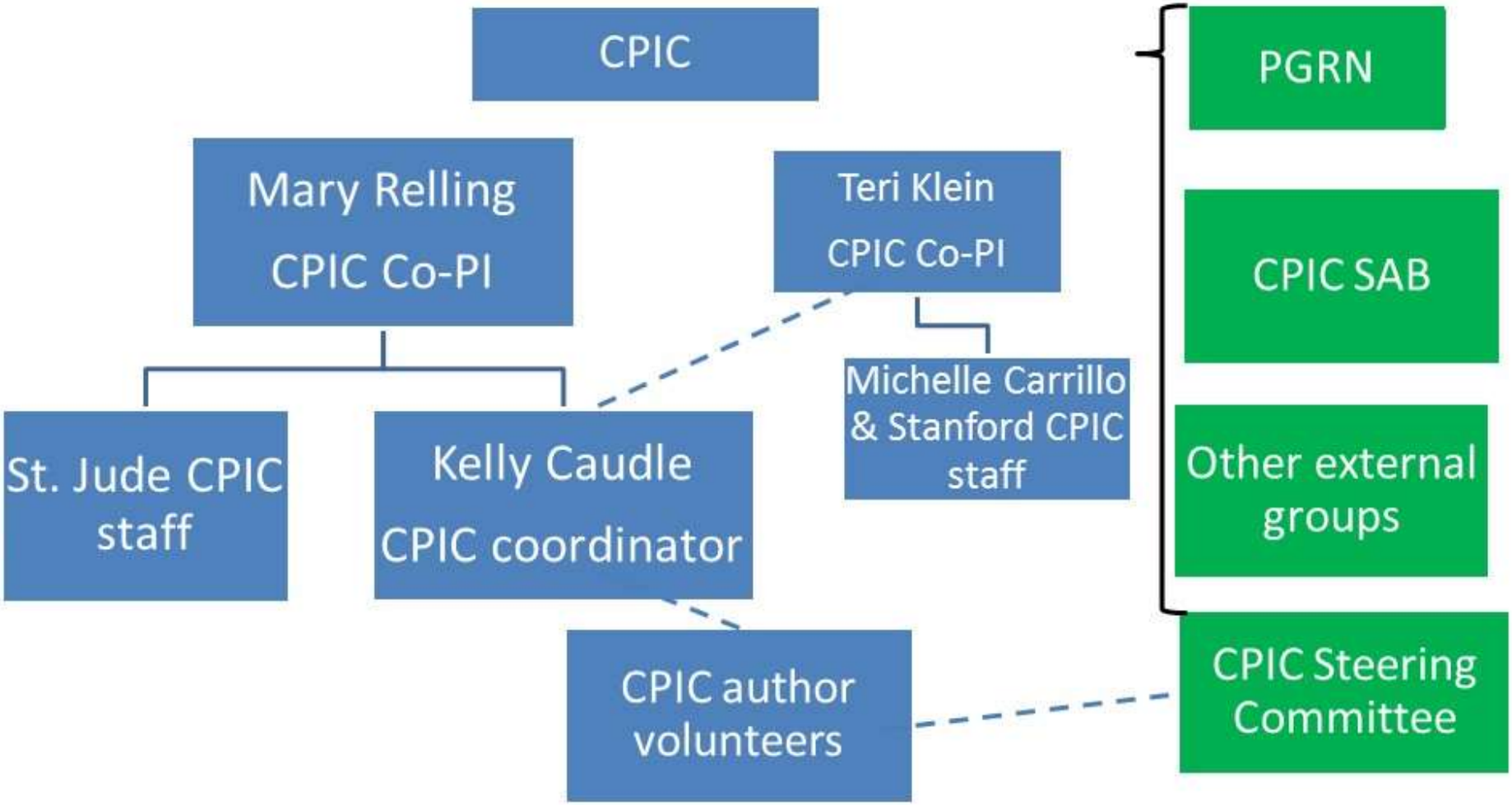
PGRN

PharmGKB

St. Jude Children's Research Hospital

ALSAC • Danny Thomas, Founder

Finding cures. Saving children.


CPIC
Mary Relling
CPIC Co-PI
Teri Klein
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Kelly Caudle
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Michelle Carrillo & Stanford CPIC staff
CPIC author volunteers
PGRN
CPIC SAB
Other external groups
CPIC Steering Committee

Scientific Advisory Board

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- John David Nolan, M.D., Ph.D., Cerner
- Robert Nussbaum, M.D. University of California, San Francisco
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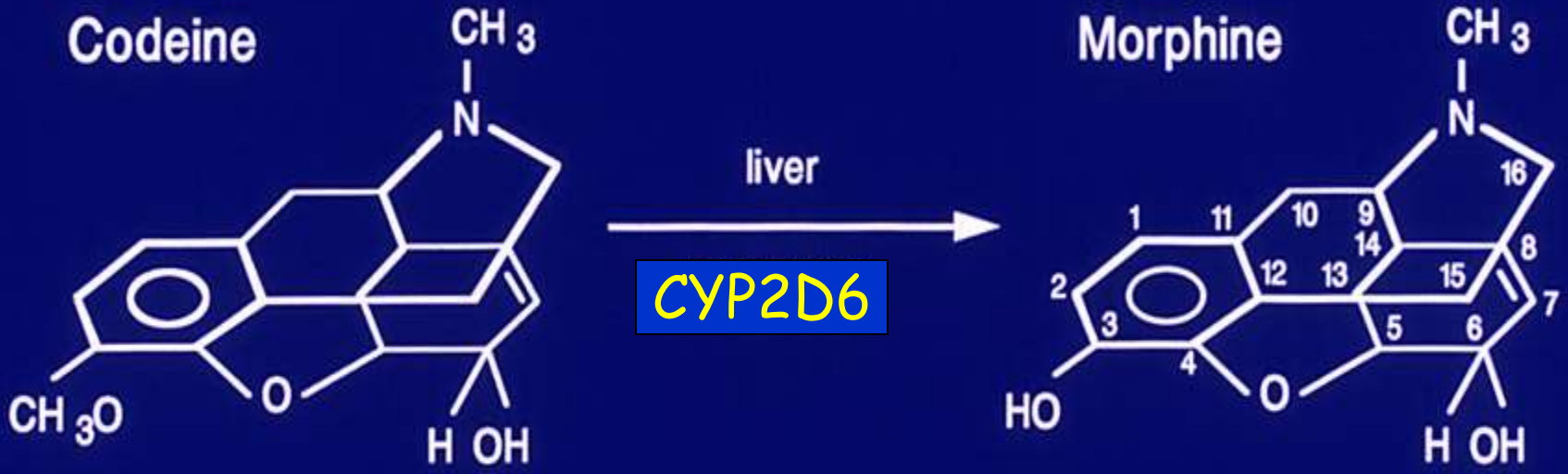
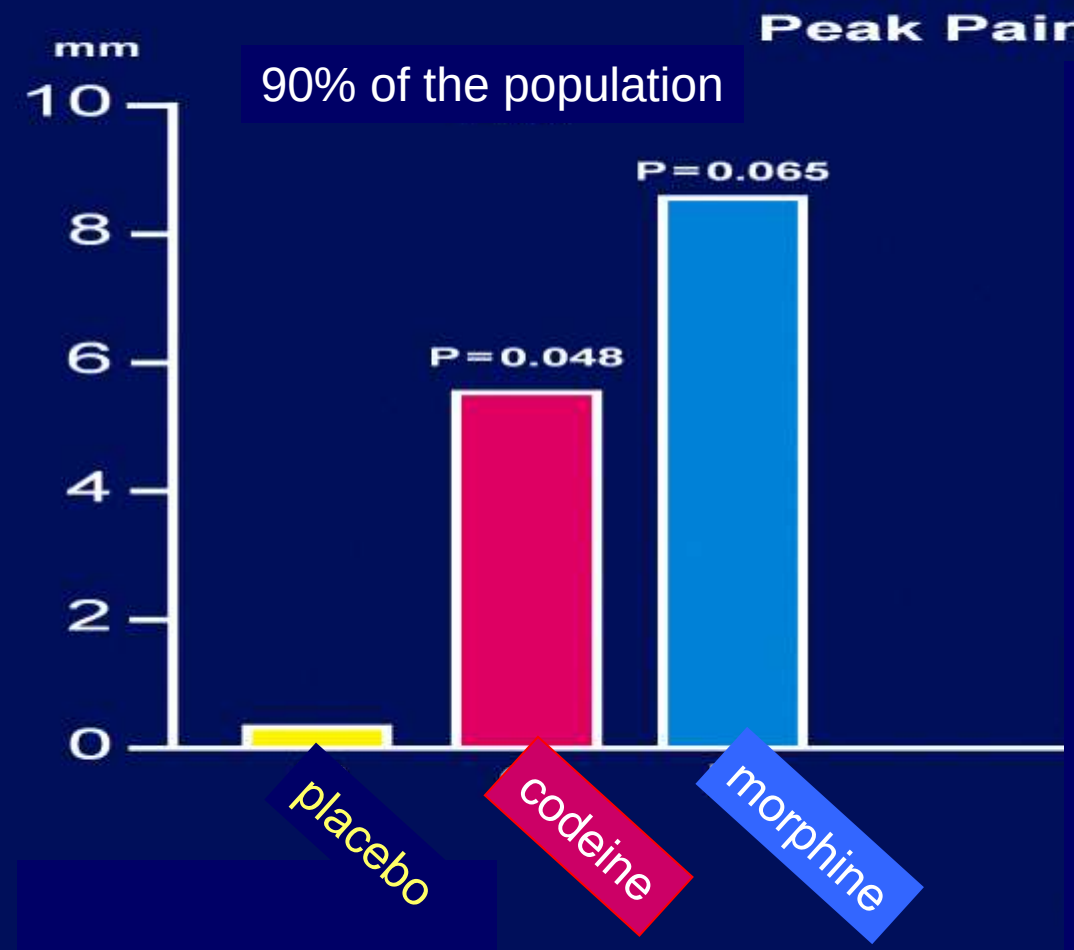


Vol. 152, April 15, 1988
1988
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 411-416

Codeine is the same as placebo to 10% of the population

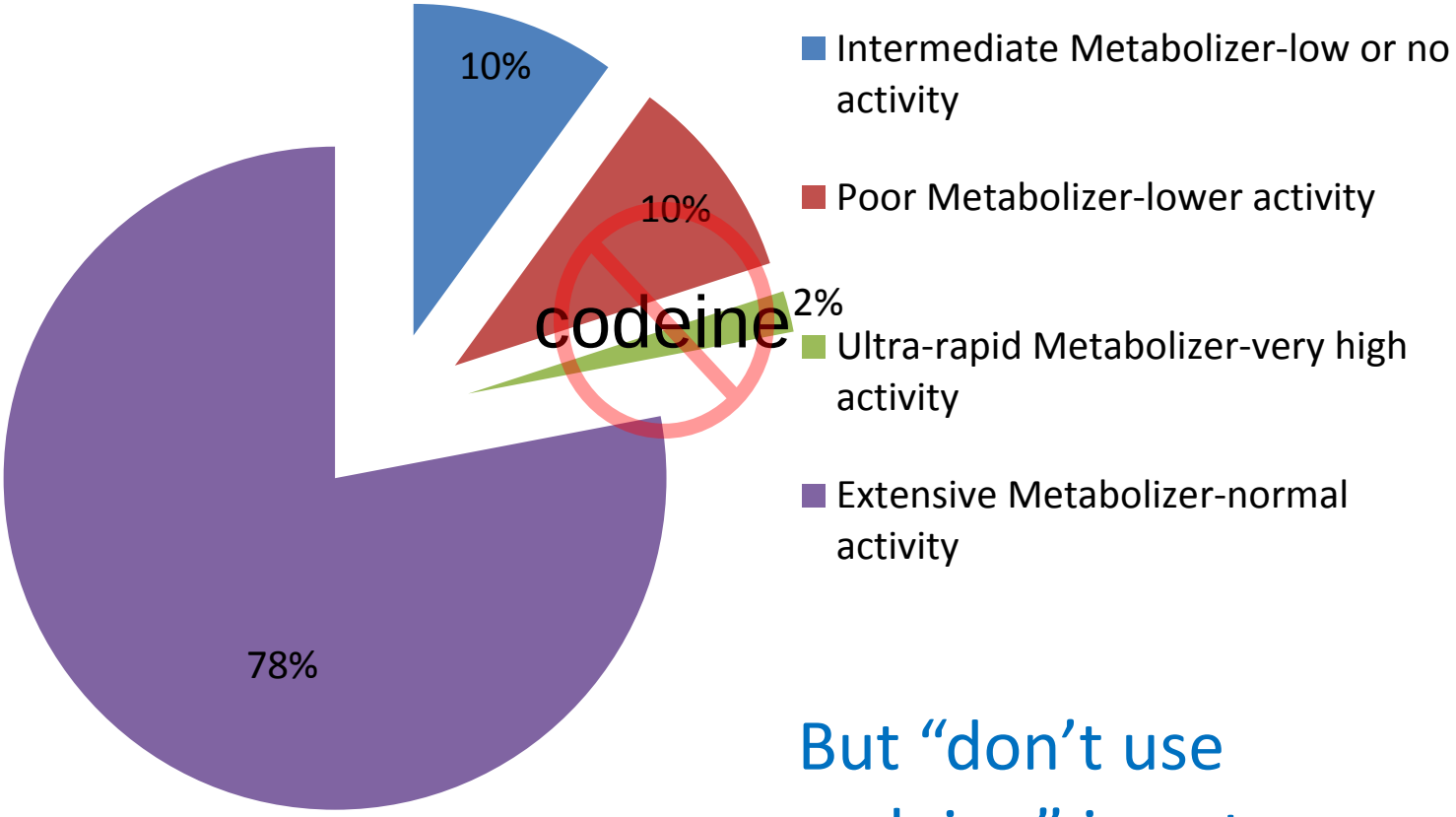


90% of the population

Poulsen et al *Eur J Clin Pharm* 1996;51:289-95

And too active for 1-2% of the population

12% of the population should not take codeine based on CYP2D6



But “don’t use codeine” is not enough…..

But genetic testing for this and other drugs remains extremely uncommon….

Realization:
There is no implementation fairy who is going to magically make this happen…..

If the pharmacogenomics research community doesn't take on implementation, who else will?

2009/2010 Survey of pgen "experts": 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.

Goal of CPIC

- Accelerate implementation of research discoveries in pharmacogenomics into the clinic.
- CPIC accomplishes this goal primarily by creating and providing freely available, peer-reviewed, updatable, and detailed gene/drug pharmacogenetic clinical practice guidelines.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

- 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.

- Posted on PharmGKB and capitalize on PharmGKB resources
- Freely available, no limits on use
- Peer reviewed, CPT first right of refusal to publish, standardized format, minimum set of elements
- Grading of evidence and of recommendations
- Can be updated on PharmGKB ahead of publications
- Authorship, COI policy
- Closely follow IOM practices
  - Curr Drug Metab. 2014 Feb;15(2):209-17

History

PGRN

I & II: 2000-2010—network of ~ 8 UO1 research groups and PharmGKB

III: 2010-2015—funded PGRN-wide projects such as the Translational Pharmacogenomics Project (TPP)

IV: 2015-2020—3 P50 research groups and 4 R24 resources (including CPIC and PharmGKB)

2011-present: NHGRI GMWG

CPIC

Started late 2009

Some funding (part of existing funding and part of TPP 2013-2015)

Separate R24s funded for CPIC and PharmGKB July 2015 to June 2018

NIGMS Launches a New Research Network Focused on Preci

posted Jul 17, 2015, 10:41 AM by Graham Johnson [updated Aug 7, 2015, 2:11 PM]

Pharmacogenomics Research Network

PGRN

www.pgrn.org

The National Institute of General Medical Sciences has sponsored the Pharmacogenomics Research Network PGRN-Hub, which serves to catalyze scientific collaborations in precision medicine.

The **three PGRN centers** are listed below alphabetically by principal investigator:

Center for Pharmacogenomics of Statin Therapy
Ronald Krauss, MD, Children's Hospital Oakland Research Institute (Calif.)
Aldons Jake Lusis, PhD, University of California, Los Angeles

Center for Precision Medicine in Leukemia
Mary V. Relling, PharmD, St. Jude Children's Research Hospital, Memphis, Tenn.
Mignon Loh, MD, University of California Benioff Children's Hospital

Center for Improving Prediction of Drug Action
Dan M. Roden, Vanderbilt University School of Medicine, Nashville, Tenn.
Elizabeth J. Phillips, MD, Vanderbilt University School of Medicine, Nashville, Tenn.
Joshua C. Denny, MD, MS, Vanderbilt University

PGRN enabling resources are listed below alphabetically by principal investigator:

PharmGKB: Pharmacogenomics Knowledge for Precision Medicine
Russ Altman, MD PhD, Standford University
Teri Klein, PhD, Standford University

PGRN Hub
Kathy Giacomini PhD, University of California San Francisco
Graham Johnson PhD, University of California San Francisco

F-CAP: Functionalization of Variants in Clinically Actionable Pharmacogenes
Doug Fowler, University of Washington
Allan Rettie, University of Washington

Clinical Pharmacogenetics Implementation Consortium (CPIC)
Mary V. Relling, PharmD, St. Jude Children's Research Hospital, Memphis, Tenn.
Teri Klein, PhD, Standford University

Specific Aims

1. Create, curate, and update CPIC gene/drug guidelines for all gene/drug groupings that are clinically actionable (CPIC Level A and B); expand the guidelines to include definitive clinical recommendations for non-actionable drugs linked to otherwise actionable genes (CPIC Level C).

2. Enhance access to and input into guidelines by external groups such as NIH's Pharmacogenomics PGRN, NIH's Genomic Medicine Working group, AHRQ's www.guidelines.gov, NIH's Genetic Test Registry, PubMed, FDA, ClinGen, IOM's Genomic Medicine roundtable, professional societies, and EHR vendors by systematically evaluating community usage of CPIC guidelines on a quantitative, qualitative, and ongoing basis to respond to the community and make enhancements as needed.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

- As of January 2016:
  - >160 Members
    - Clinicians and scientists
    - 86 institutions
    - 16 countries
  - 14 Observers (NIH and FDA)
  - CPIC Informatics
    - 19 members from 11 organizations

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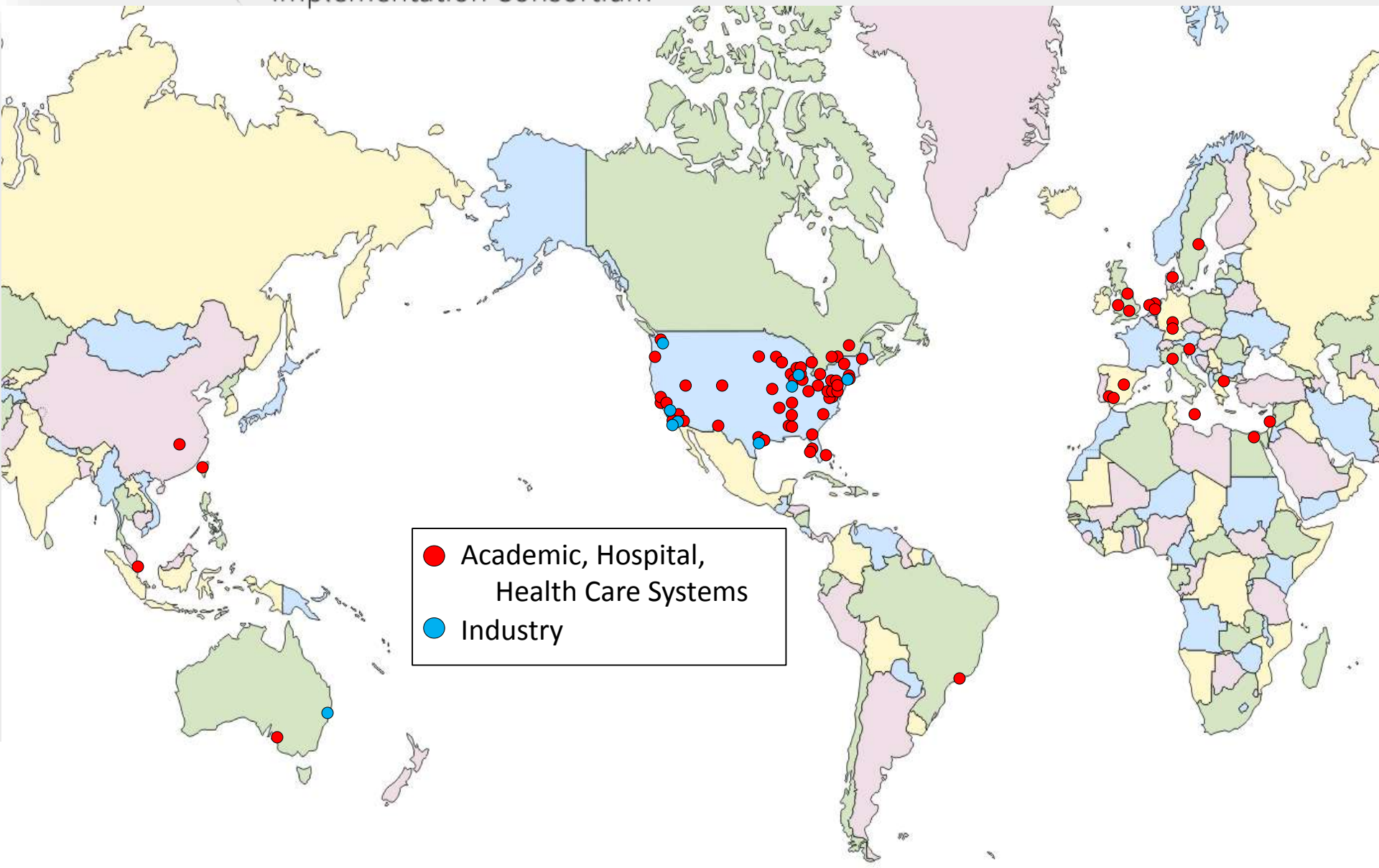
Clinical Pharmacogenetics Implementation Consortium

2016 Members



CPIC Guidelines

2011

- *TPMT* – thiopurines
  - Updated March 2013
- *CYP2C19* – clopidogrel
  - Updated Sept 2013
- *CYP2C9, VKORC*1 – warfarin
  - Update underway

2012

- *CYP2D6* – codeine
  - Updated Apr 2014
- *HLA-B* – abacavir
  - Updated Feb 2014
- *SLCO1B1* – simvastatin
  - Updated Oct 2014

2013

- *HLA-B* – allopurinol
  - Updated Oct 2015
- *CYP2D6, CYP2C19* – TCAs
  - Update underway
- *HLA-B* -- carbamazepine
- *DPYD* -- 5FU / capecitabine

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir

Guidelines in progress (as of 1/1/2016)

- *CYP2C19* -- voriconazole
- *CYP2D6* – tamoxifen
- *CYP2D6* – ondansetron
- RYR1—succinylcholine

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Current estimate: 17 genes, 86 drugs with pharmacogenetically-based prescribing

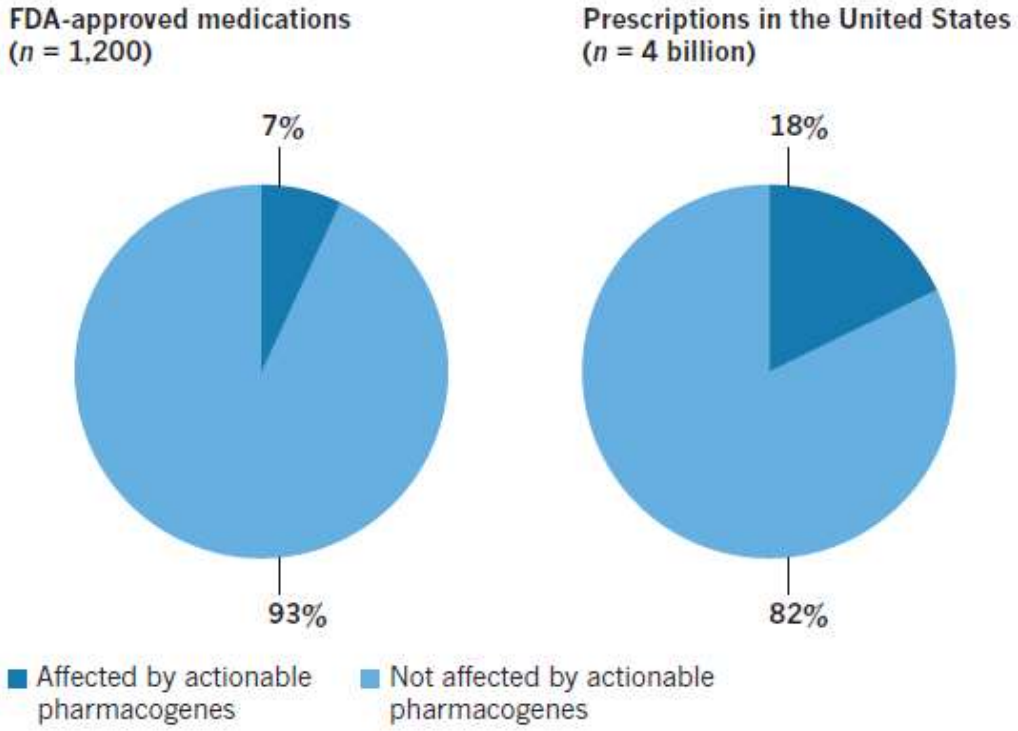
Number of current and planned CPIC genes, drugs and anticipated guidelines.	Genes	Drugs	Anticipated number of unique guidelines
Strong or Moderate prescribing action-CPIC level A	14	36	20 (17 published)
Optional prescribing actions-CPIC level B	7[a]	50	9
No prescribing actions-CPIC level C	16[b]	47	20

[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).

Feb 2016

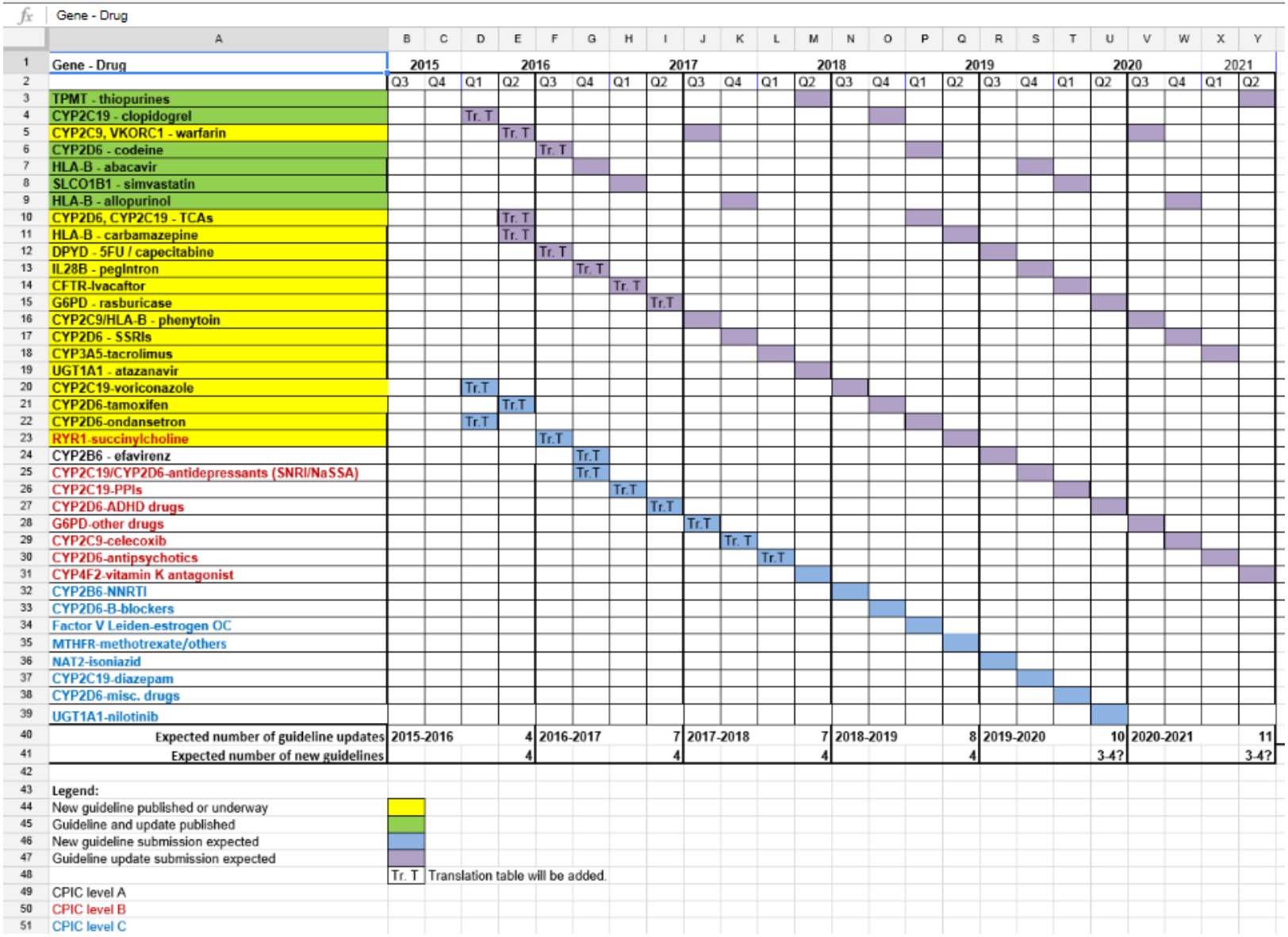
How many gene/drug pairs should be used in the clinic now?

- ~ 1200 chemical entities approved as drugs, ~ 18,000 genes
- Actionable: ~ 17 genes, ~ 87 drugs (~ 30 guidelines)
  - http://www.pharmgkb.org/page/cpicGeneDrugPairs



Relling & Evans, Nature, 2015

Timetable for CPIC guidelines and updates



Gene - Drug	2015 Q3	2015 Q4	2016 Q1	2016 Q2	2016 Q3	2016 Q4	2017 Q1	2017 Q2	2017 Q3	2017 Q4	2018 Q1	2018 Q2	2018 Q3	2018 Q4	2019 Q1	2019 Q2	2019 Q3	2019 Q4	2020 Q1	2020 Q2	2020 Q3	2020 Q4	2021 Q1	2021 Q2
TPMT - thiopurines																								
CYP2C19 - clopidogrel			Tr. T																					
CYP2C9, VKORC1 - warfarin				Tr. T																				
CYP2D6 - codeine					Tr. T																			
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IL28B - pegIntron						Tr. T																		
CFTR-Ivacaftor							Tr. T																	
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CYP2D6 - SSRIs																								
CYP3A5-tacrolimus																								
UGT1A1 - atazanavir																								
CYP2C19-voriconazole			Tr.T																					
CYP2D6-tamoxifen				Tr.T																				
CYP2D6-ondansetron			Tr.T																					
RYR1-succinylcholine					Tr.T																			
CYP2B6 - efavirenz						Tr.T																		
CYP2C19/CYP2D6-antidepressants (SNRI/NaSSA)						Tr.T																		
CYP2C19-PPIs							Tr.T																	
CYP2D6-ADHD drugs								Tr.T																
G6PD-other drugs									Tr.T															
CYP2C9-celecoxib										Tr. T														
CYP2D6-antipsychotics											Tr.T													
CYP4F2-vitamin K antagonist																								
CYP2B6-NNRTI																								
CYP2D6-B-blockers																								
Factor V Leiden-estrogen OC																								
MTHFR-methotrexate/others																								
NAT2-isoniazid																								
CYP2C19-diazepam																								
CYP2D6-misc. drugs																								
UGT1A1-nilotinib																								
Expected number of guideline updates	2015-2016			4	2016-2017			7	2017-2018			7	2018-2019			8	2019-2020			10	2020-2021			11
Expected number of new guidelines				4				4				4				4				3-4?				3-4?

Legend:

- New guideline published or underway
- Guideline and update published
- New guideline submission expected
- Guideline update submission expected

Tr. T Translation table will be added.

CPIC level A

CPIC level B

CPIC level C

Feb 2016

PRECISION MEDICINE IN L... PRECISION MEDICINE IN L... http--www.ascpt.org-Port... Suggested Sites Clinical Applications
CPIC

Member Resources

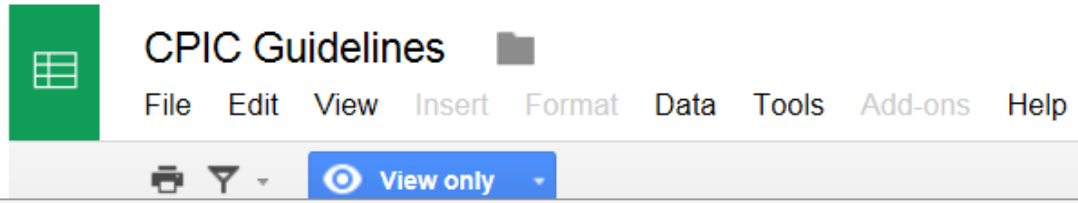
Manage your CPIC profile (including your password)

Conference call minutes

CPIC guideline drafts (for member review)

CPIC SOP

CPIC Informatics Working Group



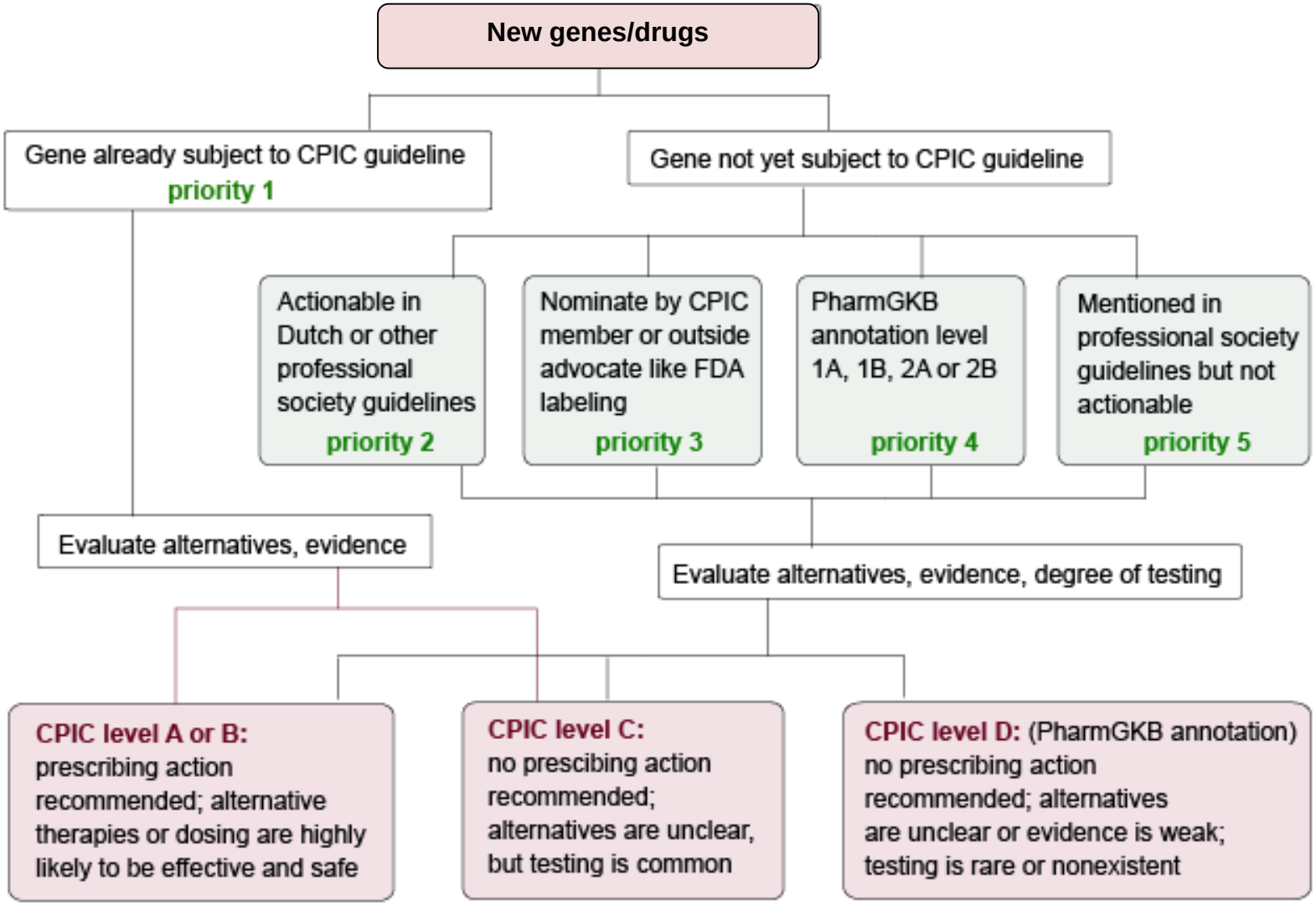
Dosing recommendations: strength based on evidence

Strong recommendation for the statement
Moderate recommendation for the statement
Optional recommendation for the statement

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. December 1, 2009; 1-161. Page 2, Table #2*. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed June 25, 2006.

Initial Prioritization Considerations for New Gene/Drug Groups

(may change over time as evidence and experience accumulates)



https://cpicpgx.org/genes-drugs/

https://cpicpgx.org/genes-drugs/
Member Resources – CPIC
Genes-Drugs – CPIC
PRECISION MEDICINE IN L...
PRECISION MEDICINE IN L...
http--www.ascpt.org-Port...
Suggested Sites
Clinical Applications
St Jude
Web Slice Gallery
CPIC
Mary Relling Log

Genes-Drugs

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 preemptive (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 invites feedback on existing and planned gene/drug guidelines.

- View CPIC's process for prioritizing genes/drugs
- View CPIC's levels for genes/drugs

Download Table (CSV)

Search:

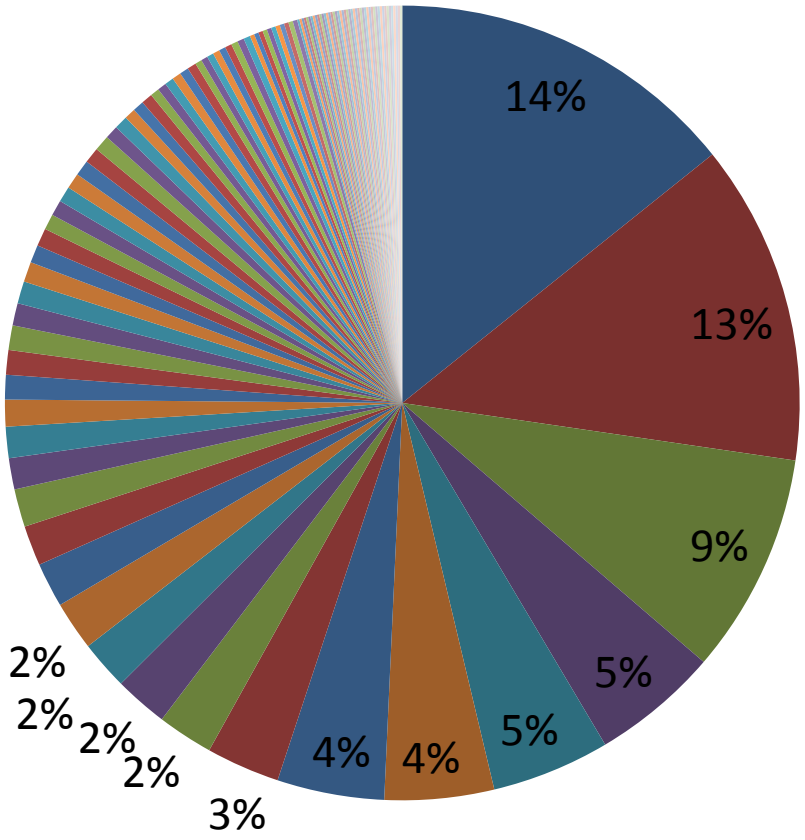
#	GENE	DRUG	GUIDELINE ON	CPIC	PHARMGKB LEVEL	CPIC PUBLICATIONS

125%

Table 3: Elements of CPIC guidelines and supplements

Review the gene(s) and drug(s)
Define important phenotypes or genotypes for the gene
Define which variants constitute alleles
Assign function to alleles
Translation of diplotypes into phenotypes
Prescribing recommendations based on test results
Update recommendations based on new evidence
Report allele frequencies in race/ethnic/ancestral groups
Summarize evidence supporting the prescribing recommendations
Provide algorithms for CDS for pharmacogenetic testing
Provide example language for test interpretation to use in EHR
Provide example language for interruptive alerts to use in EHR

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
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- (*2/*40)2N
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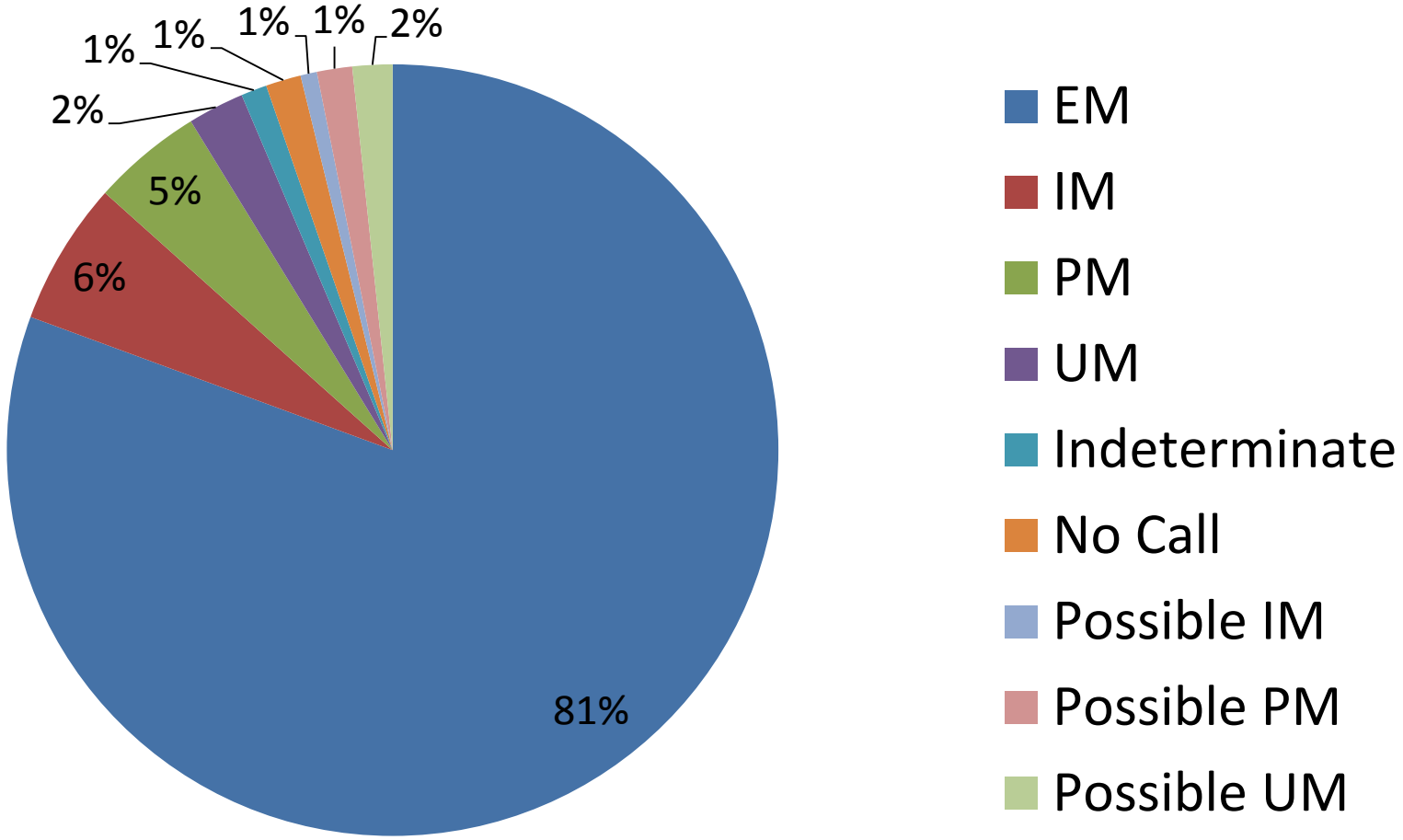
- (*2/*10)3N
- (*3/*17)2N
- (*29/*40)2N
- (*29/*29)2N
- (*18/*18)1N
- (*1/*4)2/2/1N
- (*1/*4)4N
- (*4/*41)3N
- (*1/*4)2/3/2N
- (*1/*6)1N

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



Main tables in CPIC guideline

- Main Table 1: example translations of diplotypes to phenotypes
- Main Table 2: prescribing recommendations linked to phenotypes, standard grading for strength of recommendation
- Suppl Table: define each allele (one row per allele, one column per variant), assign function with citations, provide MAF in race groups
- Suppl Table: provide diplotype possibilities, assign phenotype, assign actionability, estimate frequencies in race groups, provide example CDS
- Suppl Table: summarize all relevant evidence that backs up prescribing recommendations, standard grading system

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Table 1: 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

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

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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]

Main tables in CPIC guideline

- Main Table 1: example translations of diplotypes to phenotypes
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	rsID	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs36754001	rs28399504	rs36754002	rs36754003	rs55752065	rs17882687		
	dbSNP URL	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=113164681	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=111490789	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=17878739	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=7902257	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=12248560	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=36754001	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=28399504	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=367543002	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=367543003	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=55752065	http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=17882687		
CYP2C19 Allele	Allele Functional Status													
*1	Normal function	C	C	T	G	C	G	A	C	T	T	A	A	A
*2	No function													
*3	No function													
*4A	No function							G						
*4B	No function					T		G						
*5	No function													
*6	No function													
*7	No function													
*8	No function													
*9	Decreased function													
*10	Decreased function													
*11	Normal function													
*12	Unknown													
*13	Normal function													
*14	Unknown										C			
*15	Normal function											C		
*16	Decreased function													
*17	Increased function					T								
*18	Normal function													
*19	Decreased function													G

Supplemental Table S2. Association between allelic variants and DPD function		
Functional Status	**Alleles**	**Phenotype**
Functional / normal activity/ wild-type[1]	*1	
Non-functional, variant, or mutant / no activity	*2A	Associated with toxicity in most (2-6), but not all (7, 8). Observed in patients with low DPD activity (5, 8-15) and DPD deficiency (1). Observed in patients with severe or fatal toxicity (9, 16-20). Associated with reduced 5-fluorouracil clearance (11, 15) and inactive catalytic activity (21).
	*13	Associated with toxicity (6). Observed in patients with low DPD activity (22, 23). Observed in patients with severe or fatal toxicity (14). Associated with reduced 5-fluorouracil clearance (6).
	rs67376798	Observed in individuals with low DPD activity (14, 24). Associated with toxicity (2, 4-6, 17). Associated with reduced 5-fluorouracil clearance (6, 15).
Probable Reduced-function / decreased activity (these alleles are mostly very rare and so reports have been rare)	*3	Observed in individuals with DPD deficiency (1, 25).
	*7	Observed in individuals with DPD deficiency (1).
	*8	Observed in individuals with low DPD activity (1).
	*9B	Observed in individuals with low DPD activity (25, 26).
	*10	Observed in individuals with DPD deficiency (1).
	*11	Observed in individuals with low DPD activity (27).
	*12	Observed in individuals with low DPD activity (27).
Unknown/unclear/contradictory evidence	*4†	Observed in individuals with low DPD activity (22, 28), but not in another study (29). Associated with toxicity (30, 31).
	*5†	Associated with toxicity in some (32)

Alleles

Each allele in this table is discussed in the corresponding CPIC guideline manuscript or supplement listed below.

- Links in the “Allele” column lead to summary pages for the allele, including manually curated literature in PharmGKB.
- Links in the “Gene” column lead to summary pages for the gene, including manually curated literature, VIP gene summaries (if available), relat drug-centered pathways (if available), and more.
- Links in the “Guideline” column lead to guideline summaries on PharmGKB, including dosing recommendations for the corresponding allele(s)

There is also a CSV version of this table for download.

There is also a CSV version of this table for download.

	ALLELE	GENE	GUIDELINE
1	CFTR G178R	CFTR	• ivacaftor guideline
2	CFTR F508del(CTT)	CFTR	• ivacaftor guideline
3	CFTR F508del(TCT)	CFTR	• ivacaftor guideline
4	CFTR S549N	CFTR	• ivacaftor guideline
5	CFTR S549R(A>C)	CFTR	• ivacaftor guideline

Main tables in CPIC guideline

- Main Table 1: example translations of diplotypes to phenotypes
- Main Table 2: prescribing recommendations linked to phenotypes, standard grading for strength of recommendation
- Suppl Table: define each allele (one row per allele, one column per variant), assign function with citations, provide MAF in race groups
- Suppl Table: provide diplotype possibilities, assign phenotype, assign actionability, estimate frequencies in race groups, provide example CDS
- Suppl Table: summarize all relevant evidence that backs up prescribing recommendations, standard grading system

CPIC Translation Tables: diplotype to phenotype to actionability

Genotype Test Result for *SLCO1B1*	Coded Genotype/Phenotype Summary[a]	EHR Priority Result Notation[b]
*1a/*1a	None	Normal/Routine/Low Risk
*1a/*1b	None	Normal/Routine/Low Risk
*1a/*2	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*3	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*4	Indeterminate	None
*1a/*5	SLCO1B1- Intermediate Function	Abnormal/Priority/High Risk
*1a/*6	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*7	Indeterminate	None
*1a/*8	Indeterminate	None
*1a/*9	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*10	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*11	Indeterminate	None
*1a/*12	Indeterminate	None
*1a/*13	Indeterminate	None
*1a/*14	SLCO1B1 Increased Function	None
*1a/*15	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*16	Indeterminate	None
*1a/*17	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*18	Indeterminate	None
*1a/*19	Indeterminate	None

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

Main tables in CPIC guideline

- Main Table 1: example translations of diplotypes to phenotypes
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- Suppl Table: define each allele (one row per allele, one column per variant), assign function with citations, provide MAF in race groups
- Suppl Table: provide diplotype possibilities, assign phenotype, assign actionability, estimate frequencies in race groups, provide example CDS
- Suppl Table: summarize all relevant evidence that backs up prescribing recommendations, standard grading system

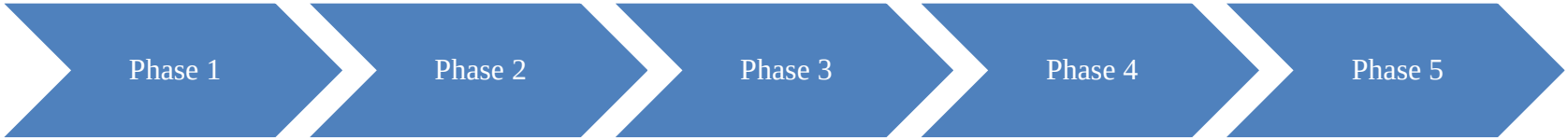
Evidence for CYP3A5 and tacrolimus

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

All tables reference either allele function, phenotype, or both, but the terms were not standardized

- Main Table 1: example translations of diplotypes to phenotypes
- Main Table 2: prescribing recommendations linked to phenotypes, standard grading for strength of recommendation
- Suppl Table: define each allele (one row per allele, one column per variant), assign function with citations, provide MAF in race groups
- Suppl Table: provide diplotype possibilities, assign phenotype, assign actionability, estimate frequencies in race groups, provide example CDS
- Suppl Table: summarize all relevant evidence that backs up prescribing recommendations, standard grading system

CPIC Phenotype Term Standardization Project



- **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).

Group memberships for Delphi process surveys for 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

Final 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*

Final Terms-Phenotype

Term/Gene Category	Final Term*	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Phenotype-Drug Metabolizing Enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	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*
Phenotype-Transporters (SLCO1B1)	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*
Phenotype-High risk genotype status (HLA-B)	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	

Next Steps

- Use final terms in CPIC Guidelines
- Dissemination
  - Abstract submitted to American Medical Informatics Association (AMIA) Translational Bioinformatics Meeting
  - Manuscript submitted
- Work with groups for endorsement
  - Association of Molecular Pathology
  - IOM's DiGITIZE Action Collaborative
  - LOINC-Terms accepted December 2016

LOINC

50956-2 HLA-B*57:01 [Presence]

NAME

Fully-Specified Name:	Component	Property	Time	System	Scale	Method
	HLA-B*57:01	Pr	Pt	Bld/Tiss	Ord	

PART DEFINITION/DESCRIPTION(S)

Part of HLA-B57 allele family that is associated with Abacavir hypersensitivity reaction (AHSR)

Source: SignatureTissues

The human leukocyte antigen B (HLA-B) plays an important role in how the immune system recognizes and responds to pathogens. HLA-B belongs to a class of molecules that are found on the surface of most cells. These molecules are responsible for presenting peptides to immune cells. Peptides derived from normal human proteins are recognized as such, whereas foreign peptides derived from pathogens trigger an immune response. The antiretroviral medication abacavir specifically interacts with HLA-B*57:01 and alters the repertoire of self-peptides that are presented to T lymphocytes, which activates an immune reaction known as a hypersensitivity reaction. [PMID: 24561393] See https://www.pharmgkb.org/gene/PA35056 for more information and dosing guidelines for drugs impacted by HLA-B genetic variation.

Source: Clinical Pharmacogenetics Implementation Consortium

BASIC ATTRIBUTES

Class/Type:	HLA/Lab
Created On:	2007/10/31
Last Updated in Version:	2.54
Order vs. Obs.:	Both
Status:	Active. Change Reason: This test is commonly performed on cells found in saliva and buccal swabs as well as blood specimens. Changed specimen from 'Bld' to 'Bld/Tiss' to represent both specimen types.

PREFERRED ANSWER LIST (LL360-9)

SEQ#	Answer	Answer ID
1	Positive	LA6576-8
2	Negative	LA6577-6

Groups in process of endorsing/adopting CPIC standardized phenotype terms

- PGx Nomenclature Work Group
- ClinGen
- International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) Pharmacogenetics Committee
- CAP's Pharmacogenetics WG

CPIC Guideline Users

- Identified 67 CPIC guideline users:
  - 30 using CPIC guidelines to inform implementation
    - 20 Academic/Non-profit/Health-care system
    - 9 Commercial (Clinical or direct-to-consumer laboratory)
    - 1 Government (IGNITE)
  - 58 using CPIC guidelines as part of teaching, training, or competency tool
    - 18 Academic/Non-profit/Health-care system
    - 14 Commercial
    - 12 Educational Resource/CE
    - 4 Government
    - 10 Professional Societies

https://cpicpgx.org/resources/
Member Reso...
Genes-Drugs –...
Resources –...
PRECISION MEDICINE IN L...
PRECISION MEDICINE IN L...
http--www.ascpt.org-Port...
Suggested Sites
Clinical Applications
St Jude
Web Slice Galle
CPIC
Mary Relling

Resources

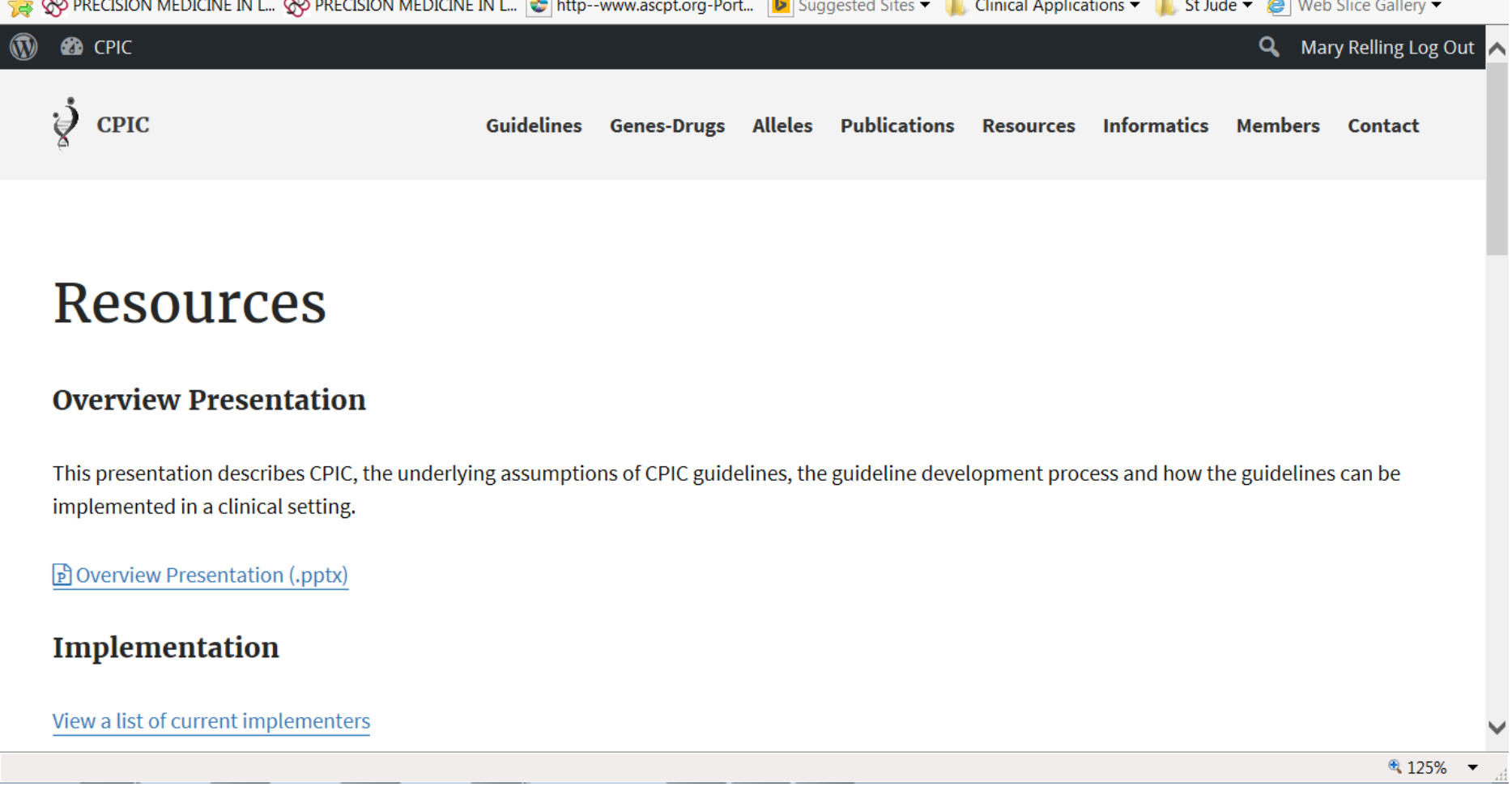
Overview Presentation

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)

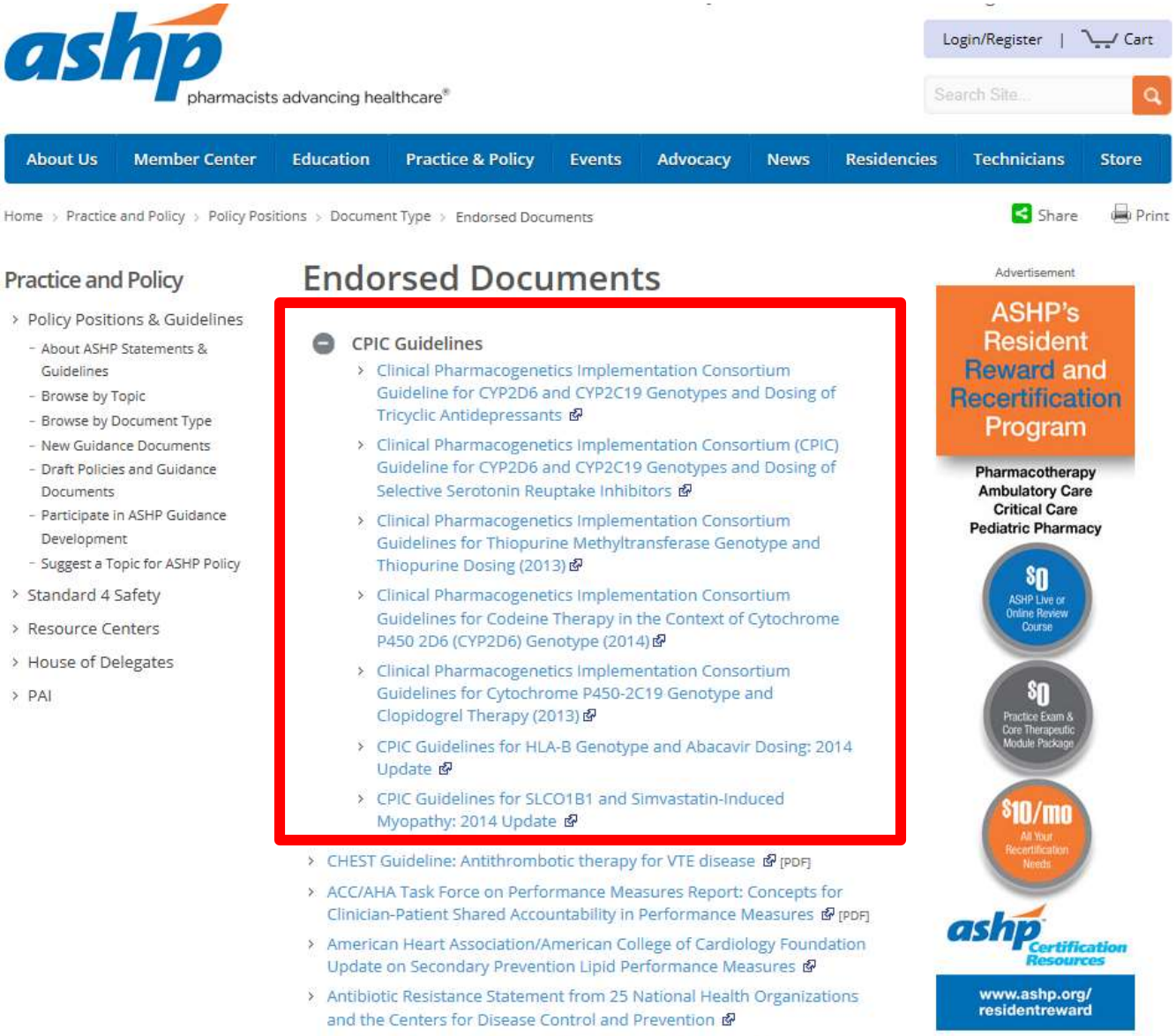
Implementation

View a list of current implementers



22 implementers listed

ASHP is endorsing CPIC guidelines



External interactions with other groups

- Endorsement by professional societies
  - ASCPT, ASHP
- Continue interactions with www.guidelines.gov, NIH's GTR, PubMed, FDA, NHGRI's Genomic Medicine Working Group, IOM's Genomic Medicine Roundtable, DIGITiZE, AMP, PGRN, AMIA, and eMERGE
- ClinGen/ClinVar
  - CPIC has a 4-star review status (i.e. professional guideline) for submissions to ClinVar
  - However, submissions are labor-intensive

Chairs

Teri E. Klein, PhD, FACMI

Howard L. McLeod, PharmD

Pharmacogenomic Domain WG

Integrating knowledge about human genetic variation to inform drug response.

Pharmacogenomics Working Group Goals:

- Evaluate PGx genes, their impact on drugs, and provide additional annotation that supplements existing pharmacogenetic guidelines.
- Develop systematic methods for representing and depositing knowledge from the Pharmacogenomics (PGx) Working Group, Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB into ClinGen and ClinVar on a regular schedule.
- Participate in discussions on the reconciliation of disparate nomenclatures in pharmacogenetics, including:
  - Build working relationships with CPIC to develop standardized terminology for functional status and allele definitions, and, engage genetic testing laboratories to consistently apply these standardized definitions.
  - Work with the American College of Medical Genetics and Genomics (ACMG) to develop a nomenclature appropriate for PGx variants similar to that of disease variants for pathogenicity.
  - Support the development with the Center for Disease Control (CDC) Nomenclature group for standards for PGx assays such that it is clear what is being tested on a specific gene (e.g., CYP2D6 star system means what actual SNPs were tested).
- Interact with other ClinGen WGs to harmonize the final contributions to the ClinGen resource.

Switch to ClinVar slides

Biggest consumers of effort

- Need to clearly define each allele using standardized system, assign function to alleles
- Fine-tune system for evaluating and grading evidence

CPIC recent priorities

- Continue to write new guidelines and update old ones
- Further standardize evidence review
- Streamline table building; add phenotype-by-race frequencies
- Make all elements needed for CDS “machine readable”
- Standardized terms for allele fx and phenotypes
- Provided actionable pharmacogenes for ACMG secondary findings
- Helped ASCPT operationalize endorsements
- CPIC trademarked
- Renewing contract with ASCPT/CPT as journal
- Established website independent from PharmGKB-cpicpgx.org
- Established SAB
- Added list of implementers as users

Changes over last 6 yrs

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- More emphasis on process of guideline development, authorship policies
- Prioritization scheme for gene/drug pairs
- More comprehensive listing of alleles
- More formalized interactions with “external” groups
- More emphasis on EHR compatibility: translation tables suitable, standardization of terms, CDS language

CPIC issues to discuss

- How best to assess usage of CPIC guidelines?
- How to improve interactions with external groups?
- How to prioritize given limited resources?
- Plan for sustainability over time
- How to interact with SAB?
- Timeline: grant renewal application likely due summer of 2017

Acknowledgements

- PGRN
- PharmGKB
  - Teri Klein
  - Russ Altman
  - Michelle Whirl-Carrillo
  - PharmGKB curators
- CPIC members/observers
- CPIC informatics working group
  - James Hoffman
  - Michelle Whirl-Carrillo
  - Bob Freimuth
- CPIC Steering Committee
  - Mary Relling
  - Julie Johnson
  - Teri Klein
  - Dan Roden
  - Rachel Tyndale

Guidelines.gov

Number of CPIC guideline page views reported by guidelines.gov (through July 2015)		
Title	Date Posted	Page Views
Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing.	7/26/2013	10159
Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing.	7/26/2013	10253
Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.	7/26/2013	14623
Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.	7/26/2013	10171
Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.	2/14/2014	7648
Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing.	2/14/2014	6961
Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update.	8/29/2014	12543
Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing.	8/29/2014	1842
Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and PEG interferon-α–based regimens.	8/29/2014	2054
Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype.	12/5/2014	1738
The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update.	3/13/2015	11874
Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype.	3/13/2015	1223

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Relative Citation Ratio (RCR): A new metric that uses citation rates to measure influence at the article level

Bruce Ian Hutchins, Xin Yuan, James M Anderson, George M Santangelo

doi: http://dx.doi.org/10.1101/029629

Posted October 22, 2015.

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Abstract

Despite their recognized limitations, bibliometric assessments of scientific productivity have been widely adopted. We describe here an improved method that makes novel use of the co-citation network of each article to field-normalize the number of citations it has received. The resulting Relative Citation Ratio is article-level and field-independent, and provides an alternative to the invalid practice of using Journal Impact Factors to identify influential papers. To illustrate one application of our method, we analyzed 88,835 articles published between 2003 and 2010, and found that the National Institutes of Health awardees who authored those papers occupy relatively stable positions of influence across all disciplines. We demonstrate that the values generated by this method strongly correlate with the opinions of subject matter experts in biomedical research, and suggest that the same approach should be generally applicable to articles published in all areas of science. A beta version of iCite, our web tool for calculating Relative Citation Ratios of articles listed in PubMed, is available at https://icite.od.nih.gov .

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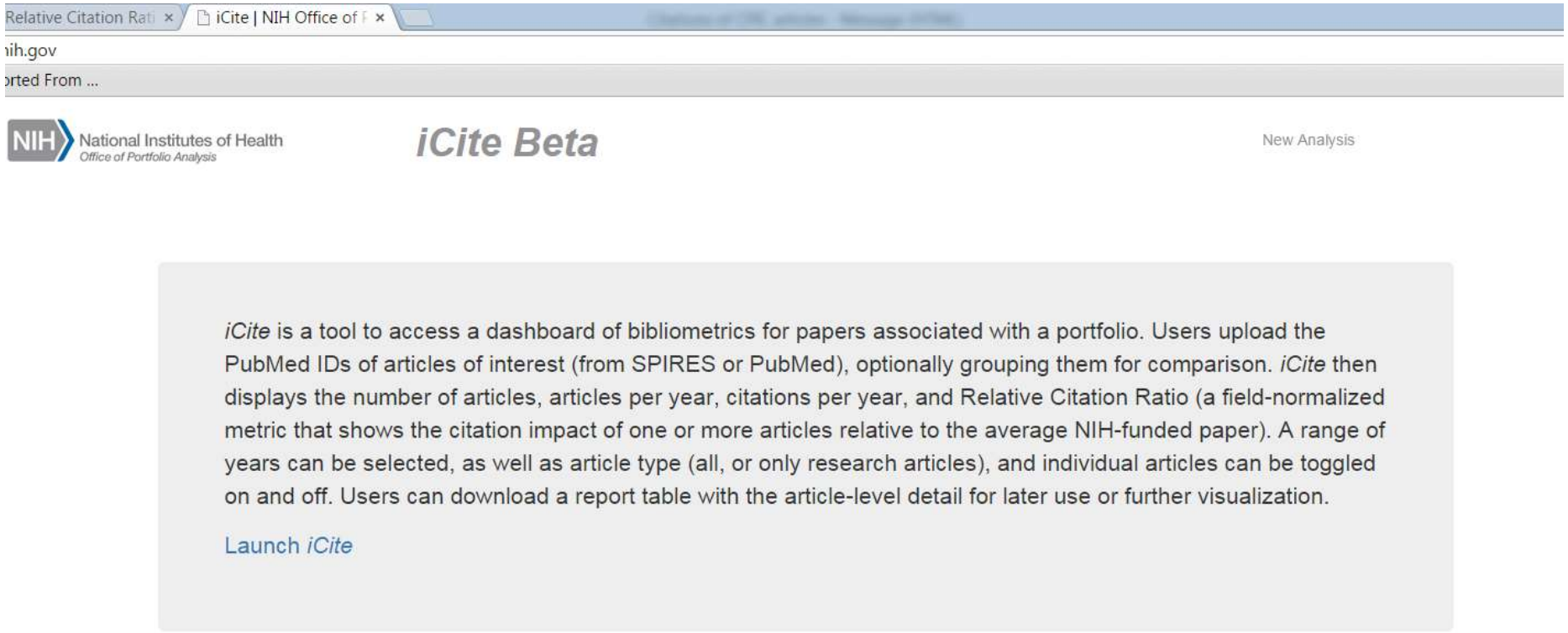
Subject Area

Scientific Communication

Subject Areas

All Articles

- Animal Behavior and Cognition
- Biochemistry
- Bioengineering
- Bioinformatics
- Biophysics
- Cancer Biology
- Cell Biology
- Developmental Biology
- Ecology
- Evolutionary Biology
- Genetics
- Genomics
- Immunology



cites/year of each paper, normalized to the citations per year received by NIH-funded papers in the same field and year. A paper with an RCR of 1.0 has received the same number of cites/year as the average NIH-funded paper in its field, while a paper with an RCR of 2.0 has received twice as many cites/year as the average NIH-funded paper in its field. (Average high-impact Nature article ~ 4).

Year	Title	Authors	RCR
2013	Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing.	Caudle, K E; Thorn, C F; Klein, T E; Swen, J J; McLeod, H L; Diasio, R B; Schwab, M	4.44
2013	Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.	Scott, S A; Sangkuhl, K; Stein, C M; Hulot, J-S; Mega, J L; Roden, D M; Klein, T E; Sabatine, M S; Johnson, J A; Shuldiner, A R;	8.97
2013	Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing.	Leckband, S G; Kelsoe, J R; Dunnenberger, H M; George, A L; Tran, E; Berger, R; Müller, D J; Whirl-Carrillo, M; Caudle, K E; Pirmohamed, M;	4.92
2013	Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.	Hicks, J K; Swen, J J; Thorn, C F; Sangkuhl, K; Kharasch, E D; Ellingrod, V L; Skaar, T C; Müller, D J; Gaedigk, A; Stingl, J C;	10.66
2013	Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update.	Relling, M V; Gardner, E E; Sandborn, W J; Schmiegelow, K; Pui, C-H; Yee, S W; Stein, C M; Carrillo, M; Evans, W E; Hicks, J K; Schwab, M; Klein, T E	9.59
2013	Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing.	Hershfield, M S; Callaghan, J T; Tassaneeyakul, W; Mushiroda, T; Thorn, C F; Klein, T E; Lee, M T M	6.19
2012	The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy.	Wilke, R A; Ramsey, L B; Johnson, S G; Maxwell, W D; McLeod, H L; Voora, D; Krauss, R M; Roden, D M; Feng, Q; Cooper-Dehoff, R M; Gong, L; Klein, T E; Wadelius, M; Niemi, M;	7.69
2012	Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing.	Martin, M A; Klein, T E; Dong, B J; Pirmohamed, M; Haas, D W; Kroetz, D L;	4.52
2012	Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype.	Crews, K R; Gaedigk, A; Dunnenberger, H M; Klein, T E; Shen, D D; Callaghan, J T; Kharasch, E D; Skaar, T C;	13.47
2011	Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing.	Johnson, J A; Gong, L; Whirl-Carrillo, M; Gage, B F; Scott, S A; Stein, C M; Anderson, J L; Kimmel, S E; Lee, M T M; Pirmohamed, M; Wadelius, M; Klein, T E; Altman, R B;	9.68
2011	Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy.	Scott, S A; Sangkuhl, K; Gardner, E E; Stein, C M; Hulot, J-S; Johnson, J A; Roden, D M; Klein, T E; Shuldiner, A R;	8.86
2011	Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.	Relling, M V; Gardner, E E; Sandborn, W J; Schmiegelow, K; Pui, C-H; Yee, S W; Stein, C M; Carrillo, M; Evans, W E; Klein, T E;	11.04
	CPIC: Clinical Pharmacogenetics Implementation		9.61

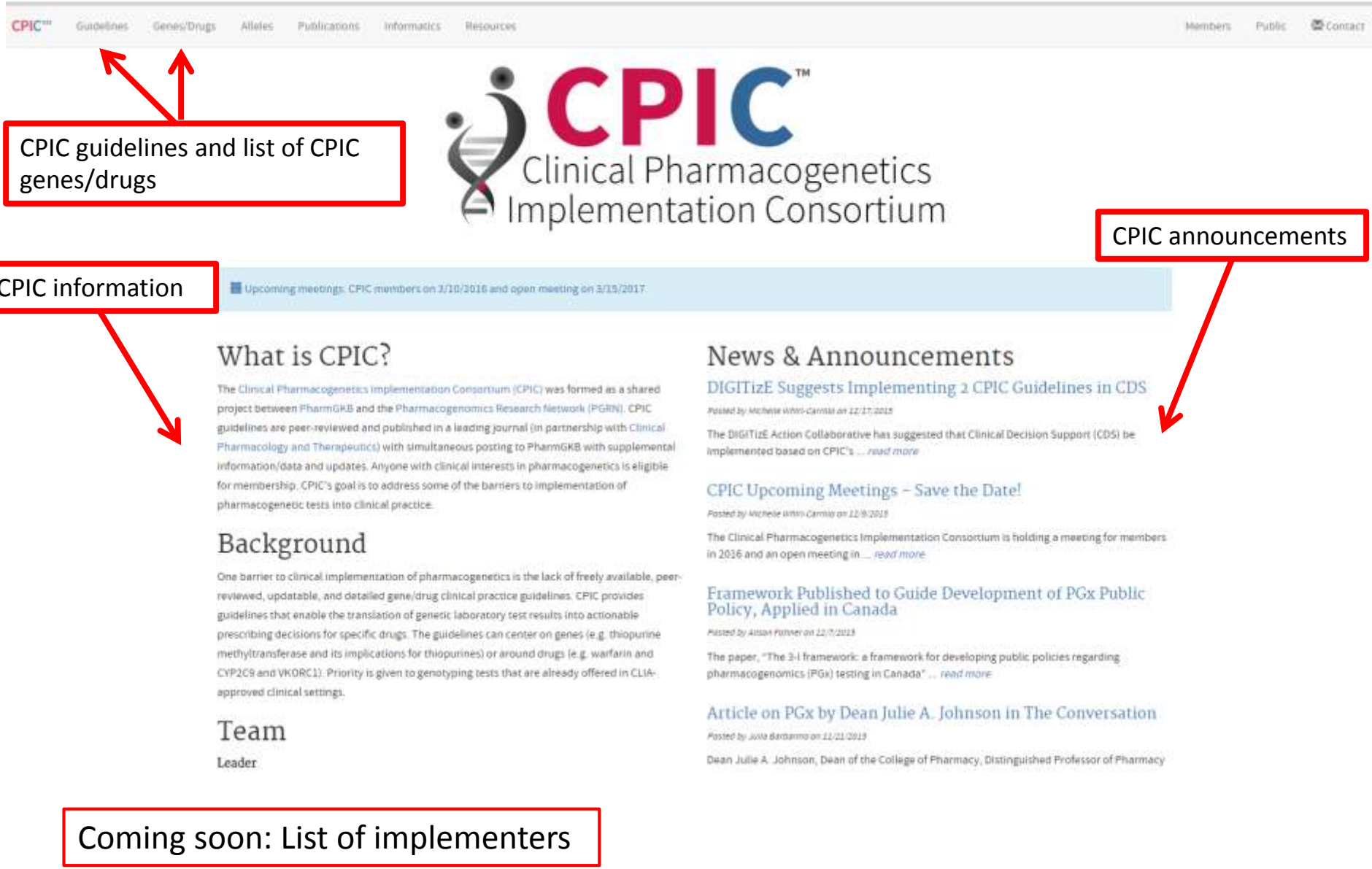
CPIC meetings

- **CPIC luncheon meeting**—open to CPIC members
  - Thursday March 10th, 2016 Noon-1:30 PM
  - Hilton Bayfront Hotel, San Diego, CA
  - Email: kelly.caudle@stjude.org to attend

- **CPIC Meeting** (a specialty meeting of the PGRN)
  - Wednesday March 15th, 2017
  - Marriott Wardman Park Hotel, Washington DC
  - Further details pending.

- To standardize phenotype terms in the CPIC guidelines and harmonize terms with external groups (e.g., ClinGen, IOM, etc.) to facilitate use in Electronic Health Records
  - Allele functional status terms (Table 1 in guideline)
    - Low, absent, high, intermediate
  - Phenotype (i.e. from diplotypes; Table 2 in guideline)
    - UM, EM, IM, PM

CPIC website: www.cpicpgx.org



Coming soon: List of implementers

CPIC Resources

CPIC information available at cpicpgx.org

CPIC slides

CPIC projects

CPIC logo

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)

Term Standardization for Clinical Pharmacogenetic Test Results

CPIC is leading an effort to standardize terms for clinical pharmacogenetic tests. The goal of the project is to create standardized terms to be used in CPIC guidelines (specifically Tables 1 and 2) and in the larger pharmacogenetics community. A list of phenotype term options based on an extensive literature review and scanning of sample laboratory reports is being developed. Refinement of the terms will be performed using a modified Delphi method in the context of expert opinions.

- **Brief overview** of the project and final results (.pptx)
- **Proposal** for Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes (.pdf)
- Delphi 1 survey results by question (.pdf)
- Delphi 2 survey results (.pdf)
- Delphi 3 survey results (.pdf)
- Delphi 4 survey results (.pdf)
- **Final terms** for the CPIC Term Standardization Project (.pdf)

CPIC Logo Graphics

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	600px width PNG	SVG
logo with full name	200px width PNG	400px width PNG	600px width PNG	SVG
logo source (& other logos)	Adobe Illustrator (.ai)			

CPIC Dosing Guideline for simvastatin and SLCO1B1

last updated 06/30/2014

Summary

The FDA recommends against 80mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at lower simvastatin doses (40mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered.

Find genotype-based dosing recommendation

Pick rs4149056 alleles: No selection No selection

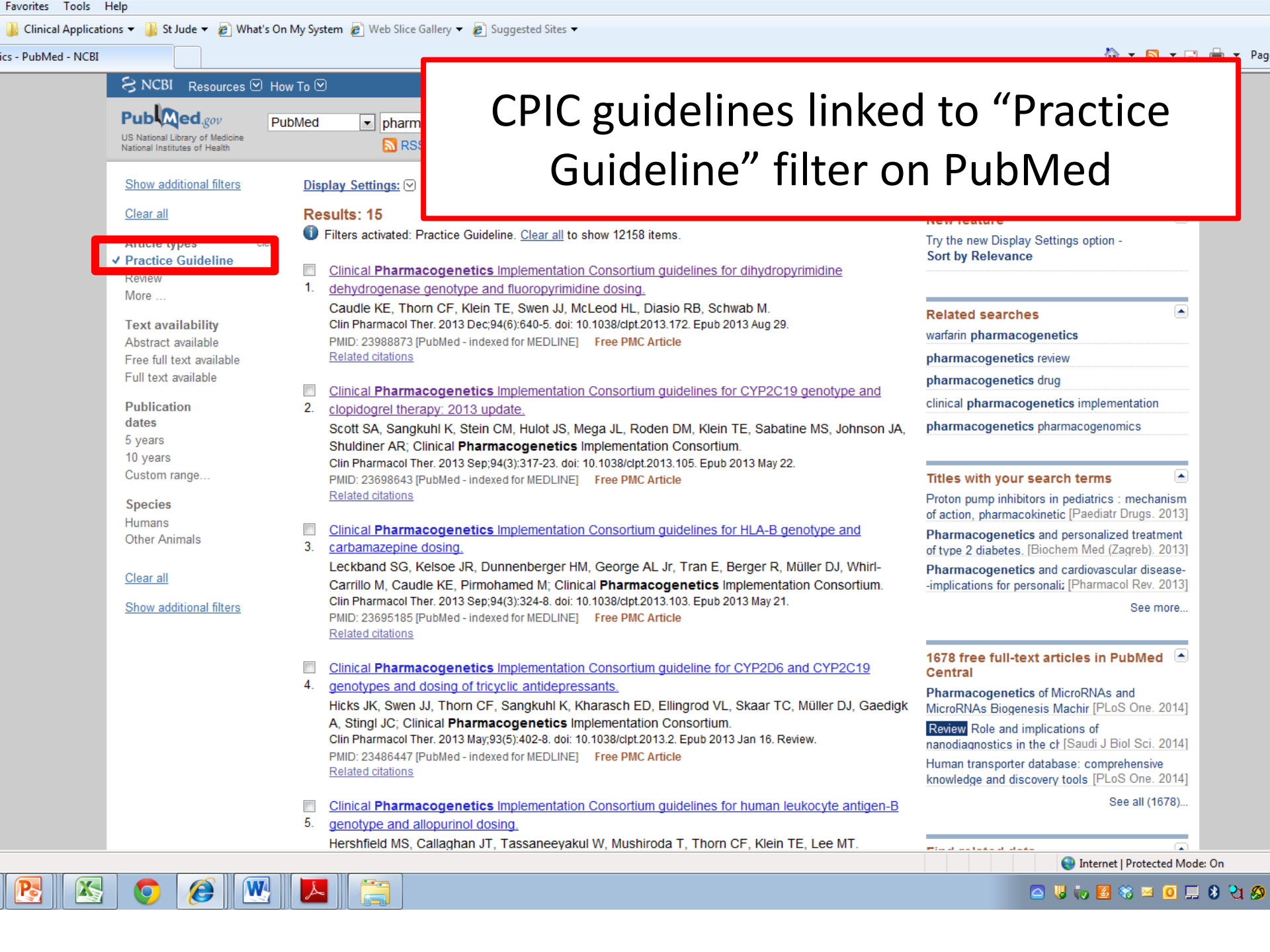
Annotation

June 2014 Update

Advance online publication 9 July 2014.

- The 2014 update of CPIC guideline regarding SLCO1B1 and simvastatin-induced myopathy, has been published in Clinical Pharmacology and Therapeutics. CPIC extensively reviewed the literature from February 2011 to December 2013 and concluded the dosing recommendations provided in the 2012 CPIC guideline for SLCO1B1 and simvastatin-induced myopathy have not changed. However, this updated guideline also provides a brief review regarding SLCO1B1 genotype and risk of myopathy for other statins. Furthermore, comprehensive translation tables mapping SLCO1B1 genotypes to coded genotype/phenotype summaries, EHR priority result notation and interpretation (consultation) text were created to facilitate incorporation of SLCO1B1 pharmacogenetics into an electronic health record with clinical decision support."
- This guideline is applicable to:
  - adult patients
  - pediatric patients
- Excerpt from the 2014 simvastatin dosing guideline:
  - "For simvastatin, the evidence linking myopathy to rs4149056 in SLCO1B1 is of high quality, and this association has been reproduced in randomized trials and clinical practice-based cohorts. Conversely, the association of rs4149056 with myopathy has been less compelling for other statins. We therefore focus this guideline on simvastatin."
    "In 2011 and updated in 2013, the FDA added warnings to the simvastatin product label to direct providers away from initiating at the 80 mg simvastatin dose. "
    "At lower simvastatin doses (e.g., 40 mg daily), it is our position that SLCO1B1 genotype (if available) could be used to warn providers about modest increases in myopathy risk for patients with a C allele at rs4149056. In these circumstances, we recommend a lower dose of simvastatin or use an alternative statin (e.g. pravastatin or rosuvastatin) and we also highlight the potential utility of routine CK surveillance (Table 2). If patients with a C allele at rs4149056 do not achieve optimal LDL cholesterol-lowering efficacy with a lower dose (e.g. 20 mg) of simvastatin, we recommend the prescribing physician consider an alternate statin based on (i) potency differences (i.e., use a lower dose of a higher potency statin such as atorvastatin, rosuvastatin, or pitavastatin), (ii) drug-drug interactions (e.g., boceprevir, clarithromycin, cyclosporine, strong CYP3A4 inhibitors, etc.), and (iii) relevant co-morbidities (e.g., trauma, significant renal impairment, post-solid organ transplant, thyroid disease etc.)."
    "At the time of this writing, there are no data available regarding SLCO1B1 genotype effects on simvastatin response or myopathy in pediatric patient populations, although there is no reason to suspect that the polymorphisms in SLCO1B1 will affect simvastatin's metabolism differently in children compared to adults."
- Download and read:
  - The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update
  - 2014 supplement
  - 2014 SLCO1B1 translation table

CPIC guidelines are posted on PharmGKB (www.pharmgkb.org)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Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, Skaar TC, Müller DJ, Gaedigk A, Stingl JC; Clinical Pharmacogenetics Implementation Consortium.
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5. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing.
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Clin Pharmacol Ther. 2013 Dec;94(6):640-5. doi: 10.1038/clpt.2013.172. Epub 2013 Aug 29.

Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing.

Caudle KE[1], Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M.

Author information

Abstract

The fluoropyrimidines are the mainstay chemotherapeutic agents for the treatment of many types of cancers. Detoxifying metabolism of fluoropyrimidines requires dihydropyrimidine dehydrogenase (DPD, encoded by the DPYD gene), and reduced or absent activity of this enzyme can result in severe, and sometimes fatal, toxicity. We summarize evidence from the published literature supporting this association and provide dosing recommendations for fluoropyrimidines based on DPYD genotype (updates at http://www.pharmgkb.org).

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Review [Review of methods for determination of dihydropyrimidine dehydrogen: [Przegl Lek. 2012]

[Detection of dihydropyrimidine dehydrogenase deficiency before treatment by fl [Therapie. 2007]

The contribution of deleterious DPYD gene sequence \ [Cancer Chemother Pharmacol. 2010]

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