Tailoring pharmacotherapy to improve outcomes

2019 ASCPT Oscar B. Hunter Award

Mary V. Relling
Memphis, TN USA
## Previous Recipients

<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>Mary V. Relling, PharmD</td>
</tr>
<tr>
<td>2018</td>
<td>William J. Jusko, PhD</td>
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<td>2017</td>
<td>N/A</td>
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<tr>
<td>2016</td>
<td>Brian L. Strom, MD, MPH</td>
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<td>2015</td>
<td>Michel Eichelbaum, MD</td>
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<td>2014</td>
<td>Edward M. Sellers, MD, PhD</td>
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<td>2013</td>
<td>William E. Evans, PharmD</td>
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<td>2012</td>
<td>D. Craig Brater, MD</td>
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<td>2011</td>
<td>Garret A. FitzGerald, MD</td>
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<td>2010</td>
<td>Leslie Z. Benet, PhD</td>
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<td>2009</td>
<td>Sir Colin Dollery, MD</td>
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<td>2008</td>
<td>Marcus M. Reidenberg, MD</td>
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<td>2007</td>
<td>Terrence F. Blaschke, MD</td>
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<td>2006</td>
<td>Neal Benowitz, MD</td>
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<td>2005</td>
<td>Arthur J. Atkinson Jr., MD</td>
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<td>2004</td>
<td>Lewis B. Sheiner, MD</td>
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<td>2003</td>
<td>Louis Lemberger, MD, PhD</td>
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<td>2002</td>
<td>Sumner J. Yaffe, MD</td>
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<td>2001</td>
<td>Alan Nies, MD</td>
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<td>2000</td>
<td>Paul S. Lietman, MD, PhD</td>
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<td>Alvan R. Feinstein, MD</td>
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<td>1998</td>
<td>Richard M. Weinshilboum, MD</td>
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<td>J. Richard Crout, MD, FACP</td>
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<td>1996</td>
<td>Folke Sjoqvist, MD, PhD</td>
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<td>Daniel L. Azarnoff, MD</td>
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<td>Kenneth L. Melmon, MD</td>
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<td>Werner Kalow, MD</td>
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<td>1992</td>
<td>Paul Calabresi, MD</td>
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<td>1991</td>
<td>Elliott S. Vesell, MD</td>
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<td>Walter F. Riker, Jr., MD</td>
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<td>John J. Burns, PhD</td>
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<td>Leo E. Hollister, MD</td>
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<td>1987</td>
<td>Jan Koch-Weser, MD</td>
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<td>1986</td>
<td>Leon I. Goldberg, MD, PhD</td>
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<td>Raymond W. Houde, MD</td>
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<td>George H. Hitchings, PhD, ScD</td>
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<td>1983</td>
<td>C. Gordon Zubrod, MD</td>
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<td>1982</td>
<td>Gerhard Levy, PharmD</td>
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<td>Albert Sjoersma, MD, PhD</td>
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<td>1980</td>
<td>John A. Oates, MD</td>
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<td>1979</td>
<td>Ray W. Gifford, Jr., MD, MD 1978 - Walter Modell, MD</td>
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<td>1977</td>
<td>Harris Isbell, MD</td>
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<td>1976</td>
<td>Louis Goodman, MD and Alfred Gilman, PhD</td>
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<td>1975</td>
<td>Louis Lasagna, MD</td>
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<td>1974</td>
<td>Raymond P. Ahlquist, PhD</td>
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<td>1973</td>
<td>George C. Cotzias, MD</td>
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<td>1972</td>
<td>Edward D. Freis, MD</td>
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<td>1971</td>
<td>Maxwell Finland, MD</td>
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<td>Bernard B. Brodie, MD</td>
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<td>Arthur Grollman, MD</td>
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<td>Sidney Farber, MD</td>
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<td>George W. Thorn, MD</td>
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<td>Irvin H. Page, MD</td>
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<td>1965</td>
<td>William B. Castle, MD</td>
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<td>1964</td>
<td>Henry K. Beecher, MD</td>
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<td>1963</td>
<td>Albert B. Sabin, MD</td>
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<td>1962</td>
<td>Charles B. Huggins, MD</td>
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<td>1961</td>
<td>Hattie E. Alexander, MD</td>
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<td>1960</td>
<td>John H. Moyer, III, MD</td>
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<tr>
<td>1959</td>
<td>Tom D. Spies, MD</td>
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<tr>
<td>1958</td>
<td>C. Walton Lillehei, MD</td>
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<tr>
<td>1957</td>
<td>Robert W. Wilkins, MD</td>
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<tr>
<td>1956</td>
<td>E. M. K. Geiling, MD</td>
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<tr>
<td>1955</td>
<td>Jonas E. Salk, MD</td>
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My first scientific meeting: ASCPT Annual meeting 1986 in Washington DC
Mission: advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment. No child is denied treatment based on a family's ability to pay.

- 75% of funding comes from private donors
- Treat ~ 5000 patients in any year
- New pts/year: ~ 600 cancer pts, ~300 hematology/HIV pts
- Comprehensive EHR, multidisciplinary clinical teams including pharmacists
- > 90% follow-up for at least 10 years after completion therapy (our children turn into adults)
St. Jude’s first annual report, 1962
# Pharmaceutical Dept

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Date of Employment</th>
</tr>
</thead>
<tbody>
<tr>
<td>George E. Crevar, M.S.</td>
<td>Instructor in Pharmacy</td>
<td>January 1, 1962</td>
</tr>
<tr>
<td>Gail Ogletree</td>
<td>Technologist</td>
<td>May 25, 1962</td>
</tr>
<tr>
<td>Rita Caldwell</td>
<td>Clerk and Typist</td>
<td>August 14, 1962</td>
</tr>
<tr>
<td>Larry Barker</td>
<td></td>
<td>1969-1983</td>
</tr>
<tr>
<td>William Evans</td>
<td></td>
<td>1983-2002</td>
</tr>
<tr>
<td>Mary Relling</td>
<td></td>
<td>2003-present</td>
</tr>
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![Pharmacist Working in Laboratory](image.png)
Pharmaceutical Department Goals

• Discover the basis for inter-individual differences in response to medication
• Translate research findings into patient care
• Provide best and most comprehensive pharmaceutical care
Many factors cause interindividual variability in drug effects; variability that can be lethal in serious disease (e.g. leukemia) and low-therapeutic index drugs (e.g. anticancer drugs).
Research to elucidate interpatient variability in the SJ Pharmaceutical Dept emanates from several perspectives

• From the disease
  - leukemia, solid tumors, brain tumors

• Medication safety
  - Clinical decision support (CDS, pharmacogenetics)

• From the drugs
  - MTX, MP, glucocorticoids, asparaginase, topotecan, AraC, sorafenib and TKIs, cyclophosphamide, “new agents”

• From the biochemistry/genetics
  - DMEs, nuclear hormone receptors, transporters
  - Non-coding genomic variation
Aspects unique to Pharmaceutical Dept

- Pharmaceutical Services
- Clinical PK Lab
- Pharmacokinetics Shared Resource (PK SR)
- Clinical Pharmacogenetics Implementation Consortium (CPIC)
- Education and Residency Training
  - First ASHP accredited residency in pharmacogenomics
Level of clinical pharmaceutical care is at the highest level

- Integration of clinical services with faculty research contributes to state-of-the-art consultations
- PK modeling and PG testing incorporated into routine prescribing for anticancer drugs
- Board-certified pharmacists on almost every team
- Clinical PK Lab run by the Pharmaceutical department with interpretations for every lab measure (including pharmacogenetic testing) provided by the team pharmacists
Biomedical Modelling implemented by PK SR used to build clinical TDM programs: e.g. dosing asparaginase based on serum activity and anti-asparaginase antibodies.
Total XII: Clinical trial for childhood acute lymphoblastic leukemia (ALL)—accrued 1988-1991

• Hypothesis: toxicity will be avoided and ALL cures will be increased if dosages of chemotherapy are individualized, based on individual pharmacokinetics, to achieve a desired level of plasma systemic exposure, compared to conventional body-size based dosing

• Used Bayesian modelling and optimal limited sampling (ADAPT) for the three major pulses of chemotherapy (methotrexate, cytarabine, and teniposide) to estimate clearance and do real-time adjustments of chemotherapy

• Trained clinical pharmacists to do all PK estimates and dosage adjustments
CONVENTIONAL COMPARED WITH INDIVIDUALIZED CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

WILLIAM E. EVANS, PHARM.D., MARY V. RELLING, PHARM.D., JOHN H. RODMAN, PHARM.D., WILLIAM R. CROM, PHARM.D., JAMES M. BOYETT, PH.D., AND CHING-HON PUI, M.D.

Between-course targeting of methotrexate exposure using pharmacokinetically guided dosage adjustments

Jennifer L. Pauley · John C. Panetta · Kristine R. Crews · Deqing Pei · Cheng Cheng · John McCormick · Scott C. Howard · John T. Sandlund · Sima Jeha · Raul Ribeiro · Jeffrey Rubnitz · Ching-Hon Pui · William E. Evans · Mary V. Relling
Many factors cause interindividual variability in drug effects; variability that can be lethal in serious disease (e.g. leukemia) and low-therapeutic index drugs (e.g. anticancer drugs).
Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia

Mary V Relling, Ching-Hon Pui, John T Sandlund, Gaston K Rivera, Michael L Hancock, James M Boyett, Erin G Schuetz, William E Evans

In complete remission at end of induction

Probability of CCR

- No anticonvulsants
- Anticonvulsants

Time from complete remission (years)

Probability of CCR

p = 0.0362

Clearance

Teniposide

Methotrexate

Cytarabine

p < 0.0001

p = 0.051

p = 0.26

Lancet 2000
CHILDREN’S ONCOLOGY GROUP

AALL1131

A Phase III Randomized Trial for Newly Diagnosed High Risk B-precursor Acute Lymphoblastic Leukemia (ALL) Testing Clofarabine (IND# 73789, NSC# 606869) in the Very High Risk Stratum

A Groupwide Phase III Study

4.1.6.2 Cytochrome P450 Interactions with Antileukemic Drugs.
Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with antileukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes.120 Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be
Many factors cause interindividual variability in drug effects; genetics are immutable.
HUMAN RBC TPMT

Weinshilboum and Sladek
TPMT phenotype determines concentrations of active thiopurine TGN metabolites

Krynetski and Evans
Pharm Res 16(3):342-9, 1999
Figure 3: Estimated cumulative incidence of radiation-associated secondary malignant brain tumour for seven children in Total XII who received preventive cranial radiotherapy and had genetic defects in thiopurine methyltransferase compared with 45 with wild-type status.

Myelosuppression was related to TPMT genotype on Total XII (BEFORE we started adjusting doses based on TPMT testing)

About 35% for TPMT hets....

Relling et al JNCI, 1999
Myelosuppression was not related to TPMT genotype on Total XIII
(AFTER we started adjusting doses based on TPMT testing)

Reduced to ~ 10% for hets....

Stocco et al Clin Pharm Ther 2009
Relapse was not related to TPMT genotype on Total XIII (AFTER we started adjusting doses based on TPMT testing)—despite preemptive 6MP dose decreases in pts with TPMT defect.

TPMT activity is a monogenic trait; a handful of variants account for > 95% of low activity variants.
Starting dose of 6MP can be individualized based on TPMT diplotype using those few variants.
Appendix VC: Dosing of 6-Mercaptopurine Based on Patient TPMT and NUDT15 Genotypes in TOT17

Day 3 of Induction: Blood draw to test for TPMT, NUDT15 genotype

Genetic test results entered in EHR before first dose of 6-MP on Day 22

TPMT: Normal Metabolizer
- NUDT15: Normal or Intermediate Metabolizer
  - Standard dose of 6-MP
    - (60 mg/m²/day) a
    - (50 mg/m²/day) b
    - (75 mg/m²/day) c

TPMT: Intermediate Metabolizer
- NUDT15: Normal or Intermediate Metabolizer
  - Dose Reduction of 6-MP
    - (10 mg/m²/day) a
    - (10 mg/m²/day) b
    - (60 mg/m²/day) c

TPMT: Poor Metabolizer
- NUDT15: Poor Metabolizer
  - Dose Reduction of 6-MP
    - (10 mg/m²/day) a
    - (10 mg/m²/day) b
    - (10 mg/m²/day) c

TPMT: Any Phenotypes
- NUDT15: Any Phenotypes
  - Dose Reduction of 6-MP
    - (10 mg/m² for 3 days a week)

a = Induction
b = Consolidation
c = Continuation (standard/high risk patients receive 6-MP at 50 mg/m²/day of Weeks 1-6 and 10-16 of continuation then 75 mg/m²/day starting Week 20)
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling, EE Gardner, WJ Sandborn, K Schmiegelow, C-H Pui, SW Yee, CM Stein, M Carrillo, WE Evans and TE Klein

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update


CPT 2010; 2013, 2018
Pharmacogenetics research at St. Jude: We have DNA samples from patients going back to 1986.

These and other samples have supported > 30 years of discovery pharmacogenetic research.
TPMT and thiopurines: example where pharmacogenetic research led to clinical implementation of pharmacogenetics

• Other than testing for $TPMT$ in patients receiving thiopurines, other actionable pharmacogenetic gene/drug pairs were not routinely used in patient care at St. Jude prior to 2011

• Pharmacogenetic research conducted by others, for other gene/drug pairs generated evidence supporting clinical use of pharmacogenetic testing, but we (and others) had not done much implementation

• Time for more clinical implementation of pharmacogenetic testing?
There is no implementation fairy who is going to magically make this happen.....
Why preemptive pharmacogenetic testing at St. Jude?

• There are multiple high-evidence gene drug pairs ready for clinical implementation
• All patients are at reasonably high risk to receive at least one high risk drug for at least one of those loci --- especially over a lifetime—so the chance that genotype data will be used is high
• Preemptive genotyping avoids the long TAT between decision to prescribe a drug and getting a genetic test available to prescribers.
• Cost of genotyping at most actionable loci is low---about the same as testing for any one gene---so it makes sense to test at multiple loci---making multigenic, preemptive genetic testing inexpensive
• We have a culture of prescribing based on evidence and a team of qualified pharmacists
• We have a good EHR that includes prescribing and dispensing info for our patients
• If we can’t do it....
<table>
<thead>
<tr>
<th>Drug</th>
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<tr>
<td>Abacavir</td>
<td>Methylene blue</td>
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<tr>
<td>Amitriptyline</td>
<td>Metoprolol</td>
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<td>Aripiprazole</td>
<td>Nitrofurantoin</td>
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<td>Aspirin</td>
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<td>Azathioprine</td>
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<td>Capecitabine</td>
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<td>Clopidogrel</td>
<td>Sulfamethoxazole-trimethoprim</td>
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<td>Codeine</td>
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<td>Fluorouracil</td>
<td>Tramadol</td>
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<td>Fluoxetine</td>
<td>Voriconazole</td>
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<tr>
<td>Haloperidol</td>
<td>Warfarin</td>
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At St. Jude, 2023 of 4245 patients (48%) received orders for at least one of 33 “high-risk” drugs in a 1-yr period.
99% of population has high-risk diplotype for at least one of 12 CPIC genes

98.5% of whites and 99.1% of blacks in US have at least one high-risk diplotype.

Dunnenberger et al *Ann Rev Pharm Tox* 2015
PG4KDS Protocol
Clinical Implementation of Pharmacogenetics

• Opened 2011
• Goal: implement preemptive pharmacogenetic testing for all active SJ patients
• Provide CDS for at least one drug for each gene before it is implemented in the EHR
• Once a gene moves into EHR, move it in for all past and future patients
• Provide information freely to patients and others
90% of patients have at least one high-risk genotype in their EHR (9 genes)

(n=3819)

(99% with top 12 CPIC genes)
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
• Formed in 2009 as joint project of PGRN and PharmGKB
• Goal: create, curate, update, make freely available specific peer reviewed, evidence-based, updatable clinical guidelines for actionable gene/drug pairs

CPIC website: www.cpicpgx.org
Research Directions in the Clinical Implementation of Pharmacogenomics: An Overview of US Programs and Projects

Simona Volpi¹, Carol J. Bult², Rex L. Chisholm³, Patricia A. Deverka⁴, Geoffrey S. Ginsburg⁵, Howard J. Jacob⁶, Melpomeni Kasapi¹, Howard L. McLeod⁷, Dan M. Roden⁸, Marc S. Williams⁹, Eric D. Green¹, Laura Lyman Rodriguez¹, Samuel Aronson¹⁰, Larisa H. Cavallari¹¹, Joshua C. Denny¹², Lynn G. Dressler¹³, Julie A. Johnson¹¹, Teri E. Klein¹⁴, J. Steven Leeder¹⁵, Micheline Piquette-Miller¹⁶, Minoli Perera¹⁷, Laura J. Rasmussen-Torvik¹⁸, Heidi L. Rehm¹⁹, Marylyn D. Ritchie²⁰, Todd C. Skaar²¹, Nikhil Wagle²², Richard Weinshilboum²³, Kristin W. Weitzel²⁴, Robert Wildin²⁵, John Wilson²⁶, Teri A. Manolio¹ and Mary V. Relling²⁷

Volpi et al Clin Pharm Ther 2018
Resources used by implementers: 34/36 use CPIC

<table>
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<tr>
<th>Resource</th>
<th>Description</th>
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<tr>
<td>Pharmacogenomics Research Network (PGRN)</td>
<td>The mission of the PGRN is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and ADRs adverse drug effects.</td>
<td><a href="http://www.pgrn.org/">http://www.pgrn.org/</a></td>
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<tr>
<td>PharmGKB</td>
<td>PharmGKB is a publicly available, online knowledgebase responsible for the aggregation, curation, integration, and dissemination of knowledge regarding the impact of genomic variation on drug response. The main goal of PharmGKB is to aid researchers in understanding how variation in a person’s genome affects how he or she responds to a drug.</td>
<td><a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a></td>
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<tr>
<td>PharmCAT</td>
<td>PharmCAT is developing a software tool to extract all CPIC guideline PGx variants from a genomic dataset (represented as a VCF), interpret the variant alleles, and generate a report. The CPIC-pipeline report can then be used to make future treatment decisions. This project was created to address the lack of a freely available resource able to automate the annotation of VCF files with appropriate haplotypes or diplotypes from CPIC guidelines. The project is open-source and any code script is posted in GitHub.</td>
<td><a href="https://github.com/PharmGKB/PharmCAT">https://github.com/PharmGKB/PharmCAT</a></td>
</tr>
<tr>
<td>Clinical Pharmacogenetics Implementation Consortium (CPIC)</td>
<td>CPIC provides guidelines that enable the translation of laboratory test results into actionable prescribing decisions for specific drugs. CPIC tables, created jointly with PharmGKB, allow translation of PGx test results to actionability. They are peer-reviewed and published in a leading journal with simultaneous online posting with supplemental information/data and updates. CPIC’s goal is to address some of the barriers to implementation of PGx tests into clinical practice.</td>
<td><a href="https://cpicpgx.org/">https://cpicpgx.org/</a></td>
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We are approaching implementation on 2 fronts at St. Jude

Long-term goal: preemptive pharmacogenetic testing as the standard of care... for everyone
All CPIC guidelines.
Assumption of CPIC 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 preemptive 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
Academic, Hospital, Health Care Systems

>300 members
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 Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants
JK Hicks1, JJ Sween2, CF Thorn1, K Sangkuhl3, ED Kharasch1, VI Ellingrod1, TC Skaar2, DJ Müller6, A Gaedigk9 and JC Stingl10


Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Carbamazepine Dosing
SG Leckband1,2, JG Kehoe1,2, HM Dunnenberger1, AL George Jr1, E Tran1, R Berger1, DJ Müller4, M Whirl-Carrillo5, KE Caulde6 and M Pirmohamed8


Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update
MV Relling1, EE Gardner2, WI Sandborn3, K Schmiegelow4,5, C-H Pui6, SW Yee7, CM Stein8, M Carrillo9, WE Evans1, JK Hicks1, M Schwab10,11 and TE Klein9


Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update
SA Scott1, K Sangkuhl2, CM Stein3, J-S Hulot4,5, JL Mega6, DM Roden7, TE Klein8, MS Sabatine6, JA Johnson8,9,10 and AR Shuldiner11,12

Clin Pharmacol Ther. 2013 Sep;94(3):317-23

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update
Ursula Amstutz1, Linda M. Henricks2, Steven M. Offer3, Julia Barbarino4, Jan H.M. Schellens4,5, Jesse J. Sween4, Teri E. Klein3, Howard L. McLeod2, Kelly E. Caulde3, Robert B. Diasio3,9 and Matthias Schwa8

Clin Pharmacol Ther. 2013 Sep;94(3):317-23

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update
JA Johnson1, KE Caulde2, E Gong2, M Whirl-Carrillo5, CM Stein3, SA Scott8, MT Lee5, BF Gage2, SE Kimsh4, MA Pastro3, JL Anderson4, M Pirmohamed9, TE Klein7, NA Lindh11, LH Cavallar1 and M Wulfe4,5

Clin Pharmacol Ther. 2013 Sep;94(3):317-23
CPIC® Guideline for Clopidogrel and CYP2C19

Most recent guideline publication:

Updates since publication:
March 2017: The FDA-approved label for clopidogrel (Plavix) was recently updated (September 2016) and warns that patients who are CYP2C19 poor metabolizers may have diminished effectiveness of the drug as compared to patients with normal CYP2C19 function. The drug label suggests that a different platelet P2Y12 inhibitor be used in patients identified as CYP2C19 poor metabolizers. The FDA label change does not alter the recommendation from the authors that based on available evidence, the CPIC guideline is most applicable to ACS/PCI patients.

Tables and figures provided in the main manuscript of the guideline:

Table 1: Assignment of likely CYP2C19 phenotypes based on genotypes.

CPIC® Guideline for Tricyclic Antidepressants and CYP2D6 and CYP2C19

Most recent guideline publication:
Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update (December 2016)

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

Tables and figures provided in the main manuscript of the guideline:

Table 1: Assignment of likely CYP2D6 phenotypes based on genotypes.

Table 2: Dosing recommendations for tricyclic antidepressants based on CYP2D6 phenotype.

Table 3: Dosing recommendations for the tetracyclic antidepressants, clomipramine, doxepin, imipramine, and trimipramine based on CYP2C19.

CPIC® Guideline for Codeine and CYP2D6

Most recent guideline publication:
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Cytochrome P450 2D6 (CYP2D6) Genotype and Codeine Therapy: 2014 Update (April 2014)

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

Tables and figures provided in the main manuscript of the guideline:

Table 1: Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (CYP2D6) alleles.

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

Figure 1: Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolizer or see Pharmacogenomics Codeine and Mutations/Polymorphisms, Pharmacokinetics.

CPIC® Guideline for Fluoropyrimidines and DPYD

Most recent guideline publication:
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Deoxyguanosine Deaminase Genotype and Fluoropyrimidine Dosing (December 2016)

Updates since publication:
May 2016: The CPIC authors recommend that the DPYD*4, *5, and *8 alleles be categorized as “normal” activity, in part based upon the recent publications Consensus Functional Analyses of DPYD Variants of Potential Clinical Relevance in Deoxyguanosine Deaminase Activity.

Tables provided in the main manuscript of the guideline:

Table 1: Assignment of likely DPYD phenotypes based on genotypes.

Table 2: Recommendations for use of fluoropyrimidines for DPYD inhibition.

Table 3: Assignmen of likely DPYD phenotypes based on genotypes.
PG4KDS protocol

• Goal:
  • Migrate pharmacogenetic tests from the laboratory (array-based) into routine patient care, to be available preemptively
  • Goal is all CPIC actionable gene/drug pairs

• Exclusion criteria:
  • Patients who have received a prior allogeneic stem cell transplant

https://www.stjude.org/pg4kds
2011
- TPMT – thiopurines
- CYP2C19– clopidogrel
- CYP2C9, VKORC1 – warfarin

2012
- CYP2D6 – codeine
- HLA-B – abacavir
- SLCO1B1 – simvastatin

2013
- HLA-B – allopurinol
- CYP2D6, CYP2C19 – TCAs
- HLA-B – carbamazepine
- DPYD – 5FU / capecitabine
- TPMT – thiopurines—UPDATE
- CYP2C19 – clopidogrel—UPDATE

2014
- IL28B – PEG interferon α
- CFTR – Ivacaftor
- G6PD – Rasburicase
- CYP2C9, HLA-B – Phenytoin
- CYP2D6 – codeine—UPDATE
- HLA-B – abacavir—UPDATE
- SLCO1B1 – simvastatin—UPDATE
- HLA-B – allopurinol—UPDATE

2015
- CYP3A5 – tacrolimus
- CYP2D6, CYP2C19 – SSRIs
- UGT1A1 – Atazanavir
- HLA-B – allopurinol—UPDATE

2016
- CYP2C19 – voriconazole
- CYP2D6 – ondansetron
- CYP2C9, VKORC1 – warfarin—UPDATE
- CYP2D6 – thiopurines—UPDATE
- CYP2C9/HLA-phenytoin—UPDATE
- CYP2C9/celecoxib
- CYP2D6/codeine—UPDATE

2017
- CYP2D6 – tamoxifen
- HLA-B – carbamazepine—UPDATE
- DPYD – 5FU / capecitabine—UPDATE

2018
- RYR1/CACNA1S – inhaled anesthetics
- TPMT/NUDT15 – thiopurines—UPDATE

2019 (in progress)
- CYP2B6– efavirenz-submitted
- CYP2D6– atomoxetine–accepted
- CYP2C19/PPI
- CYP2C9/HLA-phenytoin—UPDATE
- CYP2C9/celecoxib
- CYP2D6/codeine—UPDATE

https://cpicpgx.org/guidelines/
2011
- TPMT – thiopurines
- CYP2C19 – clopidogrel
- CYP2C9, VKORC1 – warfarin

2012
- CYP2D6 – codeine
- HLA-B – abacavir
- SLCO1B1 – simvastatin

2013
- HLA-B – allopurinol
- CYP2D6, CYP2C19 – TCAs
- HLA-B – carbamazepine
- DPYD – 5FU / capecitabine
- TPMT – thiopurines—UPDATE
- CYP2C19 – clopidogrel—UPDATE

2014
- IL28B – PEG interferon α
- CFTR – Ivacaftor
- G6PD – Rasburicase
- CYP2C9, HLA-B – Phenytoin
- CYP2D6 – codeine—UPDATE
- HLA-B – abacavir—UPDATE
- SLCO1B1 – simvastatin—UPDATE

2015
- CYP3A5 – tacrolimus
- CYP2D6, CYP2C19 – SSRIs
- UGT1A1 – atazanavir
- HLA-B – allopurinol—UPDATE

2016
- CYP2C19 – voriconazole
- CYP2D6 – ondansetron
- CYP2C9, VKORC1 – warfarin—UPDATE
- CYP2D6, CYP2C19 – TCAs—UPDATE
- TPMT/NUDT15 – thiopurines—UPDATE
- CYP2D6/codeine—UPDATE

2017
- CYP2D6 – tamoxifen
- HLA-B – carbamazepine—UPDATE
- DPYD – 5FU / capecitabine—UPDATE

2018
- RYR1/CACNA1S – inhaled anesthetics
- HLA-B – allopurinol—UPDATE

2019 (in progress)
- CYP2B6—efavirenz-submitted
- CYP2D6—atomoxetine—accepted
- CYP2C19/PP1
- CYP2C9/HLA-phenytoin—UPDATE
- CYP2C9/codeine
- CYP2D6/codeine—UPDATE

https://cpicpgx.org/guidelines/
PG4KDS: The Process

1. Patient consent
2. Blood sample
3. Genotyping (230 genes)
4. Research database
5. Select results put in EHR
6. Clinical decision support
7. Patient education

Genotyping at Medical College of Wisconsin, now RPRD

Pharmaceutical Sciences Research database (>225 genes parsed into separate files)

- **TPMT**
- **DPYD**
- **CYP3A4**
- **GSTT1**
- **CYP4B1**
- **CYP2C19**
- **VKORC1**
- **CYP2F1**
- **NAT1**
- **CYP1A1**
- **CYP2D6**
- **SLCO1B1**
- **CYP2J2**
- **FMO3**
- **CYP2C18**
- **CYP2C9**
- **G6PD**
- **UGT1A1**
- **CYP4F2**
- **ABCC1**

Array-based CLIA-compliant Genotypes (DMET now PharmacoScan)

Extensive quality control

Prior to upload in EHR

- Concordance of self declared sex with genetics
- Concordance with prior genotyping and phenotyping results
How do we get from genotype to interruptive CDS for prescribing?

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

WARNING: Based on the genotype result, this patient is predicted to have intermediate TPMT activity. 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.
CPIC
Clinical Pharmacogenetics Implementation Consortium

Gene or drug of interest identified

Clinical guidelines developed and applied

Genotype assigned to allele

Diploype assigned to patient

Diploype interpreted into phenotype

Phenotype assigned to patient

Phenotype interpreted with respect to drug therapy

CDS developed for high-risk drugs and phenotypes

Decision outcome harmonized with existing policies

Clinicians and patients educated about policies

Prescription policy approved by institution

Impact of clinical implementation evaluated

Relling & Evans, Nature, 2015
CPIC® Guideline for Voriconazole and CYP2C19

Most Recent Guideline Publication

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

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

Tables provided in the main manuscript of the guideline

<table>
<thead>
<tr>
<th>Table 1. Assignment of likely CYP2C29 phenotype based on genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients</td>
</tr>
<tr>
<td>Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents &lt;18 years old)</td>
</tr>
</tbody>
</table>

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

Tables provided in the guideline publication supplement or referenced in the guideline

<table>
<thead>
<tr>
<th>Levels of Evidence Linking Genotype to Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Allele Definition Table</td>
</tr>
<tr>
<td>CYP2C19 Allele Functionality Table</td>
</tr>
<tr>
<td>CYP2C19 Frequency Table</td>
</tr>
<tr>
<td>CYP2C19 Diploype-Phenotype Table</td>
</tr>
<tr>
<td>Gene Resource Mapping</td>
</tr>
<tr>
<td>CYP2C19 Gene Resource Mappings</td>
</tr>
</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)

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

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
CYP2D6: 207 diplotypes observed in first 4046 pts on PG4KD$^S$
Dedicated Pharmacogenetics Section in EHR: not encounter-specific

Each gene test result is coupled with a “consult” entry.
Pre-test alerts contains prescribing and testing recommendations if a patient has not been genotyped: driven off the ABSENCE of a test result.

**WARNING**

A CYP2D6 genotype is recommended before prescribing codeine. A CYP2D6 genotype test does not appear to have been ordered for this patient. Use an alternative agent such as a non-opioid, or morphine, or HYDROMorphone (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®). Please consult a clinical pharmacist or go to www.stjude.org/pg4KDS for more information.

**Alert Action**

- Cancel
- Continue

**Add Order for:**

- CYP2D6 Genotype -> T;N, Collect Now, Blood, Fasting Required: No, ONCE
Post-test alerts contain prescribing recommendations based on the PRESENCE of a high risk test result

**WARNING**

Based on the genotype result, this patient is predicted to be a CYP2D6 poor metabolizer. If codeine is prescribed to a CYP2D6 poor metabolizer, suboptimal analgesia is likely. Other pain medications such as morphine, HYDROMorphone (e.g., Dilaudid®) or acetaminophen/hydroCODONE (e.g., Lortab®, Vicodin®) are recommended. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

**Alert Action**

- Cancel entry
- Continue w/order
Post-test alert can incorporate non-genetic info too: based on CYP2C19 phenotype, route of administration, age.
Post-test alert: based on 2 genes affecting same drug

ADJUST STARTING DOSE

Mercaptopurine can be affected by a patient’s TPMT and NUDT15 phenotype. This patient is predicted to be a TPMT NORMAL METABOLIZER and a NUDT15 POOR METABOLIZER. The patient is at risk for myelosuppression with normal doses of Mercaptopurine. Consider starting Mercaptopurine doses at 20 mg/m2/day. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

Alert Action

- Cancel Mercaptopurine
- Mercaptopurine dose altered accordingly
- Modify Mercaptopurine order

[LINK] [OK]
Phenotypes drive CDS and allow for interoperability, portability of results
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, PhD⁶, 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-

**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.

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

Genet Med advance online publication 21 July 2016
<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>
<tr>
<td>Term/Gene Category</td>
<td>Final Term*</td>
<td>Functional Definition</td>
<td>Example diplotypes/alleles</td>
</tr>
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</tr>
<tr>
<td><strong>Phenotype-Drug Metabolizing Enzymes (CYP2C19, CYP2D6, CYP3A4, CYP2C9, TPMT, DPYD, UGT1A1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 | |
Working with SNOMED to match codes to standardized phenotype terms: SNOMED CT International Browser

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

vs

<table>
<thead>
<tr>
<th>TPMT- standardized Terms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT - Normal Metabolizer (normal dose)</td>
<td></td>
</tr>
<tr>
<td>TPMT - Intermediate Metabolizer (60% dose)</td>
<td></td>
</tr>
<tr>
<td>TPMT - Poor Metabolizer (5% dose)</td>
<td></td>
</tr>
</tbody>
</table>
The incidence of duplicate genetic testing

Douglas L. Riegert-Johnson, MD¹, Daniela Macaya, MQC², Timothy W. Heffron, PhD³, and Lisa A. Boardman, MD¹

Purpose: Duplicate genetic testing (DGT) should give the same results as the initial genetic test. Therefore, DGT is indicated only in the rare instances where the initial results require confirmation. The objective of this study was to determine the incidence of DGT by reviewing TPMT, HFE, and CYP450 2D6 polymorphism testing performed in our institution’s laboratories in 2006. A secondary objective was to determine the savings in charges that resulted from a system in place to limit HFE DGT. Methods: A retrospective records review at an academic medical center.

Results: The percentage of patients having the same genetic test more than once in 2006 was 3.3% (253/7710) for TPMT, 0.3% for HFE (24/7851), and 0.9% (4/433) for CYP450 2D6 testing. Retail laboratory charges for DGT identified in 2006 were $76,728. To estimate the incidence of DGT over a longer period of time than 24 weeks, an all-time records review was performed on a subset of internal patients and found the all-time incidence of DGT for TPMT, HFE, and CYP450 2D6 testing to be 6.9%, 1.9%, and 0.9%, respectively. No case of DGT will appropriate indication for duplicate testing was found. A system in place to decrease HFE DGT is estimated to have saved $77,479 in charges for 2006 (95% CI, $35,512–184,015). Conclusions: Indicated DGT is rare, decreasing DGT could result in significant savings. Institutions should consider implementing a system to prevent DGT.

Table 1

Percentage of patients having duplicate HFE, TPMT, and CYP450 2D6 polymorphism genetic testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Cohort</th>
<th>In 2006 only</th>
<th>At anytime in the past¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>All</td>
<td>3.3% (253/7710)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Internal</td>
<td>2.5% (25/996)</td>
<td>6.9% (17/246)</td>
</tr>
<tr>
<td></td>
<td>External</td>
<td>3.4% (228/6714)</td>
<td>—</td>
</tr>
<tr>
<td>HFE</td>
<td>All</td>
<td>0.3% (24/7851)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Internal</td>
<td>0.6% (4/681)</td>
<td>1.9% (4/207)</td>
</tr>
<tr>
<td></td>
<td>External</td>
<td>0.3% (20/7170)</td>
<td>—</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Internal</td>
<td>0.9% (4/433)</td>
<td>0.9% (4/433)</td>
</tr>
</tbody>
</table>

¹Incidence of DGT at anytime in the past determined for consecutive series of internal patients only.
9 Genes and 25 Drugs Implemented

- **CYP2D6 (17%)**
  - Codeine
  - Oxycodone
  - Tramadol
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Fluoxetine
  - Paroxetine
  - Ondansetron

- **CYP2C19 (62%)**
  - Clopidogrel
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - PPIs
  - Voriconazole

- **CYP3A5 (41%)**
  - Tacrolimus

- **SLCO1B1 (13%)**
  - Simvastatin

- **TPMT/NUDT15 (11%)**
  - Mercaptopurine
  - Thioguanine
  - Azathioprine

- **DPYD (0.4%)**
  - Fluorouracil
  - Capecitabine

- **UGT1A1 (28%)**
  - Atazanavir

- **CYP2C9 (32%)**
  - Celecoxib

% indicate the % of patients enrolled on PG4KDS who have a high-risk genotype for that gene.
### Implementation Timeline: Genes and Drugs

(9 Genes and 25 Drugs: additional drugs added for existing genes over time)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>TPMT and thiopurines</td>
<td>CYP2D6 and codeine</td>
<td>CYP2D6 and tramadol</td>
<td>CYP2D6 and paroxetine, fluoxetine, amitriptyline</td>
<td>CYP2D6 and ondansetron</td>
<td>SLCO1B1 and simvastatin</td>
<td>CYP2D6 and oxycodone</td>
<td>CYP2C19 and clopidogrel</td>
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<td></td>
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<td>CYP2D6 and paroxetine</td>
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</table>
QC Metric: % of thiopurine-naïve patients diagnosed with **ALL** who had a known $TPMT$ genotype prior to initiating thiopurine therapy at St. Jude*

* Patients with an unknown $TPMT$ genotype who initiated thiopurine therapy after an allogeneic HSCT were excluded from this reporting.
Not all drugs supported by CDS at time each gene is implemented at St. Jude

- 11 year old boy at week 102 of ALL continuation therapy
- intermittent thrombocytopenia, episode of hematemesis, started omeprazole
- another episode of hematemesis; endoscopy showed esophageal varices
- AFTER consultation for increase in liver enzymes, found to have CYP2C19*17/*17 diplotype already in EHR, but no CDS built for PPIs

### Pharmacogenetics: From Bench to Byte—An Update of Guidelines

<table>
<thead>
<tr>
<th>Omeprazole</th>
<th>2,522</th>
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<th>AA#</th>
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<tbody>
<tr>
<td>IM</td>
<td>4</td>
<td>AA#</td>
<td>Yes</td>
<td>No</td>
<td></td>
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</tr>
<tr>
<td>UM</td>
<td>3</td>
<td>A</td>
<td>Yes</td>
<td>H. pylori eradication: increase dose by 100–200%. Be extra alert to insufficient response. Other: be extra alert to insufficient response. Consider dose increase by 100–200%</td>
<td>391–393</td>
<td></td>
</tr>
</tbody>
</table>

Swen JJ et al 662 VOLUME 89 NUMBER 5 | MAY 2011 | www.nature.com/cpt
Ranking of gene/drug pairs without CPIC guidelines 2018
Interpretations change over time: Adding disclaimer note to all new pgen consults

Disclaimer: The interpretation of this result is based on evidence available as of the time this consult was entered into the electronic health record. Interpretations of genomic variants can change as evidence evolves; consult with the Clinical Pharmacogenomics Service (pharmacogenomics@stjude.org) to discuss whether this interpretation should be updated.

• ~ 5% of consults have needed re-interpretation over first 8 years
• 2 incidental genetic findings of Klinefelter’s syndrome (boys with XXY)---so G6PD genotypes come back AA, AB, or BB instead of just A or B
• Blood samples after bone marrow transplant: blood ≠ host tissues
• Genotyping/phenotyping done elsewhere summarized on common, date-independent tab
• High risk results: medication reconciliation needed to catch already-dispensed meds
• Reconcile phenotype and genotype---separate tests, one interpretation: TPMT, G6PD
PG4KDS Anecdotes

• “possible” high-risk status
• Updating multiple policies differs by drug (e.g. mt-RNR1 and aminoglycosides)
• Anesthesia drugs not documented in main EHR (no CDS)
• Challenges documenting pt education
• Minimizing duplicate orders
• Avoiding privacy violations
The use of pharmacogenetics-guided prescribing is STILL not widespread
large academic center but no directed efforts at preemptive genotyping

132,340 patients and 3,211,797 hospital/clinic visits,

268,262 medication orders for 95 drugs with germline PGEN testing mentioned in their FDA-approved drug labels (49 of which were actionable by CPIC)

1.5% of prescriptions for those 95 drugs accompanied by testing, even when the FDA label “recommended or required” testing
Before you take a prescription, take the OneOme RightMed test.

PGxOne™ Plus Pharmacogenomics Test

GeneAlign

PGxOne™ Plus

50 Genes
Coverage of ~200 Genetic Variants
Over 300 Commercial Drugs

Science that benefits humanity.

Prescribe with confidence using pharmacogenetics and YouScript®.

How to Get Started with Rxright®

Right Medicine. Right from the Start.*

Rxright® is the most comprehensive pharmacogenetic program on the market, and guide your prescriber in determining how your body is likely to respond to more than 200 prescription and over-the-counter (OTC) medications before you even take the

This allows your prescriber and pharmacist to prescribe and fill medications that are right for you and help you avoid medications that may cause side effects. Locate a participating pharmacy & discover your medication profile today.

LOCATE A PHARMACY TODAY
The FDA Warns Against the use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication

Date Issued
November 1, 2018
Our job as clinical pharmacologists

• Counter-detail marketing-based use of drugs or drug tests
• Advocate for appropriate, evidence-based use of drugs and drug tests
Thank you

- University of Arizona College of Pharmacy
- University of Utah College of Pharmacy
- St. Jude Children’s Research Hospital
- University of Basel
- NIH: NCI, NIGMS, NICHD, NHGRI
- Children’s Oncology Group
- Pharmacogenomics Research Network
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• CPIC SAB

PharmGKB

CPIC
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Kristine Crews, James Hoffman

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Ulrich Broeckel, M.D.

Rachel Lorier

Amy Turner
age


Drug interactions


Inherited genetics---thiopurines

Inherited genetics---other genes

Somatically acquired genetics: MTX

Somatically acquired genetics: other drugs


Clinical implementation of pgx

adherence


- G, Maloney KW, Mascarenhas L, Ritchey AK, Termuhlen AM, Carroll WL, Relling MV, Wong FL, Bhatia S.

Multiple steps to implement a new gene/drug pair

- Diplotype interpretation; clinical consults; problem list entries
- Build interruptive CDS (clinical decision support)
- Update formulary, drug policies as needed
- Update public website
- Update pt and clinician educational materials
- Build and complete competencies for clinicians
- Approval of Pharmacogenetics Oversight Committee
- Sharing with PGRN, PharmGKB, others
## Implementation Timeline:
### 9 Genes and 22 Drugs Implemented

<table>
<thead>
<tr>
<th>Year</th>
<th>Genes/Drugs Implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>TPMT and thiopurines</td>
</tr>
<tr>
<td></td>
<td>CYP2D6 and codeine</td>
</tr>
<tr>
<td></td>
<td>CYP2D6 and tramadol</td>
</tr>
<tr>
<td>2012</td>
<td>CYP2D6 and paroxetine, fluoxetine, amitriptyline</td>
</tr>
<tr>
<td>2013</td>
<td>CYP2D6 and ondansetron</td>
</tr>
<tr>
<td></td>
<td>SLCO1B1 and simvastatin</td>
</tr>
<tr>
<td></td>
<td>CYP2D6 and oxycodone</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 and clopidogrel</td>
</tr>
<tr>
<td></td>
<td>DPYD and fluoropyrimidines</td>
</tr>
<tr>
<td></td>
<td>CYP2C19/CYP2D6 and amitriptyline</td>
</tr>
<tr>
<td>2014</td>
<td>UGT1A1 and atazanavir</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 and voriconazole</td>
</tr>
<tr>
<td></td>
<td>CYP3A5 and tacrolimus</td>
</tr>
<tr>
<td></td>
<td>CYP2C19/CYP2D6 and TCAs</td>
</tr>
<tr>
<td></td>
<td>NUDT15 and thiopurines</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 and celecoxib</td>
</tr>
<tr>
<td>2015</td>
<td>CYP2C19 and PPIs</td>
</tr>
</tbody>
</table>

[www.stjude.org/pg4kds/implement](http://www.stjude.org/pg4kds/implement)
9 Genes and 22 Drugs Implemented: % of pts with actionable genotype

- **CYP2D6 (17%)**
  - Codeine
  - Oxycodone
  - Tramadol
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Fluoxetine
  - Paroxetine
  - Ondansetron

- **CYP2C19 (62%)**
  - Clopidogrel
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Voriconazole

- **CYP3A5 (41%)**
  - Tacrolimus

- **SLCO1B1 (13%)**
  - Simvastatin

- **TPMT/NUDT15 (11%)**
  - Mercaptopurine
  - Thioguanine
  - Azathioprine

- **DPYD (0.4%)**
  - Fluorouracil
  - Capecitabine

- **UGT1A1 (28%)**
  - Atazanavir

- **CYP2C9 (32%)**
  - Celecoxib

Percentages in parenthesis indicate the proportion of patients enrolled on the PG4KDS protocol who have a high-risk genotype for that gene.
<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approached for consent</td>
<td>4735</td>
<td>--</td>
</tr>
<tr>
<td>Enrolled on protocol</td>
<td>4471</td>
<td>94</td>
</tr>
<tr>
<td>Re-consented at age of majority*</td>
<td>535</td>
<td>97</td>
</tr>
<tr>
<td>Request to be informed of pharmacogenetic test result</td>
<td>4564</td>
<td>96</td>
</tr>
<tr>
<td>Incidental findings</td>
<td>2</td>
<td>0.04%</td>
</tr>
</tbody>
</table>

*550 patients turned 18 years old after being enrolled on the PG4KDS study

Unpublished data (May 2018)
CYP2D6: 207 diplotypes observed in first 4046 pts on PG4KDS

TPMT is much simpler
From genotype or sequencing data, call gene-centric haplotypes and diplotypes—not just variants.
Passive CDS: interpretation of pgen test results always available

1.) (Medium Importance) Result Comment by EASTERNAK, 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.sjude.org/pg4kds.

Kristine Crews, Pharm D., pager 2256

2C19 RM 4-20160518
Templates based on deconstructing the consult into sections: scalable

Phenotype Assignment

Diplotype Interpretation

Phenotype interpretation, medications

Prescribing Recommendations

Educational Link

Kristine Crews, Pharm.D., pager 2256.

$CONSULT_TITLE $VERSION-$APPROVAL_DT_TM

PG4KDS Consult Builder
Hicks et al (CPT 2012)
Diplotypes entered on Pharmacogenetics Tab: not encounter-specific

Consult is one place for passive CDS
High risk phenotypes automatically populate the “Problem List”; can also manually enter as well.

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

Drive CDS off of problem list entry
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)

- **Diplootypes 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://cpicpgx.org/guidelines/)
[https://www.pharmgkb.org/page/cyp2c19RefMaterials](https://www.pharmgkb.org/page/cyp2c19RefMaterials)
Interruptive alerts (active CDS) used to guide prescribing based on genetic test results (or lack thereof)

- **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
Pre-test alerts contain prescribing and testing recommendations if a patient has not been genotyped: driven off the ABSENCE of a test result.

WARNING

A CYP2D6 genotype is recommended before prescribing codeine. A CYP2D6 genotype test does not appear to have been ordered for this patient. Use an alternative agent such as a non-opioid, or morphine, or HYDROMORPHINE (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®). Please consult a clinical pharmacist or go to www.stjude.org/pg4KDS for more information.

Alert Action

- Cancel
- Continue

Add Order for:

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

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

**Introduction:** Reporting and sharing pharmacogeneic 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 pharmacogeneic 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 pharmacogeneic terms will improve the understanding and interpretation of pharmacogeneic tests and reduce confusion by maintaining consistent nomenclature. These standard terms can also facilitate pharmacogeneic 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
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)
Post-test alerts contain prescribing recommendations based on the PRESENCE of a high risk test result.

*WARNING*

Based on the genotype result, this patient is predicted to be a CYP2D6 poor metabolizer. If codeine is prescribed to a CYP2D6 poor metabolizer, suboptimal analgesia is likely. Other pain medications such as morphine, HYDROMorphone (e.g., Dilaudid®) or acetaminophen/hydroCODONE (e.g., Lortab®, Vicodin®) are recommended. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

Alert Action

- Cancel entry
- Continue w/order
Post-test alert can incorporate non-genetic info too: based on CYP2C19 phenotype, route of administration, age.
Post-test alert: based on 2 genes affecting same drug

Mercaptopurine can be affected by a patient’s TPMT and NUDT15 phenotype. This patient is predicted to be a TPMT NORMAL METABOLIZER and a NUDT15 POOR METABOLIZER. The patient is at risk for myelosuppression with normal doses of Mercaptopurine. Consider starting Mercaptopurine doses at 20 mg/m2/day. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

Alert Action

- Cancel Mercaptopurine
- Mercaptopurine dose altered accordingly
- Modify Mercaptopurine order

LINK OK