The Clinical Pharmacogenetics Implementation Consortium (CPIC): supporting the adoption of pharmacogenetics into the EHR

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Chief Patient Safety Officer
Associate Member, Pharmaceutical Sciences
Outline

• Overview of CPIC
• Implementation resources from CPIC
  – EHR agnostic
• Term Standardization efforts
  – LOINC and SNOMED
• Looking to the future
  – Key features for knowledge bases for pharmacogenetics
One Model of Pharmacogenetics Services

PG4KDS: Clinical Implementation of Pharmacogenetics at St. Jude

Implementation Resources:
www.stjude.org/pg4kds/implement
**PG4KDS: Protocol**

**Goal:**
- Migrate pharmacogenetic tests from the laboratory (array-based) into routine patient care, to be available preemptively
  - Implement all CPIC™ level A/B gene/drug pairs

**Exclusion criteria:**
- Patients who have received a prior allogeneic stem cell transplant
- Patient who have received a prior liver transplant
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<td><strong>TPMT and thiopurines</strong></td>
<td><strong>CYP2D6 and codeine</strong></td>
<td><strong>CYP2D6 and tramadol</strong></td>
<td><strong>CYP2D6 and paroxetine, fluoxetine, amitriptyline</strong></td>
<td><strong>CYP2D6 and ondansetron</strong></td>
<td><strong>SLCO1B1 and simvastatin</strong></td>
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<td><strong>CYP2D6 and oxycodone</strong></td>
<td><strong>CYP2C19 and clopidogrel</strong></td>
<td><strong>DPYD and fluoropyrimidines</strong></td>
<td><strong>CYP2C19/CYP2D6 and amitriptyline</strong></td>
<td><strong>UGT1A1 and atazanavir</strong></td>
<td><strong>CYP3A5 and tacrolimus</strong></td>
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<td><strong>CYP2C19 and voriconazole</strong></td>
<td><strong>CYP2C19/CYP2D6 and TCAs</strong></td>
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Consult is one place for passive CDS
Passive CDS: interpretation of pgen test results always available

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
Deconstruct the interpretive consult for each genetic test result into sections with standardized language; scalable to add additional diplotypes
Active CDS

TPMT Pre-pharmacogenetic test warning: no TPMT test result is in EHR

PGEN TESTING

TPMT genotype test is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine). A TPMT genotype test does not appear to have been ordered for this patient.

Alert Action

- cancel
- continue

Add Order for:

- TPMT Genotype -> T;N, Collect Now, Blood, ONCE

[History] [Add'l info] [OK]
Active CDS
TPMT post-test alert:
patient has a high-risk phenotype and is prescribed a thiopurine

Note: could be driven off (a) a secondary entry (high-risk phenotype = “problem”) or (b) directly off of test result

**WARNING**

Based on the genotype result, this patient is predicted to be a TPMT-INTERMEDIATE METABOLIZER. The patient is at risk for myelosuppression with normal doses of 6-mercaptopurine. Consider starting 6-mercaptopurine doses at 30 - 70% of the normal dose. Please consult a clinical pharmacist or review the pharmacogenetics tab for more information.

**Alert Action**

- Cancel entry
- Dose altered accordingly
- Modify
Deconstruct the interpretive consult for each genetic test result into sections with standardized language; scalable to add additional diplotype
Development, implementation, and evaluation of active CDS for multiple pharmacogenetic test results reported preemptively.
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
CPIC formed in 2009

- Goal: 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 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 CPIC website ahead of publications
• Authorship, COI policy
• Closely follow IOM practices
NIGMS Launches a New Research Network Focused on Precision Medicine


Pharmacogenomics Research Network

PGRN enabling resources are listed below alphabetically by principal investigator:

The Nation: PGRN-Hub

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

The three F

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

Cen

Clinical Pharmacogenetics Implementation Consortium (CPIC)
Mary V. Relling, PharmD, St. Jude Children's Research Hospital, Memphis, Tenn.
Teri Klein, PhD, Stanford University
CPIC open meeting on 3/15/2017 in Washington DC – more details on the meetings page

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

Background
One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling1, EE Gardner1, WJ Sandborn2, KSchmiegelow3,4, C-H Pui5, SW Yee6, CM Stein7, M Carrillo8, WE Evans1 and TE Klein8

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy

SA Scott1, KSangkuhl2, EE Gardner3, CM Stein4,5, J-S Hulot6,7, JA Johnson8,9,10, DM Roden11,12, TE Klein2 and AR Shuldiner13,14

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing

JA Johnson1, LGong2, M Whirl-Carrillo3, BF Gage3, SA Scott4, CM Stein5, JL Anderson6, SE Kimm MTM Lee2, M Pirmohamed11, M Wadelius12, TE Klein2 and RB Altman2,13

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen-B Genotype and Allopurinol Dosing

MS Hershfield1,2, JT Callaghan3,4,5, W Tassaneeyakul6, T Mushiroda7, CF Thorn8, TE Klein8 and MTM Lee9,10,11

Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype Abacavir Dosing

RA Wilke1,2, LB Ramsey3, SG Johnson4,5, WD Maxwell6, HL McLeod7, DVoora8, RM Krauss9, DM Roden1,2, Q Feng1,2, RM Cooper-DeHoff10, LGong11, TE Klein11,12, M Wadelius13 and M Niemi14

Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Carbamazepine Dosing

SG Leckband1,2, JR Kelsoe1,2, HM Dunnenberger3, AL George Jr4, ET Tran1, R Berger1, DJ Müller5,6, M Whirl-Carrillo7, KE Caudle3 and M Pirmohamed8

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype

R Crews1, A Gaedigk2, HM Dunnenberger3, TE Klein4, DD Shen5,6, JT Callaghan7,8, ED Kharasch9 and TC Skaar7
<table>
<thead>
<tr>
<th>CPIC LEVEL</th>
<th>CLINICAL CONTEXT</th>
<th>LEVEL OF EVIDENCE</th>
<th>STRENGTH OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing</td>
<td>At least one moderate or strong action (change in prescribing) recommended.</td>
</tr>
<tr>
<td>B</td>
<td>Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing</td>
<td>Preponderance of evidence is weak with little conflicting data</td>
<td>At least one optional action (change in prescribing) is recommended.</td>
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<tr>
<td>C</td>
<td>There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.</td>
<td>Evidence levels can vary</td>
<td>No prescribing actions are recommended.</td>
</tr>
<tr>
<td>D</td>
<td>There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.</td>
<td>Evidence levels can vary</td>
<td>No prescribing actions are recommended.</td>
</tr>
</tbody>
</table>
Current estimate: 17 genes, 87 drugs with pharmacogenetically-based prescribing

<table>
<thead>
<tr>
<th>Number of current and planned CPIC genes, drugs and anticipated guidelines.</th>
<th>Genes</th>
<th>Drugs</th>
<th>Anticipated number of unique guidelines</th>
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</thead>
<tbody>
<tr>
<td>Strong or Moderate prescribing action-CPIC level A</td>
<td>14</td>
<td>36</td>
<td>20 (17 published)</td>
</tr>
<tr>
<td>Optional prescribing actions-CPIC level B</td>
<td>7(^a)</td>
<td>50</td>
<td>9</td>
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<tr>
<td>No prescribing actions-CPIC level C</td>
<td>16(^b)</td>
<td>47</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\)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).
CPIC Informatics Working Group

• Growing interest in informatics aspects of CPIC guidelines and clinical implementation of pharmacogenetics

• Goal: 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.

• Working group leaders
  – Bob Freimuth (Mayo Clinic)
  – James Hoffman (St. Jude)
  – Michelle Carrillo (PharmGKB)
CPIC Informatics Working Group: Initial Focus

• Create comprehensive translation tables from genotype to phenotype to clinical recommendation for CPIC guidelines
  – Define structure and process to efficiently develop and maintain in the most useful format(s)
  – Publish as part of CPIC guidelines
CPIC Informatics: Supporting Guideline Implementation

Guideline Development

CPIC

Coordinate Refinements

Genotype

Phenotype

Recommendation

Guideline Adoption

Implementers

Feedback

CPIC Informatics

Creation and Maintenance of Translation Tables

- Human-readable
- Semi-structured text
- Formal knowledge representation
## CPIC Implementation Resources

<table>
<thead>
<tr>
<th>Table in CPIC Guideline</th>
<th>Description</th>
<th>Intended Use</th>
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</thead>
<tbody>
<tr>
<td>Translation of genotype test result into interpreted phenotype</td>
<td>Provides a crosswalk from genotype to interpreted phenotype. Includes diplotype in star allele nomenclature (if applicable).</td>
<td>Translates a laboratory result into a more clinically meaningful result. Phenotypes are helpful as discrete results in the EHR because they provide clinical context and can reduce the complexity needed in CDS rules.</td>
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<tr>
<td>Resources that demonstrate the genotypes that constitute the * alleles for gene X and their effect on X protein</td>
<td>Provides a crosswalk between pharmacogene star allele nomenclature, dbSNP identifier (rsID), variant nucleotide change, allele effect on protein.</td>
<td>Useful when evaluating limited published evidence to determine a potential phenotype and clinical recommendation.</td>
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</tbody>
</table>
CPIC tables allow translation of genetic test results to actionability

- Genotypes to alleles (e.g. g.94761900C>T + g.94762706A>G = CYP2C19*4B)
- Functions to alleles (e.g. CYP2C19*4B = no function)
- Alleles to diplotypes (e.g. g.94761900CT + g.94762706AG = CYP2C19*1/*4B)
- Diplotypes to phenotypes (e.g. CYP2C19*1/*4B = intermediate metabolizer)
- Interpretation of phenotypes (e.g. CYP2C19 intermediate metabolizer = altered dosing recommendations for TCAs but not clopidogrel)
- Phenotypes to actionability (e.g. intermediate metabolizer + Rx for amitriptyline = interruptive alert)

https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials
CPIC allele definition table: variants and function

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<th>Allele Functional Status</th>
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<th>T</th>
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</table>

**Position at NC_000010.11 (Homo sapiens chromosome 10, GRCh38.p2)**
CPIC tables allow translation of genetic test results to actionability

Genotypes to alleles (e.g. g.94761900C>T + g.94762706A>G = CYP2C19*4B)

Functions to alleles (e.g. CYP2C19*4B = no function)

Alleles to diplotypes (e.g. g.94761900CT + g.94762706AG = CYP2C19*1/*4B)

Diplotypes to phenotypes (e.g. CYP2C19*1/*4B = intermediate metabolizer)

Interpretation of phenotypes (e.g. CYP2C19 intermediate metabolizer = altered dosing recommendations for TCAs but not clopidogrel)

Phenotypes to actionability (e.g. intermediate metabolizer + Rx for amitriptyline = interruptive alert)

https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials
**CYP2C19 diplotype/phenotype table**

<table>
<thead>
<tr>
<th>CYP2C19 Diploptye</th>
<th>Coded Diploptye/Phenotype Summary</th>
<th>EHR Priority Result Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*2</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*3</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*4A</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*4B</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*5</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*6</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*7</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*8</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*9</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*10</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*11</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*12</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1/*13</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*14</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1/*15</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*16</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*17</td>
<td>CYP2C19 Rapid Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*18</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*19</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*22</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*23</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1/*24</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*25</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*26</td>
<td>CYP2C19 Likely Intermediate Metabolizer</td>
<td>Abnormal/ Priority/High Risk</td>
</tr>
<tr>
<td>*1/*27</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1/*28</td>
<td>CYP2C19 Normal Metabolizer</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1/*29</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1/*30</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
</tbody>
</table>

https://www.pharmgkb.org/page/cyp2c19RefMaterials
CPIC tables allow translation of genetic test results to actionability

Genotypes to alleles (e.g. g.94761900C>T + g.94762706A>G = CYP2C19*4B)

Functions to alleles (e.g. CYP2C19*4B = no function)

Alleles to diplotypes (e.g. g.94761900CT + g.94762706AG = CYP2C19*1/*4B)

Diploptypes to phenotypes (e.g. CYP2C19*1/*4B = intermediate metabolizer)

Interpretation of phenotypes (e.g. CYP2C19 intermediate metabolizer = altered dosing recommendations for TCAs but not clopidogrel)

Phenotypes to actionability (e.g. intermediate metabolizer + Rx for amitriptyline = interruptive alert)

https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials
# CPIC Implementation Resources

<table>
<thead>
<tr>
<th>Table in CPIC Guideline</th>
<th>Description</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that pertain to this guideline</td>
<td>Contains a list of the drugs covered in the guideline, referencing codes from standard terminologies (eg, RxNorm, DrugBank, ATC) and related databases (eg, PharmGKB).</td>
<td>Provides an unambiguous list of drugs that can be leveraged when creating CDS rules, using codes that are common in prescribing and pharmacy systems.</td>
</tr>
<tr>
<td>Genes that pertain to this guideline</td>
<td>Contains a list of genes covered in the guideline, referencing codes from standard nomenclatures and knowledge bases (eg, HGNC, NCBI, Ensembl, PharmGKB).</td>
<td>Useful when creating CDS rules; uses codes that can be cross-referenced to lab test results and used to look up data in knowledge databases.</td>
</tr>
</tbody>
</table>

Hoffman et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC) *JAMIA* 2016
Guideline for Tricyclic Antidepressants and CYP2D6 and CYP2C19

CPIC has updated the 2013 guideline for tricyclic antidepressants and CYP2D6 and CYP2C19. See Tables 2, 3, and 4 of the guideline for updated recommendations.

Update (December 2016)

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update

Supplemental tables:

Table provided with publication

- 2016 Supplement
- Drug Resource Mapping
  - Amitriptyline
  - Clomipramine
  - Desipramine
  - Doxepin
  - Imipramine
  - Nortriptiline
  - Trimipramine
- Amitriptyline Pre- and Post-test Alerts and Flow Chart
- Nortriptyline Pre- and Post-test Alerts and Flow Chart

CPIC Gene-specific Information Tables

These resources support CPIC guidelines by providing information regarding major ethnic groups, translations of allele type to phenotype, example resource mappings.
## CPIC Implementation Resources

<table>
<thead>
<tr>
<th>Name of Table in CPIC Guideline</th>
<th>Description</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical implementation workflow for EHR</td>
<td>Contains the steps and decision flows needed to position a pharmacogenetic result in the EHR when a systematic CDS program is implemented.</td>
<td>Combine this workflow with the pharmacogenetic genotype/phenotype summary entries for appropriate results reporting. This workflow highlights where clinical care needs to be implemented for actionable results.</td>
</tr>
<tr>
<td>Pharmacogenetic genotype/phenotype summary entries</td>
<td>Identifies required data to couple genetic result with an interpretation, including genotype, phenotype, EHR priority result notation, and example interpretation text.</td>
<td>Useful when reporting a genomic result to help clinicians understand the clinical relevance of genotype or phenotype information. It is important to have clinician input on the wording for these interpretations.</td>
</tr>
<tr>
<td>Point-of-care clinical decision support (table)</td>
<td>Describes the trigger conditions and example text for interruptive CDS alerts.</td>
<td>Useful when building the rules for interruptive CDS alerts. It is important to have clinician input on the final wording of these alerts.</td>
</tr>
<tr>
<td>Point-of-care clinical decision support (workflow)</td>
<td>Describes the evaluation criteria and decision flow needed to build rules for interruptive CDS alerts.</td>
<td>This workflow is combined with the point-of-care clinical decision support table to build interruptive CDS alerts. It should be customized to fit into local clinical workflows</td>
</tr>
</tbody>
</table>

Hoffman et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC) *JAMIA* 2016
**HLA-B*57:01 Pharmacogenetic Test Result:**

**Clinical Implementation Workflow for EHR**

1. **Enter test result in EHR**
2. **Add consultation/interpretation to EHR**
3. **Priority result?**
   - **Yes:**
     - **Pt on high-risk drug now?**
       - **Yes:** Medication evaluation or reassessment with the clinicians on service
d       - **No:**
3. **No:**

*Blue shading indicates interaction with provider*
**HLA-B*57:01 Genotype and Abacavir: Point of Care Clinical Decision Support**

1. **Abacavir order initiated**
   - **HLA-B*57:01 genetic test results on file?**
     - **Yes**
       - Priority result?
         - **Yes**
           - CDS Post-test alert or notify prescriber with recommendation
         - **No**
           - Order genetic test
     - **No**
       - CDS Pre-test Alert Message

---

Dashed lines indicate optional steps
Guideline for Tricyclic Antidepressants and CYP2D6 and CYP2C19

CPLIC has updated the 2013 guideline for tricyclic antidepressants and CYP2D6 and CYP2C19. See Tables 2, 3, and 4 of the guideline for updated recommendations.

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  - Imipramine
  - Nortriptyline
  - Trimipramine
- Amitriptyline Pre- and Post-test Alerts and Flows
- Nortriptyline Pre- and Post-test Alerts and Flows

CPIC Gene-specific Information Tables

These resources support CPIC guidelines by providing information on major ethnic groups, translations of diplotype tables, and resource mappings.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger Condition 1</td>
<td>Trigger Condition 2</td>
<td>Flow Chart Reference Point</td>
<td>CDS Context, Relative to Genetic Testing</td>
<td>CDS Alert Text</td>
</tr>
<tr>
<td>No CYP2C19 result on file</td>
<td>1</td>
<td>Pre-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. Neither a CYP2D6 nor CYP2C19 genotype appears to have been ordered for this patient. Use of an alternative agent may be recommended. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Ultrarapid Metabolizer or Rapid Metabolizer</td>
<td>2</td>
<td>Post-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. This patient is predicted to be a CYP2C19 ultrarapid/rapid metabolizer and may be at an increased risk of a sub-optimal response. Consider selecting an alternative drug not metabolized by CYP2C19. If amitriptyline is warranted utilize therapeutic drug monitoring to guide dose adjustments. A CYP2D6 genotype does not appear to have been ordered for this patient. CYP2D6 genetic status may be important for alternative drugs. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Normal Metabolizer</td>
<td>3</td>
<td>Post-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. This patient is predicted to be a CYP2C19 normal metabolizer. There is no reason to selectively adjust the dose of this medication based on the CYP2C19 result. Because a CYP2D6 genotype does not appear to have been ordered for this patient, use of an alternative agent may be recommended. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>2</td>
<td>Post-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. This patient is predicted to be a CYP2C19 intermediate metabolizer. There is no reason to selectively adjust the dose of this medication based on the CYP2C19 result. Because a CYP2D6 genotype does not appear to have been ordered for this patient, use of an alternative agent may be recommended. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
<tr>
<td>Likely CYP2C19 Intermediate Metabolizer</td>
<td>2</td>
<td>Post-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. This patient is predicted to be a likely CYP2C19 intermediate metabolizer. There is no reason to selectively adjust the dose of this medication based on the CYP2C19 result. Because a CYP2D6 genotype does not appear to have been ordered for this patient, use of an alternative agent may be recommended. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
<tr>
<td>Likely CYP2C19 Poor Metabolizer</td>
<td>2</td>
<td>Post-Test</td>
<td>CYP2D6 and CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication due to altered drug metabolism. This patient is predicted to be a likely CYP2C19 poor metabolizer and may be at an increased risk of a sub-optimal response. Consider selecting an alternative drug not metabolized by CYP2C19. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose and utilize therapeutic drug monitoring to guide dose adjustments. A CYP2D6 genotype does not appear to have been ordered for this patient. CYP2D6 genetic status may be important for alternative drugs. Please consult a clinical pharmacist for more information.</td>
<td></td>
</tr>
</tbody>
</table>
CYP2D6 AND CYP2C19 Genotype and AMITRIPTYLINE: Point of Care Clinical Decision Support

1. CDS Pre-test alert Message (additional action may be considered)
2. CDS Post-test alert or notify prescriber with recommendation (additional action may be considered)
3. CDS Pre-test alert Message (additional action may be considered)
4. CDS Post-test alert or notify prescriber with recommendation (additional action may be considered)
5. CDS Post-test alert or notify prescriber with recommendation
6. CDS Post-test alert or notify prescriber with recommendation
7. CDS Pre-test alert Message (additional action may be considered)
8. No post-test alert required continue with drug order

See Pre- and Post-test alerts tab for diplotype/phenotype specific pre-test alert examples. Circled numbers refer to specific alerts in the Pre- and Post-test alerts tab.

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.

Priority result is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.
CDS needed for clinical actionability of genetic test results

• Interpretations (passive CDS)
• Interruptive alerts (active CDS):
  – Pre-test situation:
    • Check for genetic test and, if missing, guide prescriber to consider ordering the test
  – Post-test situation:
    • Test result is high-risk and advice for prescribing alternatives should be presented
    • Test result is low-risk and no interruptive alert should be fired

But genetic test names, results, phenotypes (problems, diagnoses) are not standardized, making it difficult for EHR vendors to support efforts to build CDS based on genetic tests
CPIC Phenotype Term Standardization Project

Purpose:

• To standardize phenotype terms in the CPIC guidelines and harmonize terms with external groups (e.g., ClinGen, IOM, etc.)
  – Allele functional status terms (i.e. allele descriptive-Table 1 in guideline)
    • Low, absent, high, intermediate
  – Phenotype (i.e. diplotype descriptive-Table 2 in guideline)
    • UM, EM, IM, PM
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
CPIC Phenotype Term Standardization Project

Goal: standardize terms for allele function and on phenotypes

Phase 1
- Development
  - Created a list of options for terms (literature review and survey to genetic testing labs)

Phase 2
- 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.

Phase 3
- 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).

Phase 4
- Consensus
  - Survey 3-5: For each gene/gene group, retained top terms selected by experts.
  - Repeat process until 70% consensus achieved.

Phase 5
- 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
Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle, PharmD, PhD¹, Henry M. Dunnenberger, PharmD², Robert R. Freimuth, PhD³,
Josh F. Peterson, MD⁴,⁵, Jonathan D. Burlison, PhD¹, Michelle Whirl-Carrillo, PhD⁶,
Stuart A. Scott, PhD⁷, Heidi L. Rehm, PhD⁸, Marc S. Williams, MD⁹, Teri E. Klein, PhD⁶,
Mary V. Relling, PharmD¹, James M. Hoffman, PharmD, MS¹

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 laborato-
rians, 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

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

Final Standardized Terms: Phenotype for Drug Metabolizing Enzymes

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

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

## Final Standardized Terms: Phenotype for Drug Transporters

For example: *SLCO1B1*

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

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

For example: *HLA-B*<sup>57:01</sup>

<table>
<thead>
<tr>
<th>Final Term</th>
<th>Functional Definition</th>
<th>Example diplotypes/alleles</th>
<th>Term/Gene Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Detection of high-risk allele</td>
<td>Homozygous or heterozygous for high-risk allele</td>
<td><em>HLA-B</em>&lt;sup&gt;15:02&lt;/sup&gt;</td>
</tr>
<tr>
<td>Negative</td>
<td>High risk-allele not detected</td>
<td>No copies of high-risk allele</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up from Term Standardization: leverage to influence the field

• Use final terms in CPIC Guidelines
  – And within St. Jude

• Endorsement/adoPTION by others:
  – CAP—College of American Pathologists
  – AMP--Association of Molecular Pathology
  – IOM’s DiGITIZE Action Collaborative
  – LOINC--Terms accepted December 2016
  – International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) Pharmacogenetics Committee
  – ClinGen
  – SNOMED
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.

<table>
<thead>
<tr>
<th>Interpretation (Ungraded)</th>
<th>Exception Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>010</td>
<td>020</td>
</tr>
<tr>
<td>○ 257 This patient is an ultra-rapid metabolizer</td>
<td>○ 257 This patient is an ultra-rapid metabolizer</td>
</tr>
<tr>
<td>○ 837 This patient is a rapid metabolizer</td>
<td>○ 837 This patient is a rapid metabolizer</td>
</tr>
<tr>
<td>○ 258 This patient is a normal metabolizer</td>
<td>○ 258 This patient is a normal metabolizer</td>
</tr>
<tr>
<td>○ 259 This patient is an intermediate metabolizer</td>
<td>○ 259 This patient is an intermediate metabolizer</td>
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<td>○ 260 This patient is a poor metabolizer</td>
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Clinical Management (Ungraded)

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<th>PGX-05 (Select all that apply.)</th>
<th>PGX-06 (Select all that apply.)</th>
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<td>○ 262 An increased dose should be considered</td>
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October 26  |  **Endorsement of Clinical Pharmacogenetics Implementation Consortium (CPIC) initiative to standardize pharmacogenetic nomenclature**

August 26  |  **Presentation of New Code Crosswalk Recommendations to Advisory Panel on Clinical Diagnostic Laboratory Tests**
CPIC Informatics: working to standardize and clean up LOINC codes for all CPIC genes

<table>
<thead>
<tr>
<th>LOINC</th>
<th>LongName</th>
<th>Component</th>
<th>Property</th>
<th>Timing</th>
<th>System</th>
<th>Scale</th>
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<td>Pt</td>
<td>Bid/Tiss</td>
<td>Nar</td>
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<td>Qn</td>
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Search generated 13 hits in 0.007 secs.
Next Step: SNOMED to match codes to standardized phenotype terms

<table>
<thead>
<tr>
<th>TPMT – SNOMED CT Code</th>
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<tr>
<td>Thiopurine methyltransferase deficiency</td>
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vs

<table>
<thead>
<tr>
<th>TPMT- standardized Terms</th>
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</thead>
<tbody>
<tr>
<td>TPMT - Normal Metabolizer (normal dose)</td>
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<tr>
<td>TPMT - Intermediate Metabolizer (60% dose)</td>
</tr>
<tr>
<td>TPMT - Poor Metabolizer (5% dose)</td>
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Looking to the future

- CPIC Informatics articulated principles for knowledge resources in precision medicine based on pharmacogenomics

- Centralized knowledge base ideal
  - Could align with many principles already articulated for genomics and EHRs


CPIC’s Five Principles for Knowledge Resources

1. Pharmacogenomic knowledge resources 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.

Hoffman et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC) JAMIA 2016
CPIC’s Five Principles for Knowledge Resources

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

Hoffman et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC) JAMIA 2016
Conclusion

• CPIC systematically develops and disseminates unique implementation resources

• Intent of the resources is to:
  – Organize essential pharmacogenetic knowledge
  – Illustrate best practices
  – Ultimately, facilitate use of pharmacogenetic data at the point of care
Conclusion

• CPIC has lead term standardization efforts to facilitate improved reporting of results and sharing pharmacogenetic test results across disparate clinical information systems
  – Previous work with LOINC
  – Current focus is SNOMED

• CPIC looks to the future of knowledge resources for pharmacogenetics
Acknowledgements

• CPIC Leaders
  – Mary Relling
  – Teri Klein
• CPIC Coordinator
  – Kelly Caudle
• PGRN
• PharmGKB
  – Russ Altman
  – Teri Klein
  – 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
  – Rochelle Long
  – Dan Roden
  – Rachel Tyndale