UNC
INSTITUTE FOR
PHARMACOGENOMICS AND
INDIVIDUALIZED THERAPY

CPIC: Clinical Pharmacogenetics Implementation Consortium

December, 2011

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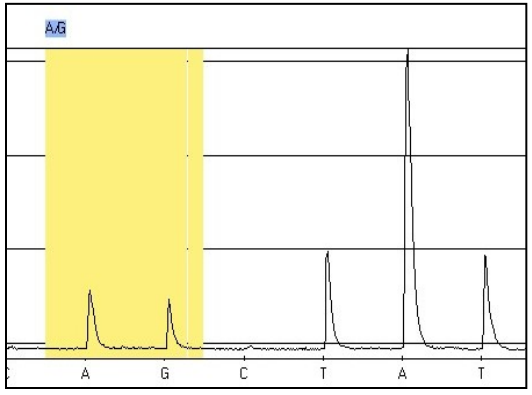
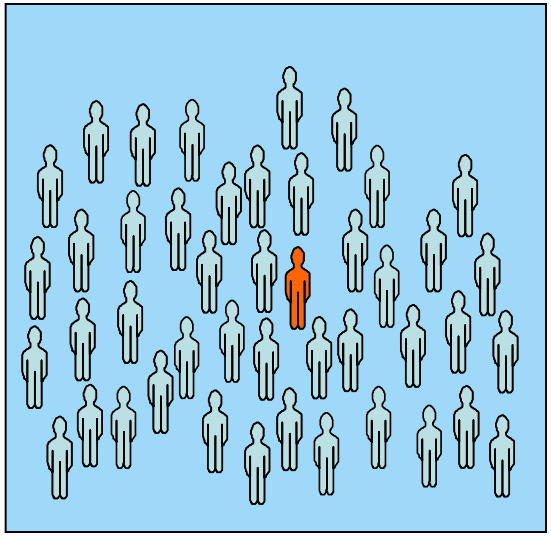
Pharmacogenetics: what is your intent?

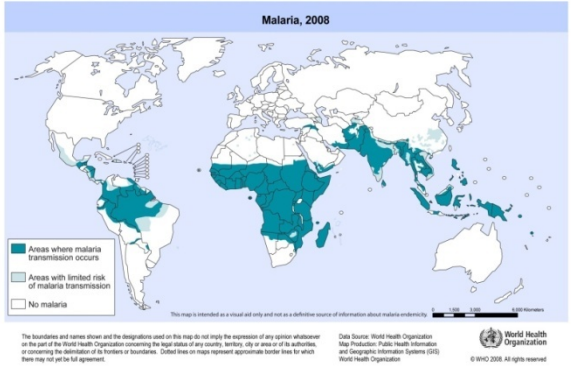
Human genetic discovery



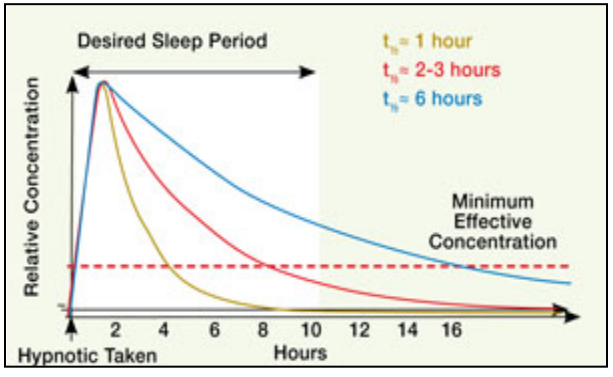
Drug Safety



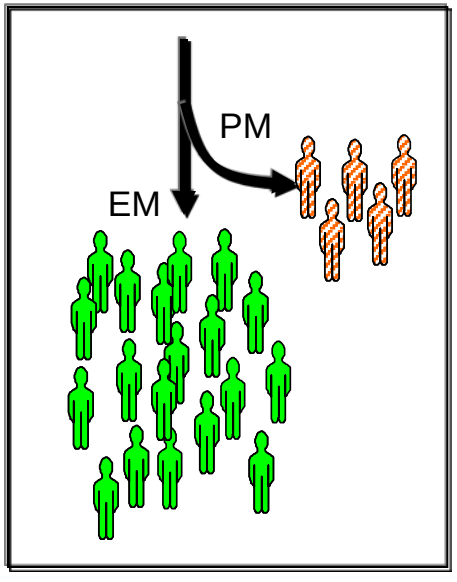
Public Policy



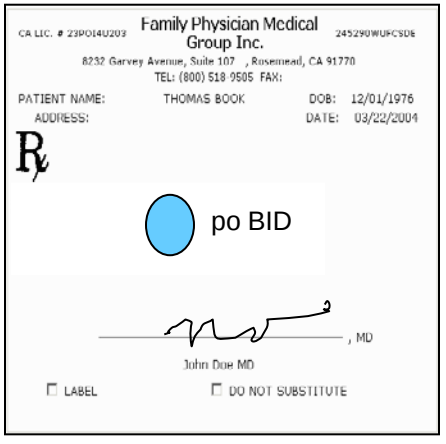
Explain variation in phenotype



Clinical trial inclusion/exclusion



Clinical practice



Translational science: The steps to success

Step I
Discovery

→

Step II
Validation

→

Step III
Integration into practice

→

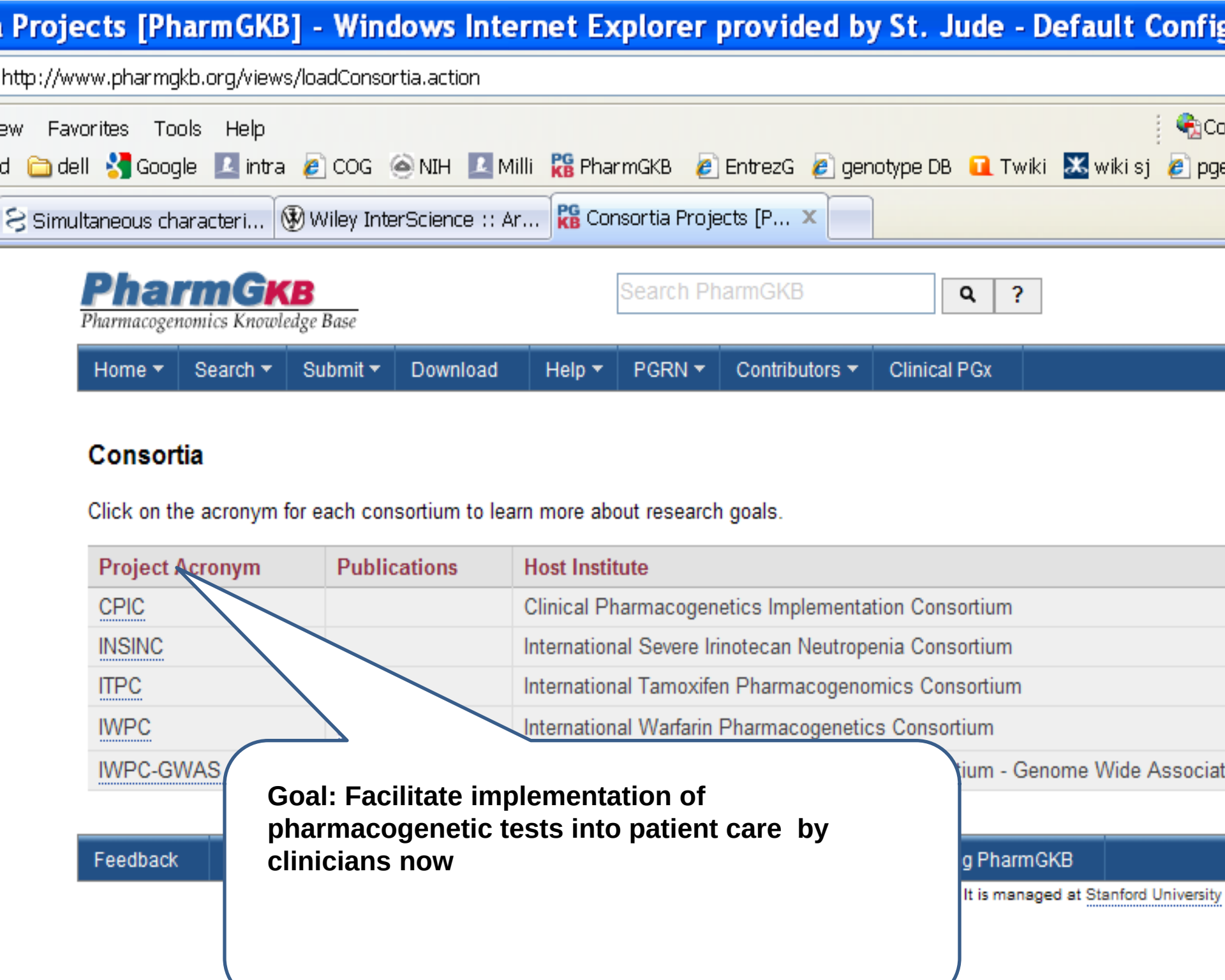
Step IV
Integration into policy

PGENI
Treating the Population.
Impacting the World.

Lots of ways to ask ‘when?’

- Is pharmacogenetics useful?
- Should a test be ordered?
- What does ‘enough data’ look like?
- Is anything ever ‘ready for prime time’?

- If a patient arrives with PGx data, is it actionable?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Consortia
Click on the acronym for each consortium to learn more about research goals.
Project Acronym
Publications
Host Institute
CPIC
Clinical Pharmacogenetics Implementation Consortium
INSINC
International Severe Irinotecan Neutropenia Consortium
ITPC
International Tamoxifen Pharmacogenomics Consortium
IWPC
International Warfarin Pharmacogenetics Consortium
IWPC-GWAS
ium - Genome Wide Associat
Goal: Facilitate implementation of pharmacogenetic tests into patient care by clinicians now
Feedback
g PharmGKB
It is managed at Stanford University

CPIC: Clinical Pharmacogenetics Implementation Consortium

Clinicians, scientists, 3rd party payers, regulators
60 members
33 institutions
Observers: NIH and FDA
8 countries

What is CPIC's deal?

•CPIC prioritizes gene-drug pairs based upon community input, and has sponsored surveys of the CPIC membership and the ASCPT membership. CPIC accepts input at any time (and a frequent contributor is FDA).

•The purpose of CPIC is to "translate genetic information into clinical actions" and to make **recommendations for actionable pharmacogenetic variants** ~~(more research needed)~~

- •those variants that are measurable, interpretable, and it's clear what to do with the genetic information. That is a core part of the structure of each guideline: to list all possible variants, predict phenotypes, and recommend what to do with that information….that's a Table in each guideline.

•This is not similar to the EGAPP exercise because not all of the published information is weighted equally – just as pharmacogenetics practioners do in practice. Therefore, the strength of the evidence is evaluated in each guideline.

DISCLOSURE

•By definition, the authors support pharmacogenetics. They want to implement pharmacogenetics now. It is left to the professional organizations (e.g., ASCO, AHA) , health systems, individual clinicians to decide whether to take up the information.

A bit more about CPIC

•CPIC assumes that testing is done in situations that enable placing the information into the medical record (could be limited point-of-care testing or comprehensive array testing and only some information is being transferred to the EMR). This means CLIA-cert. environment.

•CPIC is starting with “baby steps” that are not controversial, with clearly “clinically actionable” variants and drugs, with guidelines that are all peer-reviewed and updateable

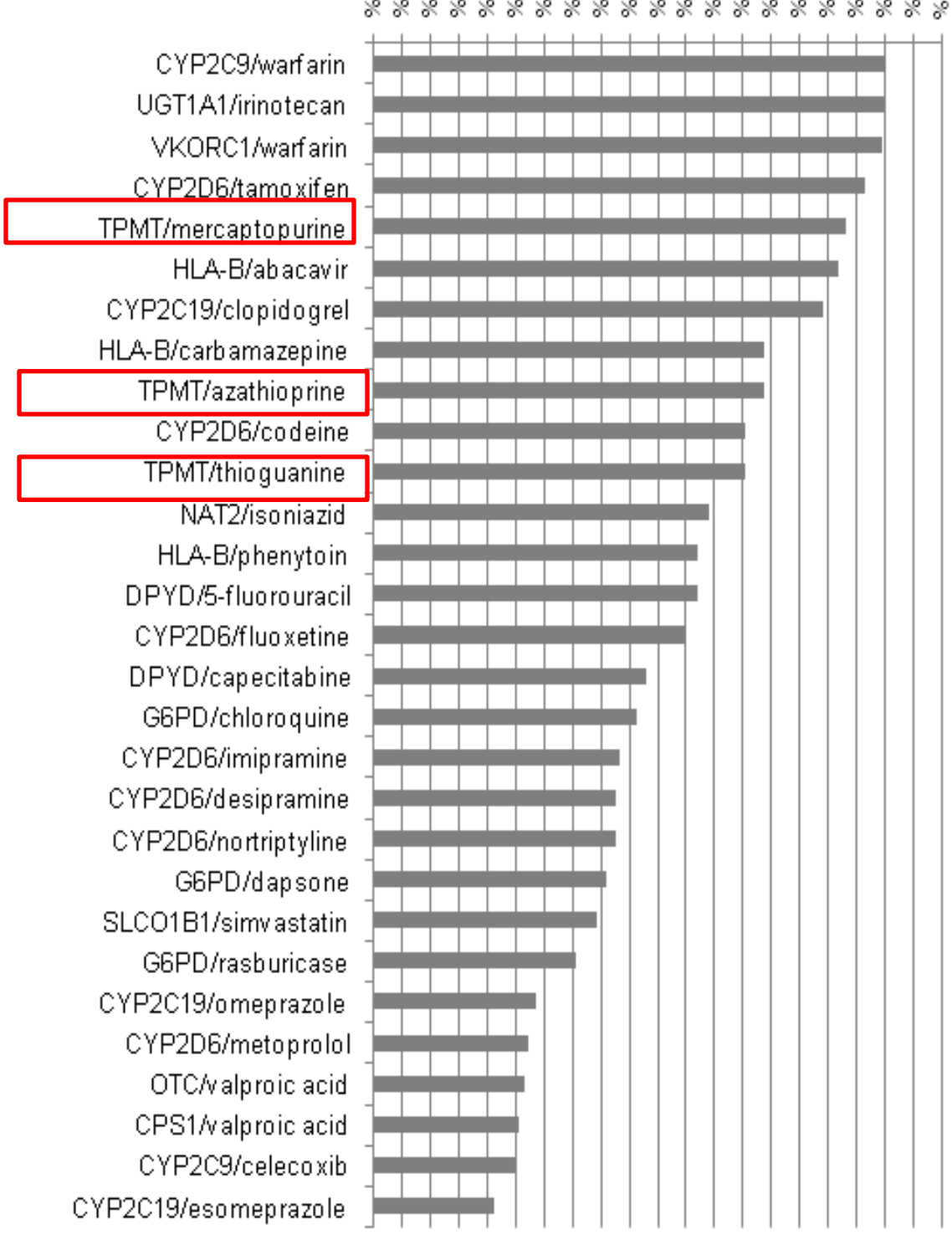
•PharmGKB reflects the CPIC guidelines, as well as the guidelines of other established groups, in the Clinical Implementation section.

•The new Genetic Testing Registry (GTR) plans to list CPIC guidelines in the consensus statements section of the GTR display. Details have already been negotiated with PubMed.

Criteria for prioritization of gene/drug pairs

- Professional organizations (e.g. American Society for Clinical Pharmacology and Therapeutics, American Society for Clinical Oncology, American Heart Association, PGRN's CPIC, etc.) recommending that genetic testing accompany that drug use in peer-reviewed guidelines
- FDA labeling recommending use of genetic testing for the affected drug
- Evidence that CMS and/or third party payors reimburse for genetic testing for that drug's use
- Lawsuits penalizing clinicians who fail to use the pharmacogenetic test
- Availability of stand-alone CLIA-approved tests for individual loci
- Clinical trials demonstrating drug effects linked to functional pharmacogenetic loci
- Narrow therapeutic index for the affected drug
- Preclinical studies demonstrating drug effects linked to functional pharmacogenetic loci
- In vitro or in vivo evidence that drug A is handled identically to drug B, with strong pharmacogenetic evidence linking the variation to drug B

Highest ranked gene/drug pairs for clinical implementation based on survey of ASCPT members



VOLUME 89 NUMBER 3 | MARCH 2011 | www.nature.com/cpt

Gene Drug Pairs	Status	Author Contact	Others Involved
TPMT - thiopurines	published	Relling	EE Gardner, WJ Sandborn, K Schmiegelow, C-H Pui, SW Yee6, CM Stein, M Whirl-Carrillo, WE Evans and TE Klein
CYP2C19 - clopidogrel	published	Shuldiner	Stuart Scott
CYP2C9, VKORC1 - warfarin	published	Julie Johnson	Li Gong, Michelle Whirl-Carrillo, Jeffrey L. Anderson, Stephen E. Kimmel, Ming Ta Michael Lee, Munir Pirmohamed, Stuart A. Scott, C. Michael Stein, Mia Wadelius, Teri E. Klein, Brian Gage, and Russ B. Altman
CYP2D6 - codeine	in press	Kris Crews	Todd Skaar, Andrea Gaedigk, Padmaja Mummaneni, Henry Dunnenberger, Teri Klein, HJ Guchelaar
DPYD - 5FU/capecitabine	initiated	Howard McLeod	Caroline Thorn
HLA-B - abacavir	under way	Deanna Kroetz	Teri Klein
HLA-B - carbamazepine	under way	Susan Leckband	Michelle Whirl-Carrillo, Munir Pirmohamed
HLA-B - phenytoin			
HLA-B - allopurinol	under way	Ming-Ta Michael Lee	Teri Klein, Caroline Thorn, Werner Pichler, Wichittra Tassaneeyakul, Taisei Mushiroda, John T. Callaghan, Michael Hershfield, Chang-Youh Tsai, Chen-Yang Shen
CYP2D6 - antidepressants			
G6PD - rasburicase, Septra			
UGT1A1 - irinotecan			
IL28B - pegIntron		Andrew Muir	David Goldstein, Teri Klein
SLCO1B1 - simvastatin	initiated	Russ Wilke	
CYP2D6, CYP2C19 - TCAs		Jesse Swen, Kevin Hicks	
CYP2D6 - SSRIs			Caryn Lerman, Susan Leckband, David Mrazek

Uniform Elements of CPIC Guidelines (Main)

- **Introduction**
- **Focused Literature Review**
- **Gene:**
  - **Background**
  - **Genetic Test Interpretation**
    - **Table 1. Assignment of likely _____ [gene] phenotypes based on *genotypes***
  - **Available Genetic Test Options**
  - **Incidental findings**
  - **Other considerations**

Uniform Elements of CPIC Guidelines (Main)

- **Drug (s):**
  - **Background**
  - **linking genetic variability to variability in drug-related phenotypes**
  - **Dosage Recommendations**
    - Table 2. **Recommended Dosing of ____ [drug/s] by ____ [gene] phenotype**
    - **Strength of recommendations grading system**
  - **Recommendations for Incidental Findings**
  - **Other considerations**
  - **Potential Benefits and Risks for the Patient**
  - **Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests**

Uniform Elements of CPIC Guidelines (Supplement)

- **Literature Review details**
- **Genetic Test Interpretation**
- **Available Genetic Test Options**
- **Supplemental Table . Genotypes that constitute the * alleles for _____**
- **Supplemental Table . Association between allelic variants and _____ [gene function]**
- **Supplemental Table . Frequencies of alleles in major race/ethnic groups**
- **Supplemental Table . Evidence linking genotype with phenotype**
  - **Levels of Evidence grading system**

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

Clin Pharmacol Ther. 2011 89:387-91

Key criteria to develop a CPIC Table 2: Gene/drug dosing recommendations

- What genotypes have such severe functional effects that a clinician would really act upon them?
  - E.g. homozygous defective vs everything else
  - E.g. ultrarapid vs everything else
  - E.g. homozygous wild-type vs heterozygote vs everything else
- What drugs are so clearly affected that a clinician would be wrong not to act on the result if it were available?

Table 2: dosing recommendations

	MP			Azathioprine		TG		
Phenotype	Implications for MP and azathioprine pharmacologic measures	Dosing recommendations for MP	Classification of recommendations[a]	Dosing recommendations for azathioprine	Classification of recommendations[a]	Implications for pharmacologic measures after TG	Dosing recommendations for TG	Classification of recommendations[a]
Homozygous wild-type or normal, high activity	Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern	Start with normal starting dose (e.g., 75 mg/m^2/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.[4,25,29]	Strong	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.[4,27,29]	Strong	Lower concentrations of TGN metabolites, but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.[4,16]	Strong
Heterozygote or intermediate activity	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Start with reduced doses (start at 30–70% of full dose: e.g., at 50 mg/m^2/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m^2) than that tolerated in wild-type patients (75 mg/m^2).[6,12] In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents.[4,13,15,21,23,25,29,31,32]	Strong	If disease treatment normally starts at the "full dose", consider starting at 30–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.[4,27,29,31]	Strong	Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with reduced doses (reduce by 30–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents.[4,16]	Moderate
Homozygous variant, mutant, low, or deficient activity	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m^2/d given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.[4,24,29,31]	Strong	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.[27,29–31,33]	Strong	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease	Start with drastically reduced doses[16] (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.[4]	Strong

MP, mercaptopurine; TG, thioguanine; TGN, thioguanine nucleotide; TIMP, secondary metabolite of MP.

[a]Rating scheme is described in **Supplementary Data** online.

Table 2: dosing recommendations

	Azathioprine		TG		
Phenotype	Dosing recommendations for azathioprine	Classification of recommendations[a]	Implications for pharmacologic measures after TG	Dosing recommendations for TG	Classification of recommendations[a]
Homozygous wild-type or normal, high activity	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.[4,27,29]	Strong	Lower concentrations of TGN metabolites, but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.[4,16]	Strong
Heterozygote or intermediate activity	If disease treatment normally starts at the "full dose", consider starting at 30–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.[4,27,29,31]	Strong	Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with reduced doses (reduce by 30–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other	Moderate

Dosing recommendations: strength based on back-up evidence

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

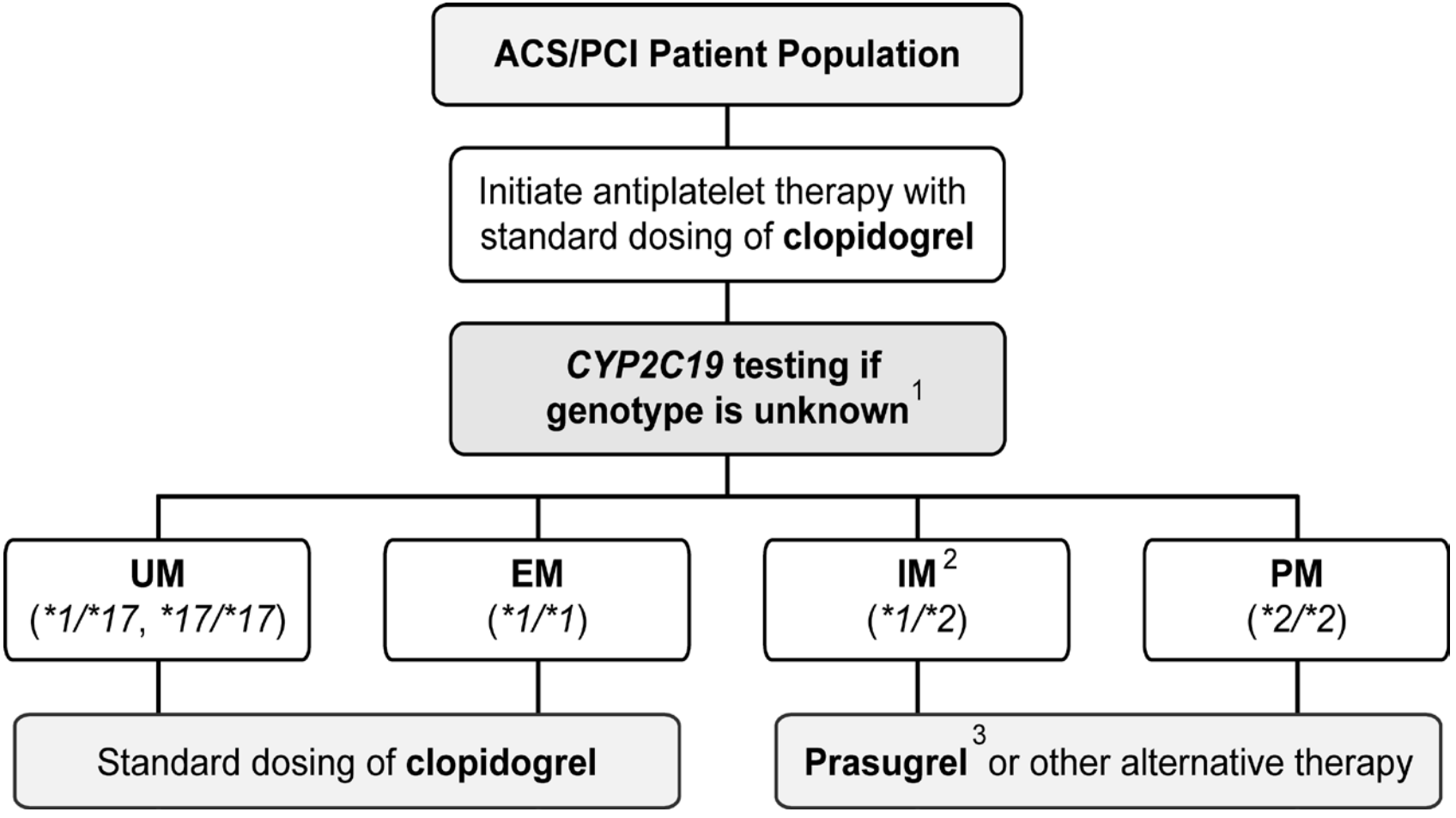
C: Optional recommendation for the statement

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.

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy

Stuart A. Scott, Katrin Sangkuhl, Eric E. Gardner, Charles M. Stein, Jean-Sebastien Hulot, Julie A. Johnson, Dan M. Roden, Teri E. Klein, Alan R. Shuldiner

Algorithm for suggested clinical actions based on *CYP2C19* genotype among coronary patients initiating antiplatelet therapy.



Scott et al, CPT, submitted

Table 2: Clopidogrel therapy based on CYP2C19 phenotype for ACS/PCI patients initiating antiplatelet therapy

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[1]
Ultrarapid Metabolizer (UM) (**1/*17*, **17/*17*) and **Extensvie Metabolizer (EM)** (**1/*1*)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[2]	Clopidogrel - label recommended dosage and administration.	Strong
Intermediate Metabolizer (IM) (**1/*2*)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Prasugrel or other alternative therapy (if no contraindication)	Moderate
Poor Metabolizer (PM) (**2/*2*)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Prasugrel or other alternative therapy (if no contraindication)	Strong

[1] See Supplement, Strength of Therapeutic Recommendations.
[2] The *CYP2C19*17* allele may be associated with increased bleeding risks (12).

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SA Scott[1], K Sangkuhl[2], EE Gardner[3], CM Stein[4,5], J-S Hulot[6,7], JA Johnson[8,9,10], DM Roden[11,12], TE Klein[2] and AR Shuldiner[13,14]

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

JA Johnson[1], L Gong[2], M Whirl-Carrillo[2], BF Gage[3], SA Scott[4], CM Stein[5], JL Anderson[6], SE Kimmel[7,8,9], MTM Lee[10], M Pirmohamed[11], M Wadelius[12], TE Klein[2] and RB Altman[2,13]

CYP2D6/ codeine in press

Clin Pharmacol Ther. 2011

A bit more about CPIC

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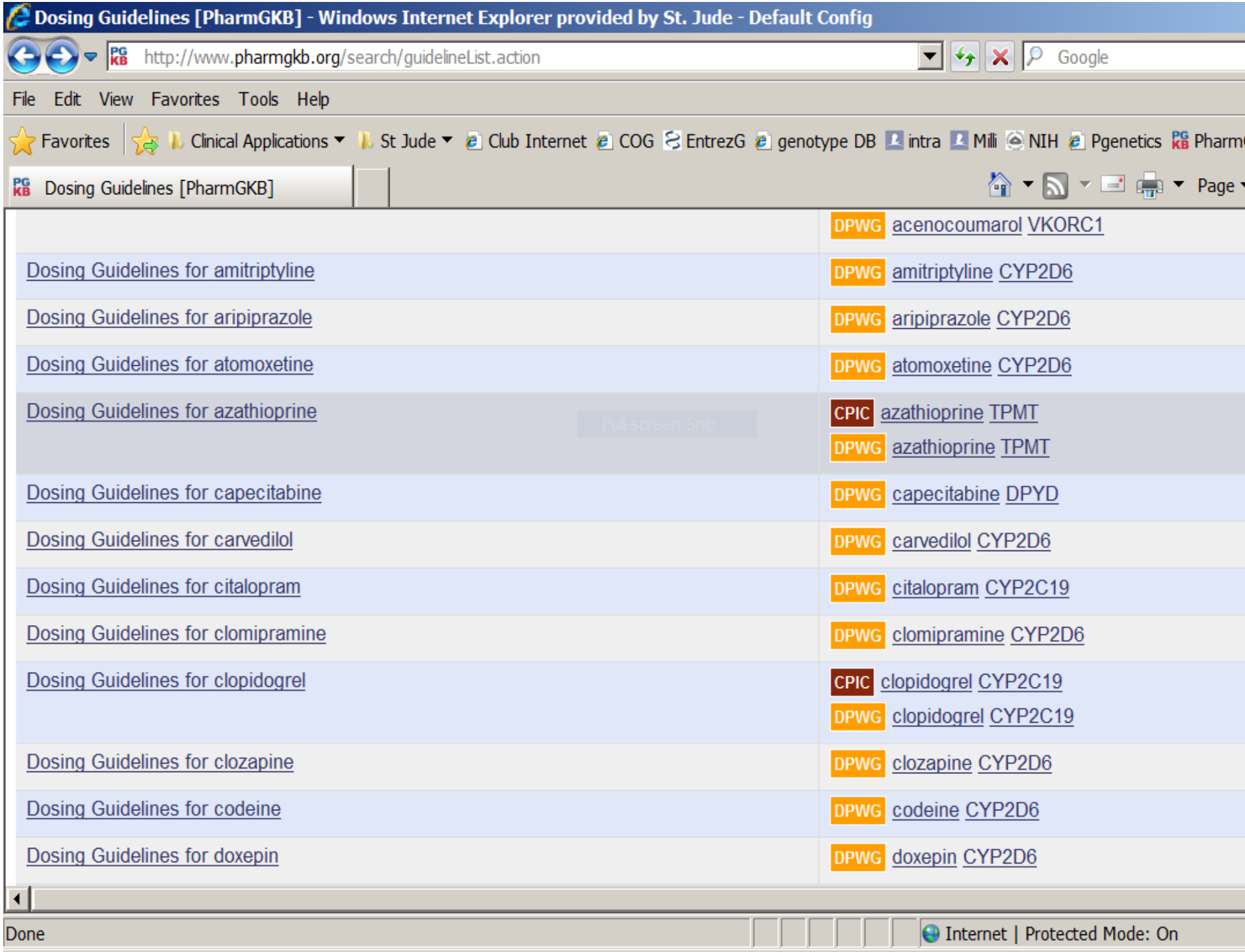
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Dosing Guidelines [PharmGKB]
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Dosing Guidelines for amitriptyline
DPWG amitriptyline CYP2D6
Dosing Guidelines for aripiprazole
DPWG aripiprazole CYP2D6
Dosing Guidelines for atomoxetine
DPWG atomoxetine CYP2D6
Dosing Guidelines for azathioprine
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DPWG azathioprine TPMT
Dosing Guidelines for capecitabine
DPWG capecitabine DPYD
Dosing Guidelines for carvedilol
DPWG carvedilol CYP2D6
Dosing Guidelines for citalopram
DPWG citalopram CYP2C19
Dosing Guidelines for clomipramine
DPWG clomipramine CYP2D6
Dosing Guidelines for clopidogrel
CPIC clopidogrel CYP2C19
DPWG clopidogrel CYP2C19
Dosing Guidelines for clozapine
DPWG clozapine CYP2D6
Dosing Guidelines for codeine
DPWG codeine CYP2D6
Dosing Guidelines for doxepin
DPWG doxepin CYP2D6
Done
Internet | Protected Mode: On

- There is a lot to do, so more active participants desired!

- We like to hear comments (even if they are obvious), for discussion in our iterative process

- In the clinic, a ‘NO’ guideline isn’t helpful