The Clinical Pharmacogenetics Implementation Consortium (CPIC) Update

CPIC™
Clinical Pharmacogenetics Implementation Consortium

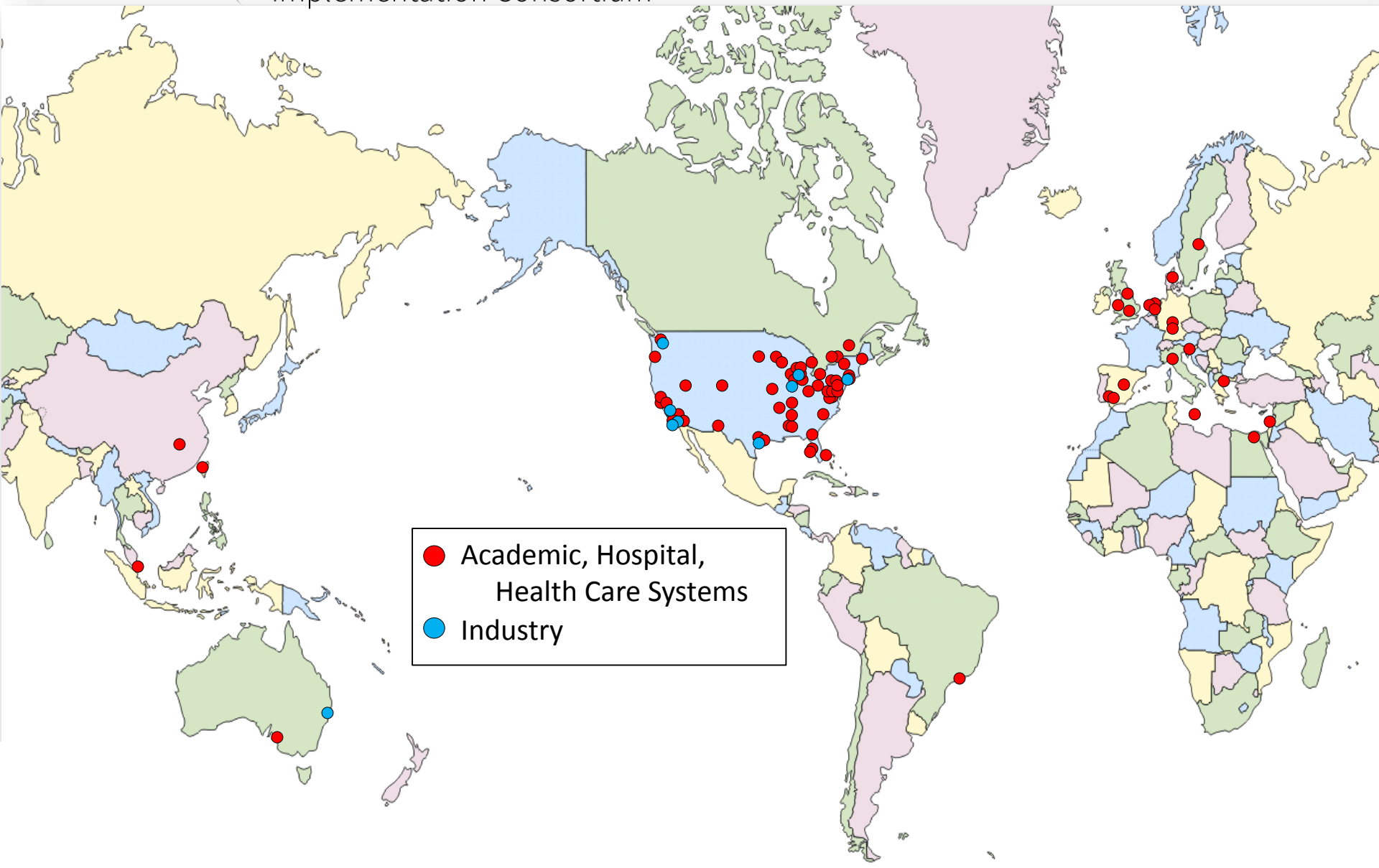
- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  - Not WHETHER tests should be ordered.
- Key Assumption:
  - Clinical high-throughput and pre-emptive genotyping will become more widespread.
  - Clinicians will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

CPIC™
Clinical Pharmacogenetics Implementation Consortium

- As of January 2017:
  - 196 Members
    - Clinicians and scientists
    - 138 institutions
    - 23 countries
  - 8 Observers (NIH and FDA)
  - CPIC Informatics
    - >20 members from 12 organizations

CPIC™
Clinical Pharmacogenetics Implementation Consortium

2017 >190 members



CPIC guideline genes (n=16) and drugs, January 2017

- *TPMT*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, **TCAs**, tamoxifen (in progress), SSRIs, **ondansetron, tropisetron**
- *CYP2C19*
  - **TCAs,** clopidogrel, **voriconazole**, SSRIs
- *VKORC1*
  - **Warfarin**
- *CYP2C9*
  - **Warfarin**, phenytoin
- *CYP4F2*
  - **Warfarin**
- *HLA-B*
  - Allopurinol, CBZ, abacavir, phenytoin
- *CFTR*
  - Ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - Rasburicase
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Simvastatin
- *IFNL3 (IL28B)*
  - Interferon
- *CYP3A5*
  - Tacrolimus
- *CYP2B6*
  - Efavirinz (in progress)
- *RYR1*
  - Inhaled anesthetics (in progress)

https://cpicpgx.org/guidelines/

Strength of Recommendation

- **Strong** recommendation for the statement**:** “The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.”
- **Moderate** recommendation for the statement: “There is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

Other Publications

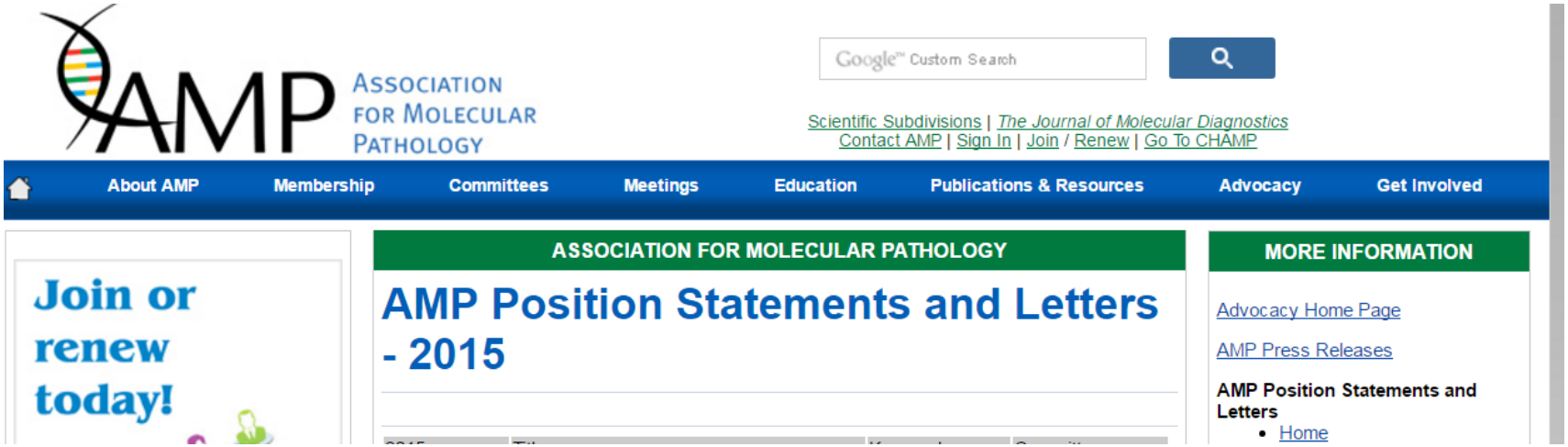
Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

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]

CPIC Informatics Working Group



	E&C in support of congressional action to ensure a CLIA moderization approach to LDPs	FDA, CMS, CLIA	Relations
October 26	Comments to FDA, CDC, and NLM on Promoting Semantic Interoperability of Laboratory Data	FDA, CDC, NLM, EHR, LOINC, SNOMED-CT	Professional Relations
October 26	**Endorsement of Clinical Pharmacogenetics Implementation Consortium (CPIC) initative to standardize pharmacogenetic nomenclature**	CPIC	Clinical Practice
August 26	Presentation of New Code Crosswalk Recommendations to Advisory Panel on Clinical Diagnostic Laboratory Tests	CMS, CLFS, PAMA, GSP, CPT, CAP	Economic Affairs

Results must be received at the CAP no later than midnight, Central Time by the due date below:

October 4, 2016

CYP2C19 – PGX-04 — PGX-06, cont'd

Clinical Scenario – *CYP2C19*

A 57-year-old Caucasian female with diabetes mellitus, currently on clopidogrel, presents to her primary care physician complaining of easy fatigability and chest pain.

Interpretation (Ungraded)

Exception Code 005 ○ 11 ○ 33

010 PGX-04	020 PGX-05	030 PGX-06
○ 257 This patient is an ultra-rapid metabolizer	○ 257 This patient is an ultra-rapid metabolizer	○ 257 This patient is an ultra-rapid metabolizer
○ 837 This patient is a rapid metabolizer	○ 837 This patient is a rapid metabolizer	○ 837 This patient is a rapid metabolizer
○ 258 This patient is a normal metabolizer	○ 258 This patient is a normal metabolizer	○ 258 This patient is a normal metabolizer
○ 259 This patient is an intermediate metabolizer	○ 259 This patient is an intermediate metabolizer	○ 259 This patient is an intermediate metabolizer
○ 260 This patient is a poor metabolizer	○ 260 This patient is a poor metabolizer	○ 260 This patient is a poor metabolizer
○ 590 Inconclusive	○ 590 Inconclusive	○ 590 Inconclusive

Clinical Management (Ungraded)

Exception Code 035 ○ 11 ○ 33

040 PGX-04 (Select all that apply.)	100 PGX-05 (Select all that apply.)	160 PGX-06 (Select all that apply.)
○ 262 An increased dose should be considered	○ 262 An increased dose should be considered	○ 262 An increased dose should be considered
○ 263 The standard dose should be considered	○ 263 The standard dose should be considered	○ 263 The standard dose should be considered
○ 264 A decreased dose should be considered	○ 264 A decreased dose should be considered	○ 264 A decreased dose should be considered

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: RegenstriefInstitute

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

ACTION COLLABORATIVES

DIGITizE: Displaying and Integrating Genetic Information Through the EHR

Sandy Aronson, M.A. (Co-Chair)
Executive Director of IT
Partners HealthCare Personalized Medicine

John David Nolen, M.D., Ph.D., M.S.P.H. (Co-Chair)
Senior Director and General Manager
for Laboratory Medicine
Cerner Corporation

Current Work and Activities

Establishing Connectivity and Pharmacogenomic Clinical Decision Support Rules to Protect Patients Carrying HLA-B*57:01 and TPMT Variants: An Implementation Guide

Use Case Types

Pharmacogenetics Standards Model

Lab Interpreted Result Concept Overview

Issue

The sequencing of the human genome has facilitated a tremendous increase in our understanding of disease. Health care practitioners now have the ability to determine in which patient a drug will be most effective or where a patient may forgo therapy due to a lack of clinical benefit. This greater understanding, combined with the technological advances that have significantly improved genome sequencing accuracy while decreasing its cost, has led to large-scale sequencing now being used in clinical practice to aid in diagnosis and to identify treatment options for patients. However, there are a number of challenges encountered when this large amount of data is integrated into medical practice. While linking health data from genomics and other fields to the electronic health record (EHR) would be of benefit for learning about disease, treatment efficacy, outcomes, and drug safety, these platforms do not currently have the ability to handle genomic information. There is a lack of standards for the data, and interoperability, scalability, privacy, security, and storage issues need to be resolved before these data can be used effectively in the

Action Collaboratives

- Global Genomic Medicine Collaborative (G2MC)

Action Collaborative Participants

- Sandy Aronson, Partners HealthCare
- J.D. Nolen, Cerner
- Mark Adams, Good Start Genetics
- Gil Alterovitz, Harvard Medical School
- Brian Anderson, athenahealth
- Jane Atkinson, NIDCR
- Larry Babb, Partners HealthCare
- Dixie Baker, Martin, Blanck and Associates
- Gillian Bell, Mission Health
- Adam Berger, FDA
- Colleen Campbell, University of Iowa
- Chris Chute, Johns Hopkins University
- Chris Coffin, Invitae
- Mauricio de Castro, Department of Defense
- Carol Edgington, McKesson
- Laurel Estabrooks, Soft Computer Corporation

Working with SNOMED to match codes to standardized phenotype terms

TPMT – SNOMED CT Code
Thiopurine methyltransferase deficiency

vs

TPMT- standardized Terms
TPMT - Normal Metabolizer (normal dose)
TPMT - Intermediate Metabolizer (60% dose)
TPMT - Poor Metabolizer (5% dose)

Chairs

Teri E. Klein, PhD, FACMI, FACMG

Marylyn D. Ritchie, PhD

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.

Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

RECEIVED 1 September 2015
REVISED 7 December 2015
ACCEPTED 13 January 2016
PUBLISHED ONLINE FIRST 28 March 2016

James M Hoffman,[1] Henry M Dunnenberger,[2] J Kevin Hicks,[3] Kelly E Caudle,[1] Michelle Whirl Carrillo,[4] Robert R Freimuth,[5] Marc S Williams,[6] Teri E Klein,[4] and Josh F Peterson[7]

CPIC Informatics Working Group

J Am Med Inform Assoc. 2016 Jul;23(4):796-801.

Box 1: Principles for the development of knowledge resources to support precision medicine

1. Pharmacogenomic interpretations must support traceability between interrogated variants, primary results, and clinical interpretations.
2. Pharmacogenomic knowledge resources must rate level of evidence for each variant as well as for the overall recommendation.
3. Knowledge resources must use standards to facilitate information exchange and enable interoperability among disparate systems.
4. Pharmacogenomic knowledge resources must support long-term reinterpretation of results.
5. Pharmacogenomic knowledge resources must be positioned to be integrated with other knowledge at the point of care.

J Am Med Inform Assoc. 2016 Jul;23(4):796-801.

New CPIC website created (cpicpgx.org)

Guidelines

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

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

In the table below, links to ***read more*** about each guideline will take you to a webpage where you can download the guideline manuscript, supplement and any other related files. There, you will also find information about when the guideline was published and the most recent update of the guideline. Links to drugs and genes in the table below will take you to more information on the PharmGKB website. On PharmGKB, you can also download guideline data in JSON format from the Downloads page.

Gene-specific tables that support the CPIC guidelines and contain information about allele frequency, function and mapping to reference sequences, diplotype-phenotype mappings and more are available here.

Search:

DRUG	GENE	SUMMARY
abacavir	HLA-B	In individuals with the HLA-B*57:01 variant allele ("HLA-B*57:01-positive"), abacavir is not recommended and should be considered only under exceptional circumstances. See full guideline for disclaimers, further details and supporting evidence. *read more*

https://cpicpgx.org/guidelines/

Guideline for Voriconazole and CYP2C19

CPIC recommends selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, alternative agents are recommended in those who are ultrarapid metabolizers or poor metabolizers, and standard dosing is recommended for initiating therapy in pediatric rapid metabolizers. Therapeutic drug monitoring is recommended to titrate dose to therapeutic trough concentrations.

Original Publication (December 2016)

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

Supplemental tables:

Table provided with publication

- 2016 Supplement
- Voriconazole resource mapping file
- Voriconazole Pre- and Post-test alerts and Flow Chart

CPIC Gene-specific Information Tables

These resources support CPIC guidelines by providing information regarding star (*) allele definitions, allele function, allele frequency by major ethnic groups, translations of diplotype to phenotype, example EHR consultation (genetic test interpretation)and gene resource mappings.

- CYP2C19 information tables

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

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
- **CYP2C19 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

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

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

Term Standardization for Clinical Pharmacogenetic Test Results

Learn about CPIC's Term Standardization Project

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
  - Image Source (PDF editable in Illustrator, etc.)

https://cpicpgx.org/resources/

Implementation

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

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

Guidelines.gov page views 7/17/2015 to 7/16/2016		
Guideline	**Posted**	**Views**
HLA-B genotype and abacavir	7/26/2013	1806
HLA-B genotype and allopurinol	7/26/2013	3036
CYP2D6 and *CYP2C19* and TCAs	7/26/2013	4432
TPMT genotype and thiopurine	7/26/2013	2236
CYP2C19 genotype and clopidogrel therapy: 2013 update	2/14/2014	2475
HLA-B genotype and carbamazepine	2/14/2014	3592
CYP2D6 genotype and codeine therapy: 2014 update	8/29/2014	2799
DPYD genotype and fluoropyrimidine	8/29/2014	2467
IFNL3 (*IL28B*) genotype and PEG interferon-α–based regimens	8/29/2014	2125
Ivacaftor therapy in the context of *CFTR* genotype.	12/5/2014	1928
SLCO1B1 and simvastatin-induced myopathy: 2014 update	3/13/2015	2155
Rasburicase therapy in the context of *G6PD* deficiency genotype	3/13/2015	2348
CYP2C9 and *HLA-B* genotypes and phenytoin dosing.	9/11/2015	3102
CYP3A5 genotype and tacrolimus dosing.	1/8/2016	1819

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- CPIC informatics working group
  - James Hoffman
  - Michelle Whirl-Carrillo
  - Bob Freimuth
- CPIC Steering Committee
  - Mary Relling
  - Julie Johnson
  - Teri Klein
  - Dan Roden
  - Rachel Tyndale
- CPIC SAB
  - Gwen McMillin
  - J.D. Nolan
  - Robert Nussbaum
  - Heidi Rehm
  - Marc Williams

PharmGKB

CPIC™ Clinical Pharmacogenetics Implementation Consortium