Tailoring pharmacotherapy to improve outcomes

2019 ASCPT Oscar B. Hunter Award

Mary V. Relling
Memphis, TN USA

PGRN

CHILDREN'S ONCOLOGY GROUP

CPIC™ Clinical Pharmacogenetics Implementation Consortium

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

ASCPT American Society for Clinical Pharmacology & Therapeutics

Previous Recipients

2019- Mary V. Relling, PharmD
2018- William J. Jusko, PhD
2017- N/A
2016 -Brian L. Strom, MD, MPH
2015 - Michel Eichelbaum, MD
2014 - Edward M. Sellers, MD, PhD
2013 - William E. Evans, PharmD
2012 – D. Craig Brater, MD
2011 – Garret A. FitzGerald, MD
2010 – Leslie Z. Benet, PhD
2009 – Sir Colin Dollery, MD
2008 - Marcus M. Reidenberg, MD
2007 - Terrence F. Blaschke, MD
2006 - Neal Benowitz, MD
2005 - Arthur J. Atkinson Jr., MD
2004 - Lewis B. Sheiner, MD
2003 - Louis Lemberger, MD, PhD
2002 - Sumner J. Yaffe, MD
2001 - Alan Nies, MD
2000 - Paul S. Lietman, MD, PhD
1999 - Alvan R. Feinstein, MD
1998 - Richard M. Weinshilboum, MD
1997 - J. Richard Crout, MD, FACP
1996 - Folke Sjoqvist, MD, PhD
1995 - Daniel L. Azarnoff, MD
1994 - Kenneth L. Melmon, MD
1993 - Werner Kalow, MD
1992 - Paul Calabresi, MD
1991 - Elliott S. Vesell, MD
1990 - Walter F. Riker, Jr., MD
1989 - John J. Burns, PhD
1988 - Leo E. Hollister, MD
1987 - Jan Koch-Weser, MD
1986 - Leon I. Goldberg, MD, PhD
1985 - Raymond W. Houde, MD
1984 - George H. Hitchings, PhD, ScD
1983 - C. Gordon Zubrod, MD
1982 - Gerhard Levy, PharmD
1981 - Albert Sjoerdsma, MD, PhD
1980 - John A. Oates, MD
1979 - Ray W. Gifford, Jr., MD 1978 - Walter Modell, MD
1977 - Harris Isbell, MD
1976 - Louis Goodman, MD and Alfred Gilman, PhD
1975 - Louis Lasagna, MD
1974 - Raymond P. Ahlquist, PhD
1973 - George C. Cotzias, MD
1972 - Edward D. Freis, MD
1971 - Maxwell Finland, MD
1970 - Bernard B. Brodie, MD
1969 - Arthur Grollman, MD
1968 - Sidney Farber, MD
1967 - George W. Thorn, MD
1966 - Irvin H. Page, MD
1965 - William B. Castle, MD
1964 - Henry K. Beecher, MD
1963 - Albert B. Sabin, MD
1962 - Charles B. Huggins, MD
1961 - Hattie E. Alexander, MD
1960 - John H. Moyer, III, MD
1959 - Tom D. Spies, MD
1958 - C. Walton Lillehei, MD
1957 - Robert W. Wilkins, MD
1956 - E. M. K. Geiling, MD
1955 - Jonas E. Salk, MD

ASCPT American Society for Clinical Pharmacology & Therapeutics

My first scientific meeting:

ASCPT Annual meeting 1986 in Washington DC

St. Jude Children's Research Hospital

- 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)

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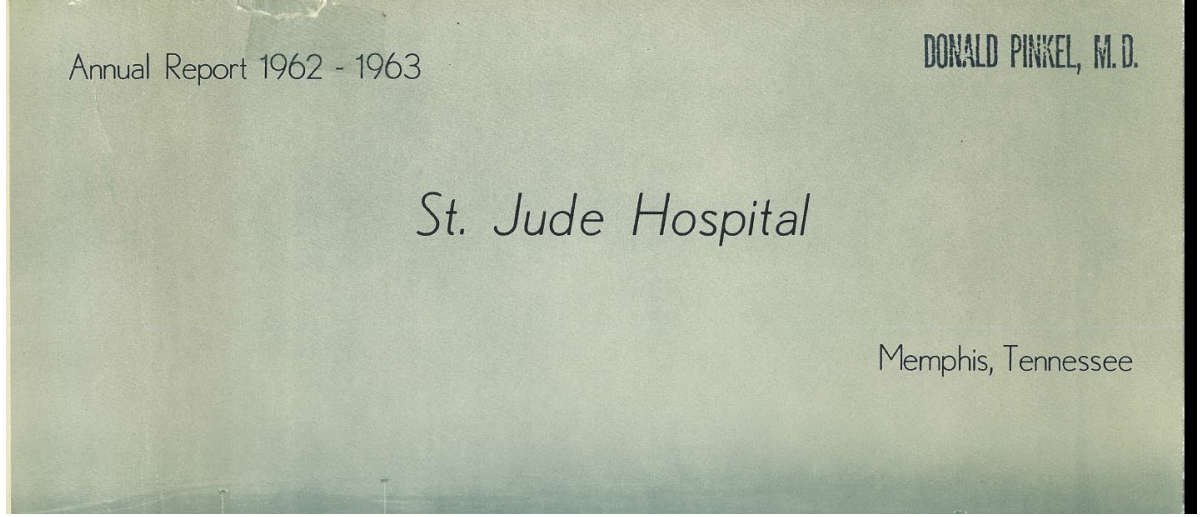
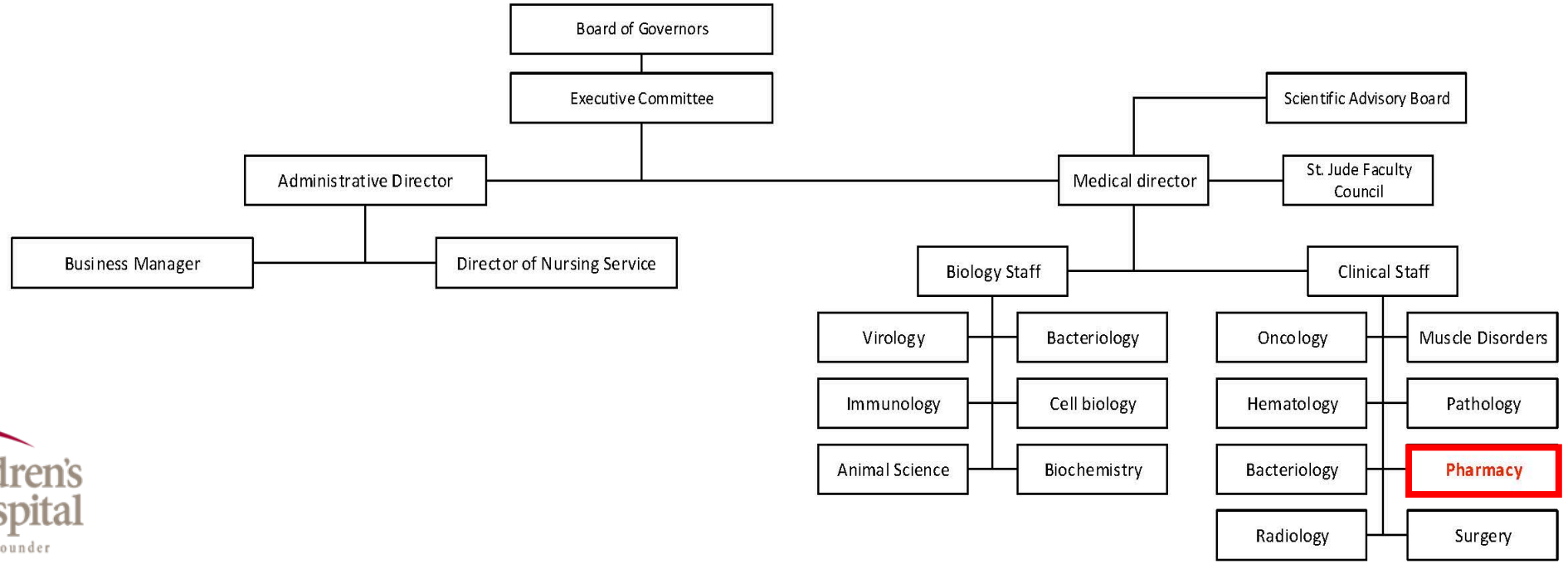


St. Jude's first annual report, 1962



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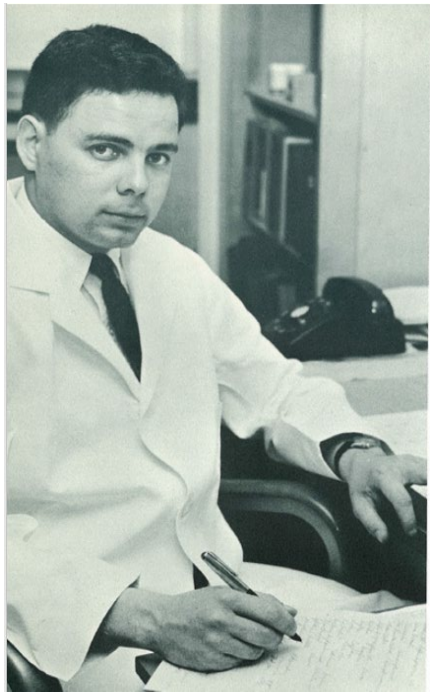

Pharmaceutical Dept

Personnel

Name	Title	Date of Employment
George E. Crevar, M.S.	Instructor in Pharmacy	January 1, 1962
Gail Ogletree	Technologist	May 25, 1962
Rita Caldwell	Clerk and Typist	August 14, 1962

Larry Barker
1969-1983

William Evans
1983-2002

Mary Relling
2003-present

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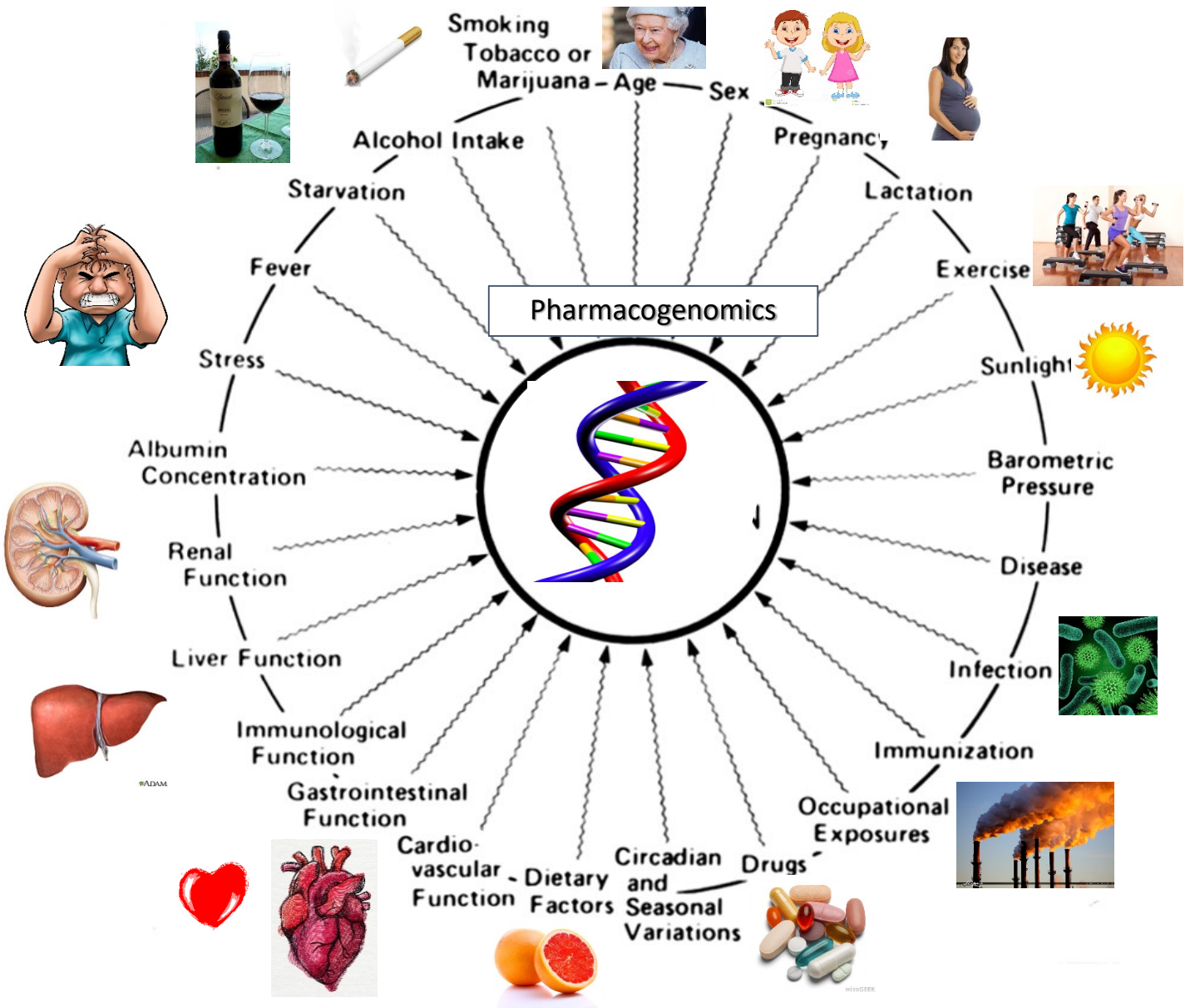
Pharmaceutical Department Goals

- 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)



Thanks to Oscar Hunter recipient William Evans for the slide

Thanks to Oscar Hunter recipient Elliott Vesell for the original, *Pharm. Ther.* 1989

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

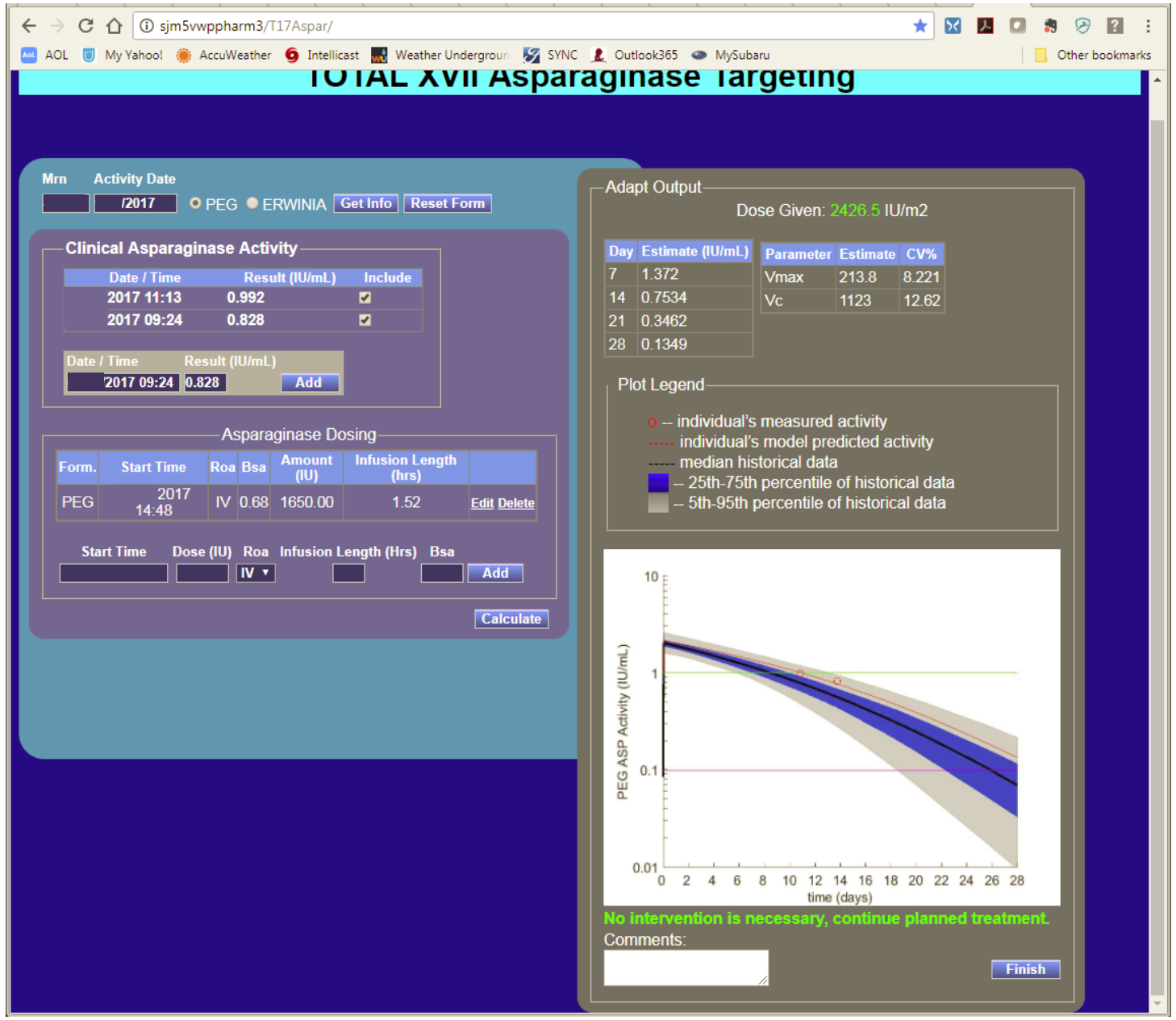
Aspects unique to Pharmaceutical Dept

- 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




Bill Crom
Bill Evans
John Rodman

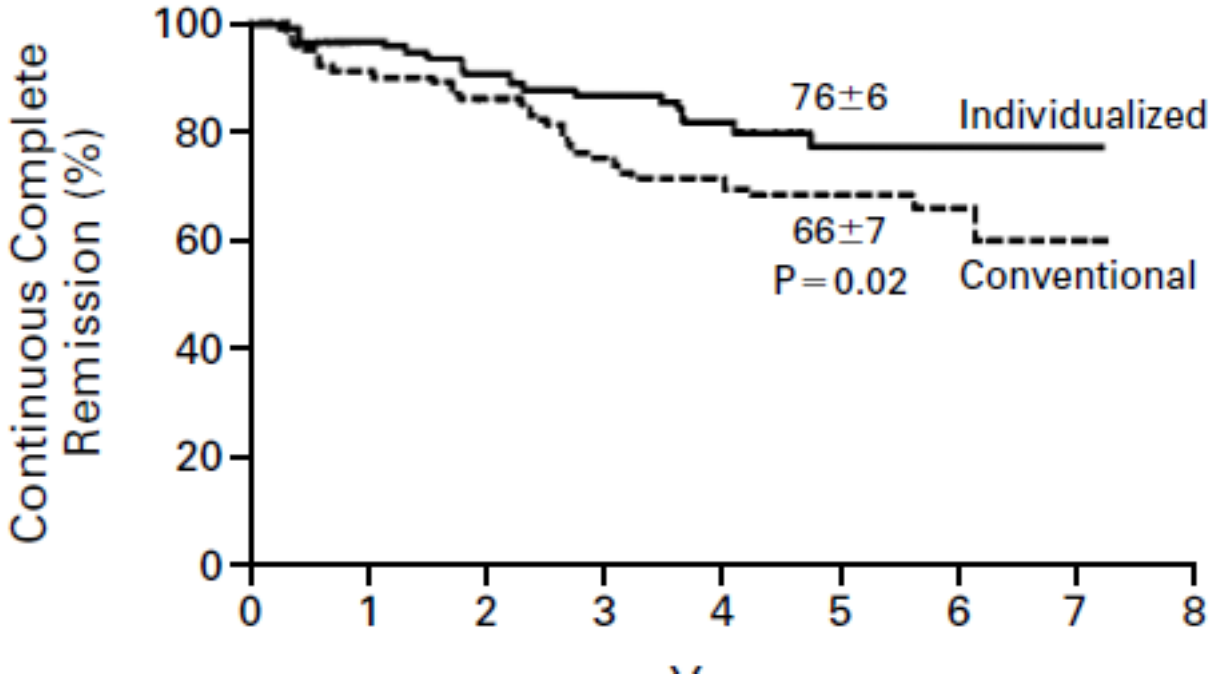
Total XII: Clinical trial for childhood acute lymphoblastic leukemia (ALL)—accrued 1988-1991

- 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


Bill Evans
Bill Zamboni
Bill Crom
DJ Murray
John Rodman
Burgess Freeman
Mike Christensen
Gary Yee
Sharyn Baker
Margaret Tonda
Chris Kearns

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.



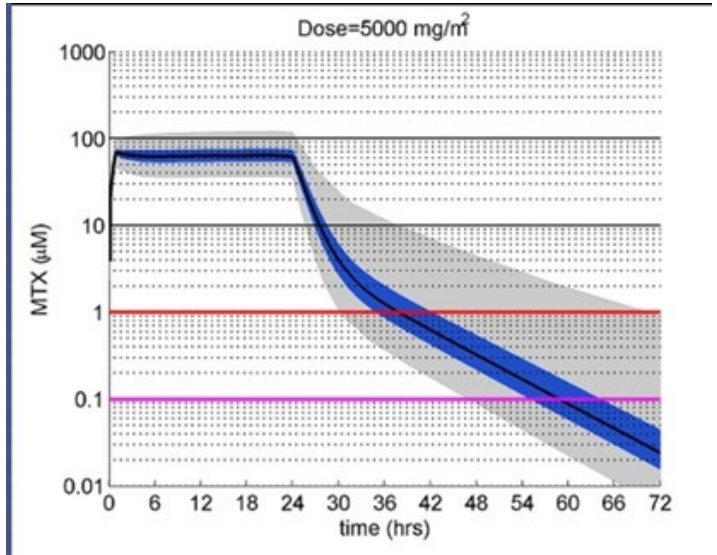
NEJM, 1998

Cancer Chemother Pharmacol (2013) 72:369–378
DOI 10.1007/s00280-013-2206-x

ORIGINAL ARTICLE

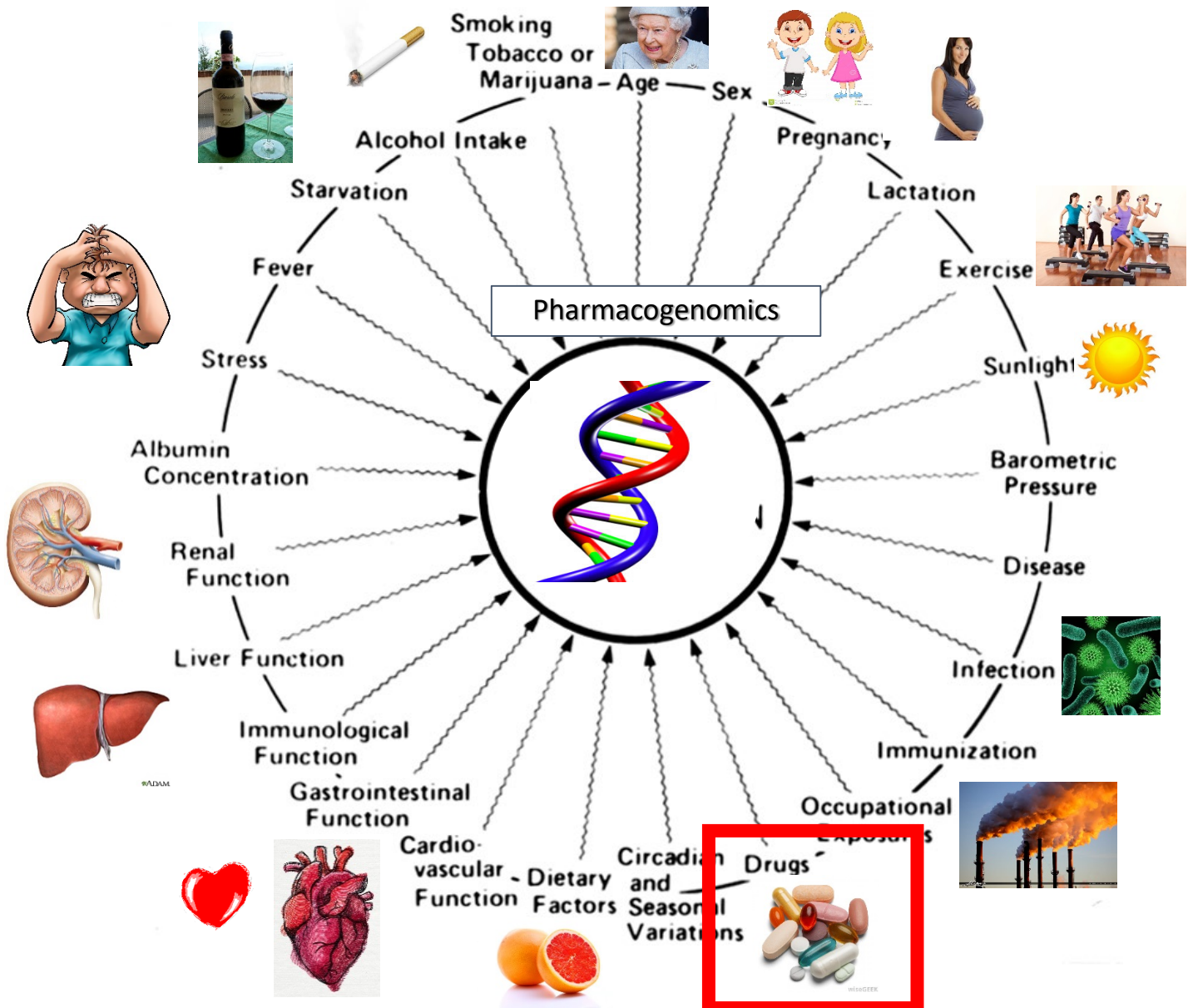
Between-course targeting of methotrexate exposure using pharmacokinetically guided dosage adjustments

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



http://mtx.stjude.org/

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)

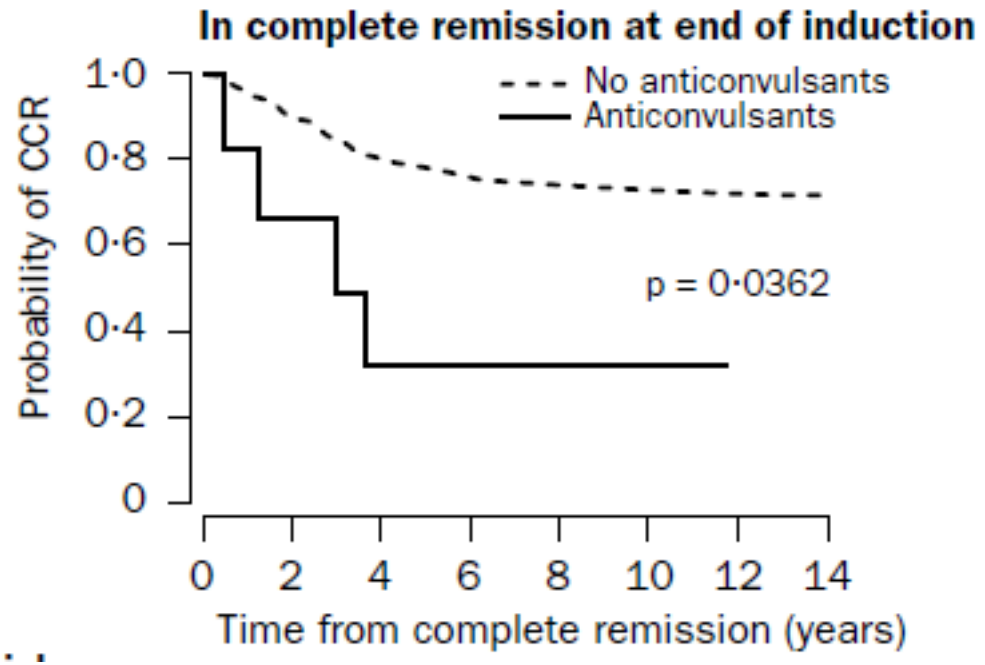


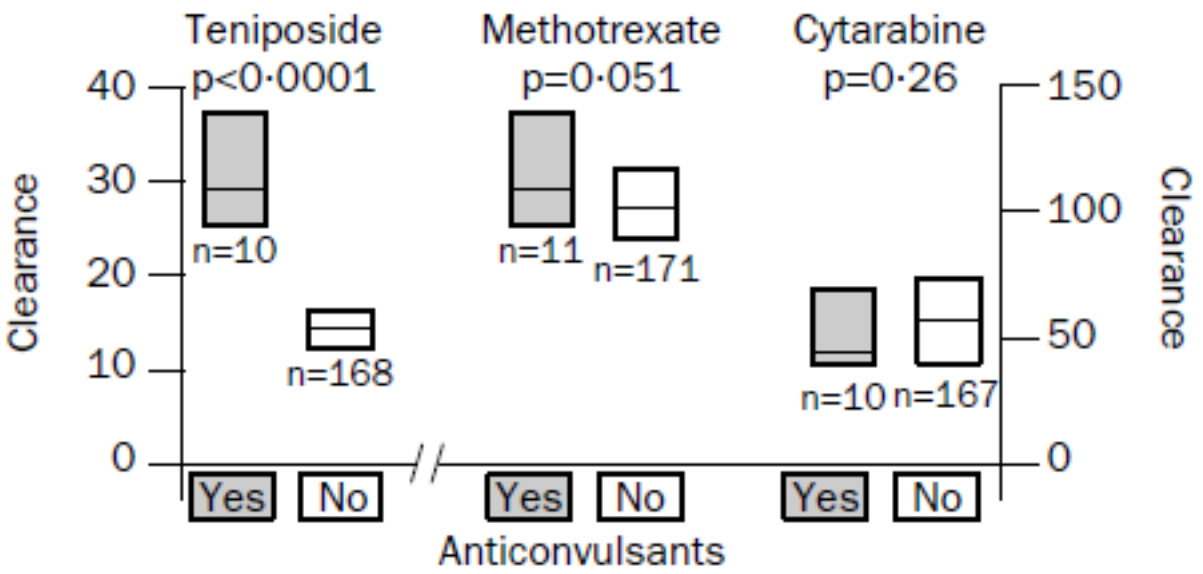
Thanks to Oscar Hunter recipient William Evans for the slide

Thanks to Oscar Hunter recipient Elliott Vesell for the original, *Pharm. Ther.* 1989

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



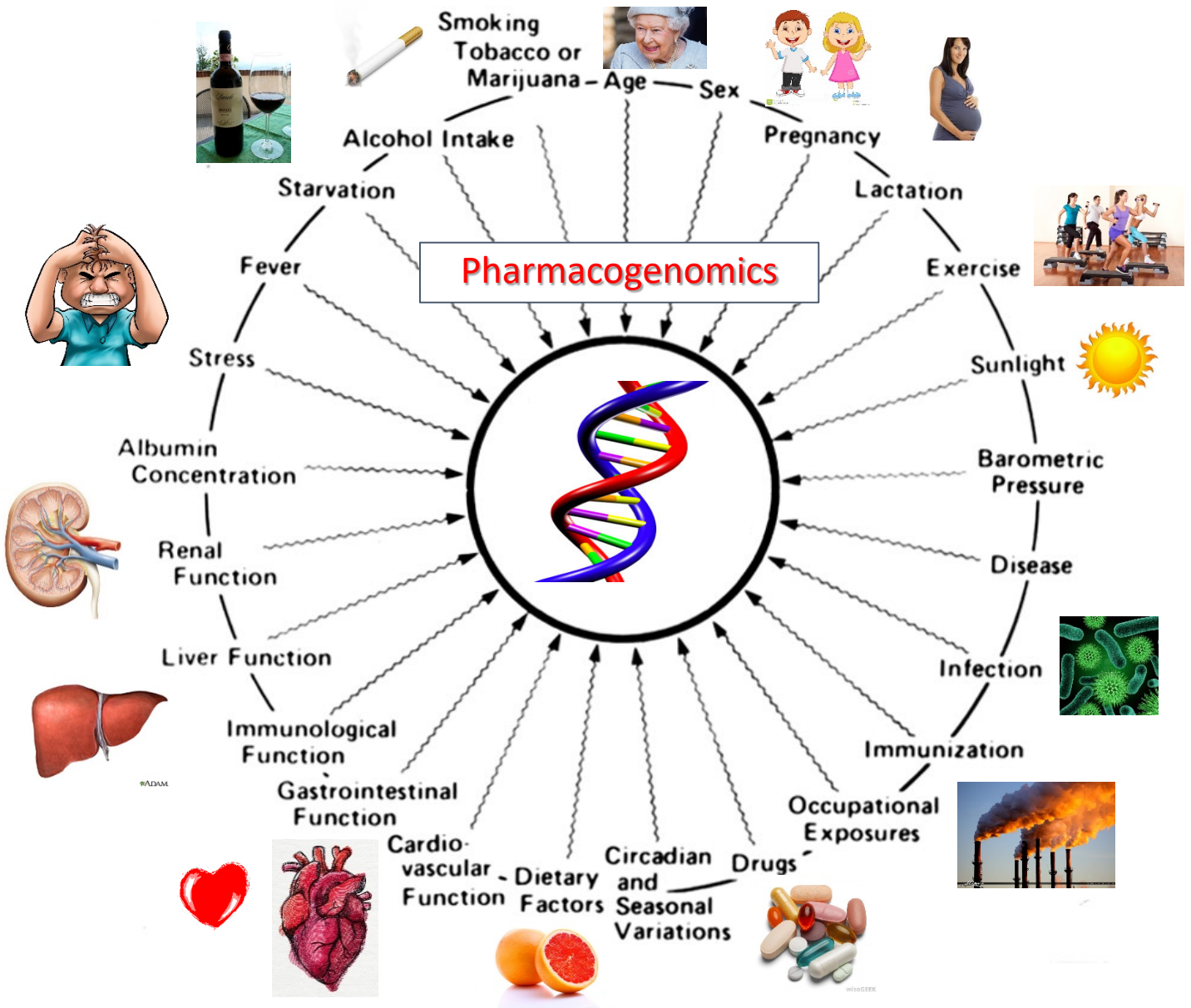


Lancet 2000

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



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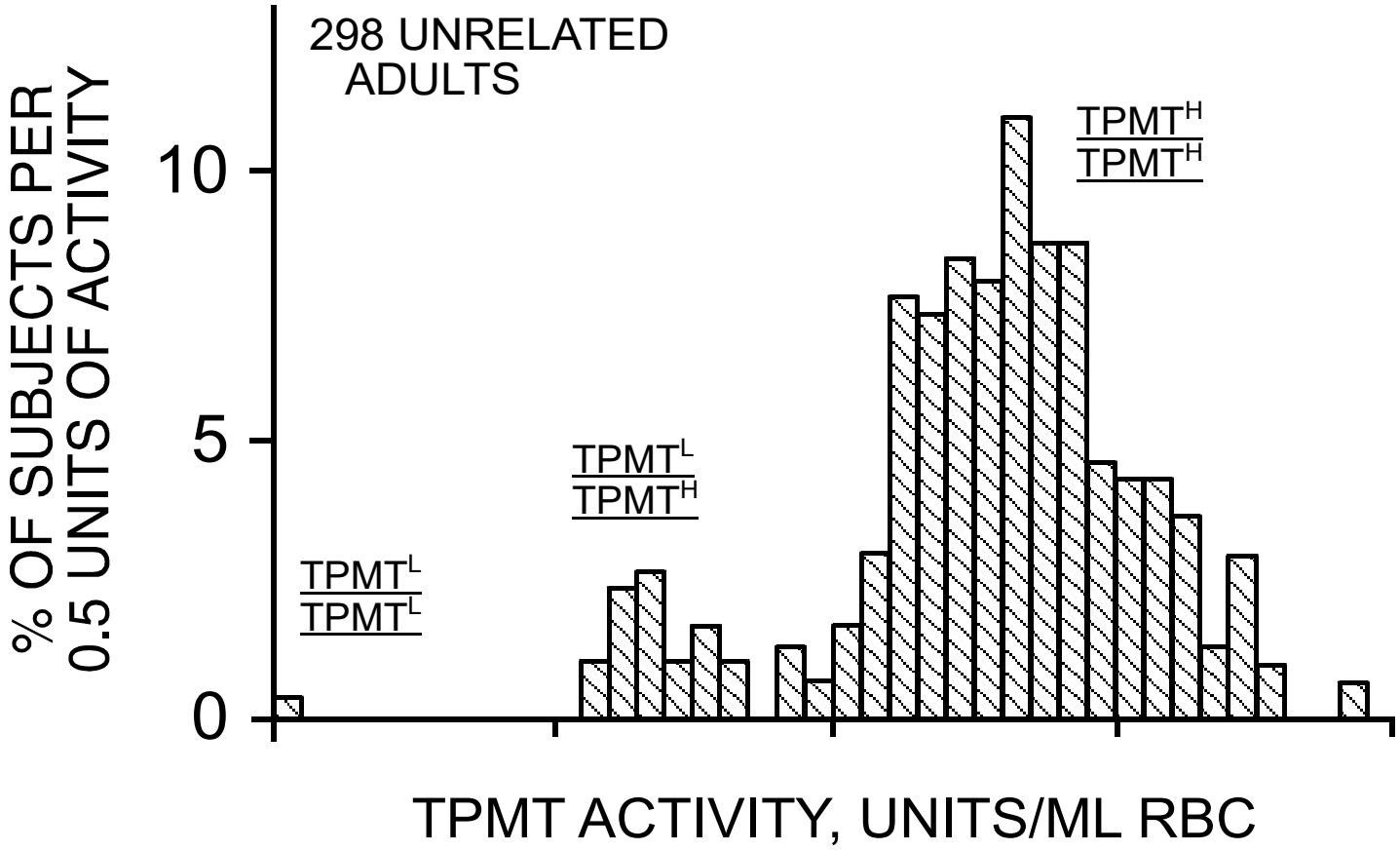
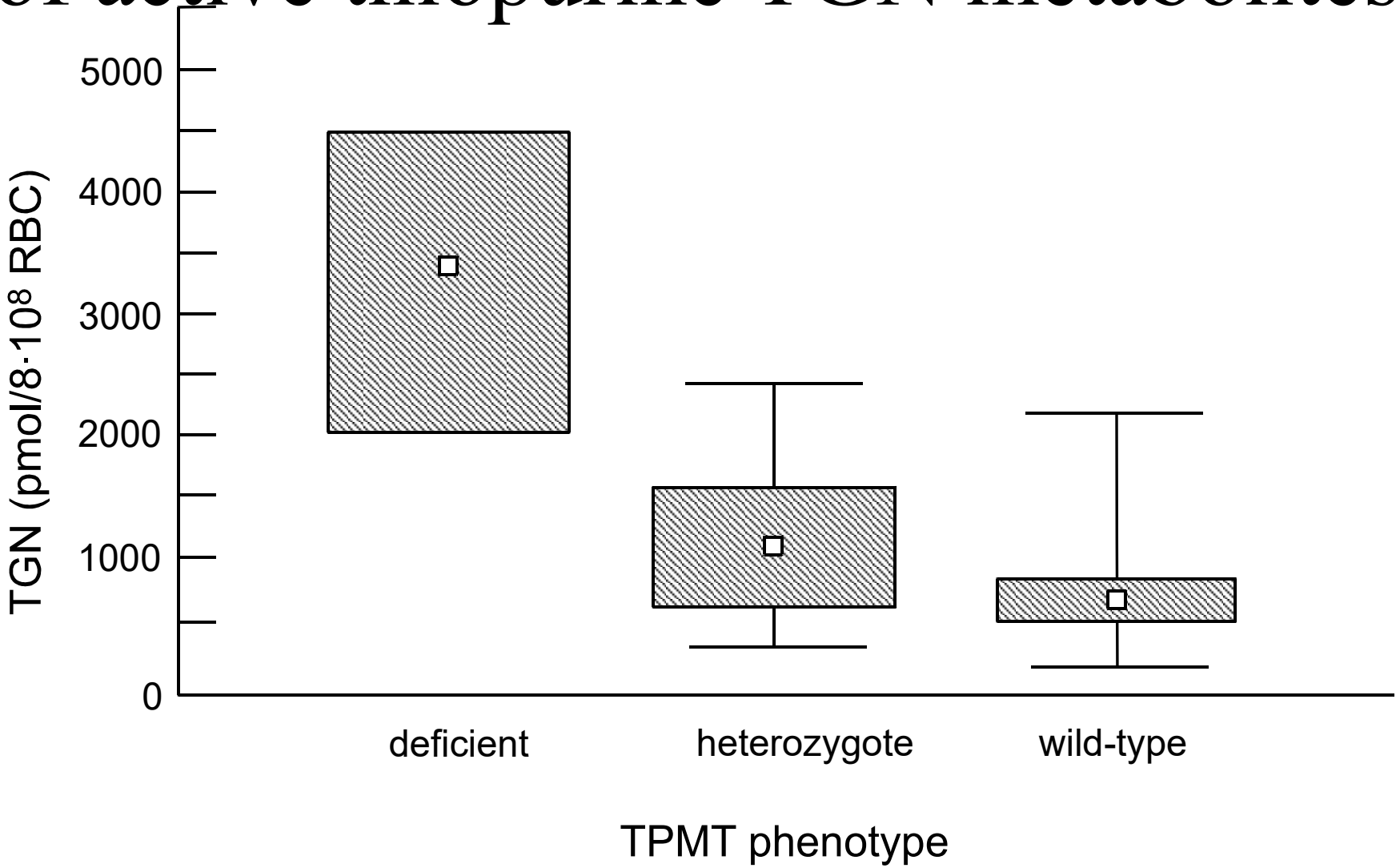
HUMAN RBC TPMT



Weinshilboum and Sladek
Am J Hum Gen 32(5):651-62, 1980

TPMT phenotype determines concentrations of active thiopurine TGN metabolites



Krynetski and Evans
Pharm Res 16(3):342-9, 1999

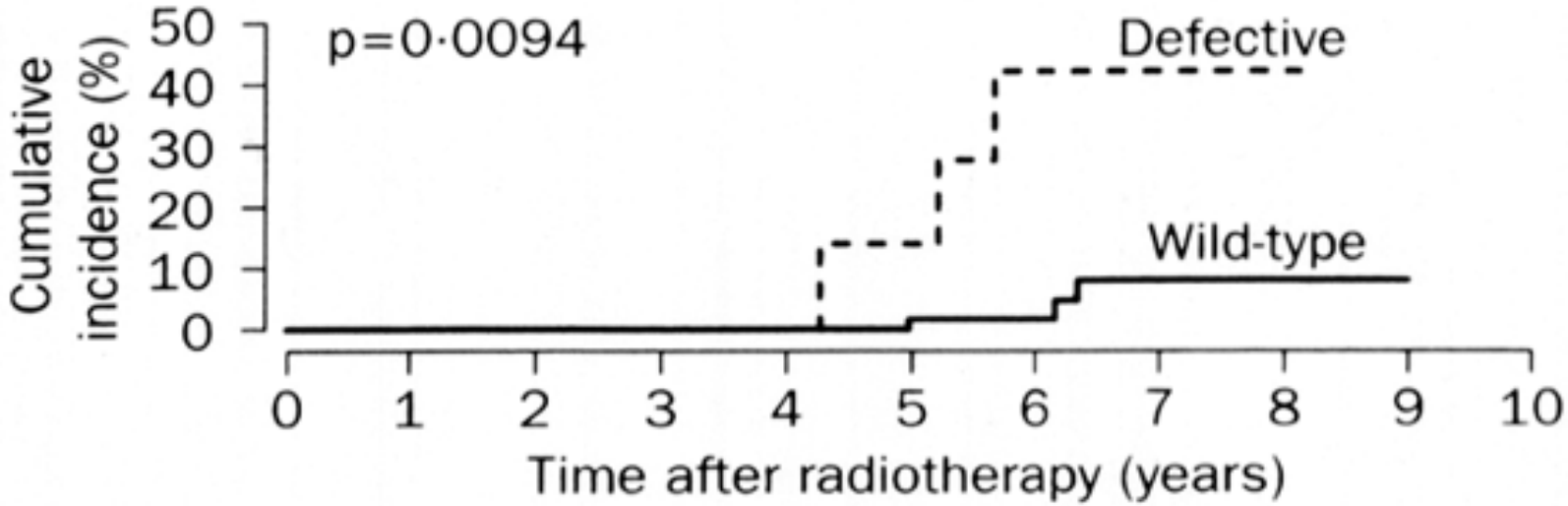
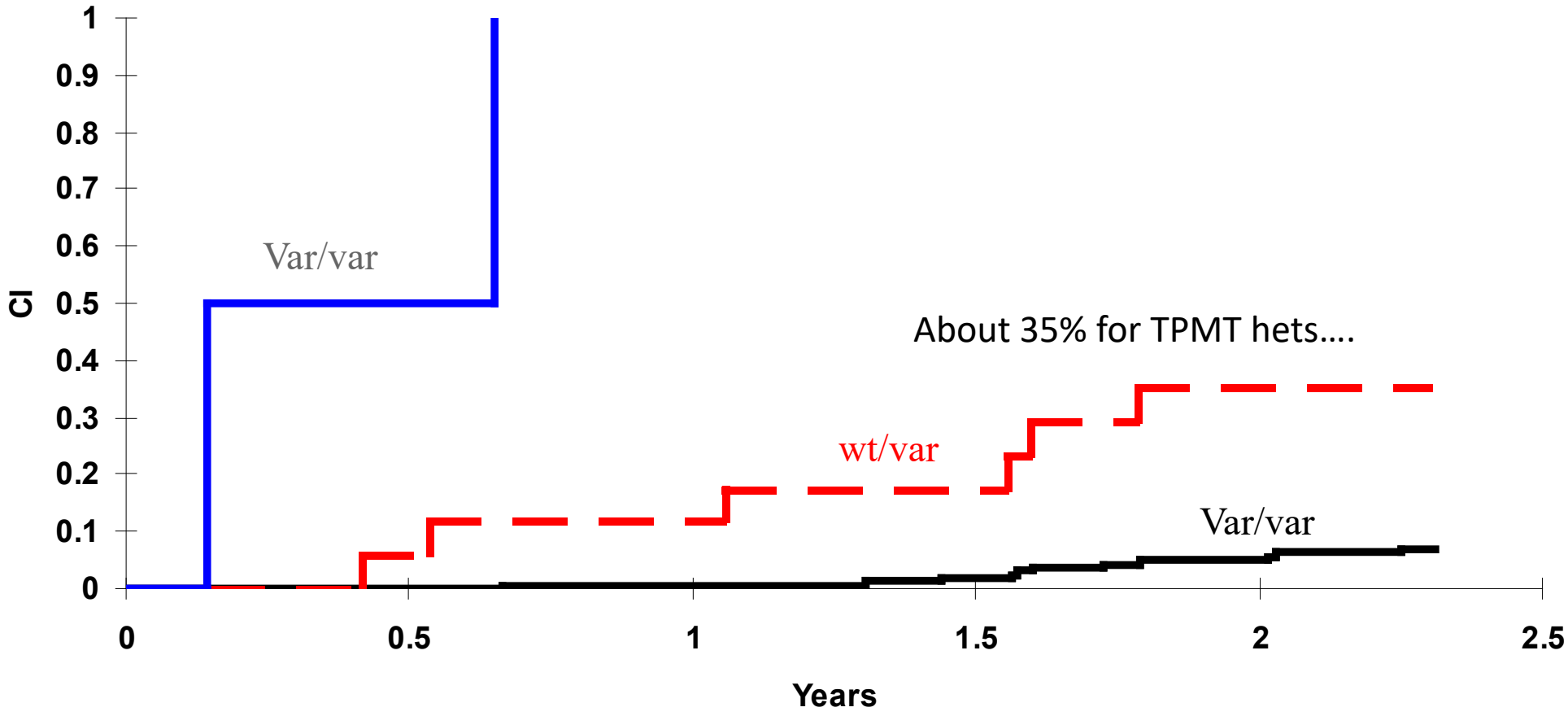


Figure 3: **Estimated cumulative incidence of radiation-associated secondary malignant brain tumour for seven children in Total XII who received preventive cranial radiotherapy and had genetic defects in thiopurine methyltransferase compared with 45 with wild-type status**

Relling, et al., *Lancet* 354:34-39, 1999

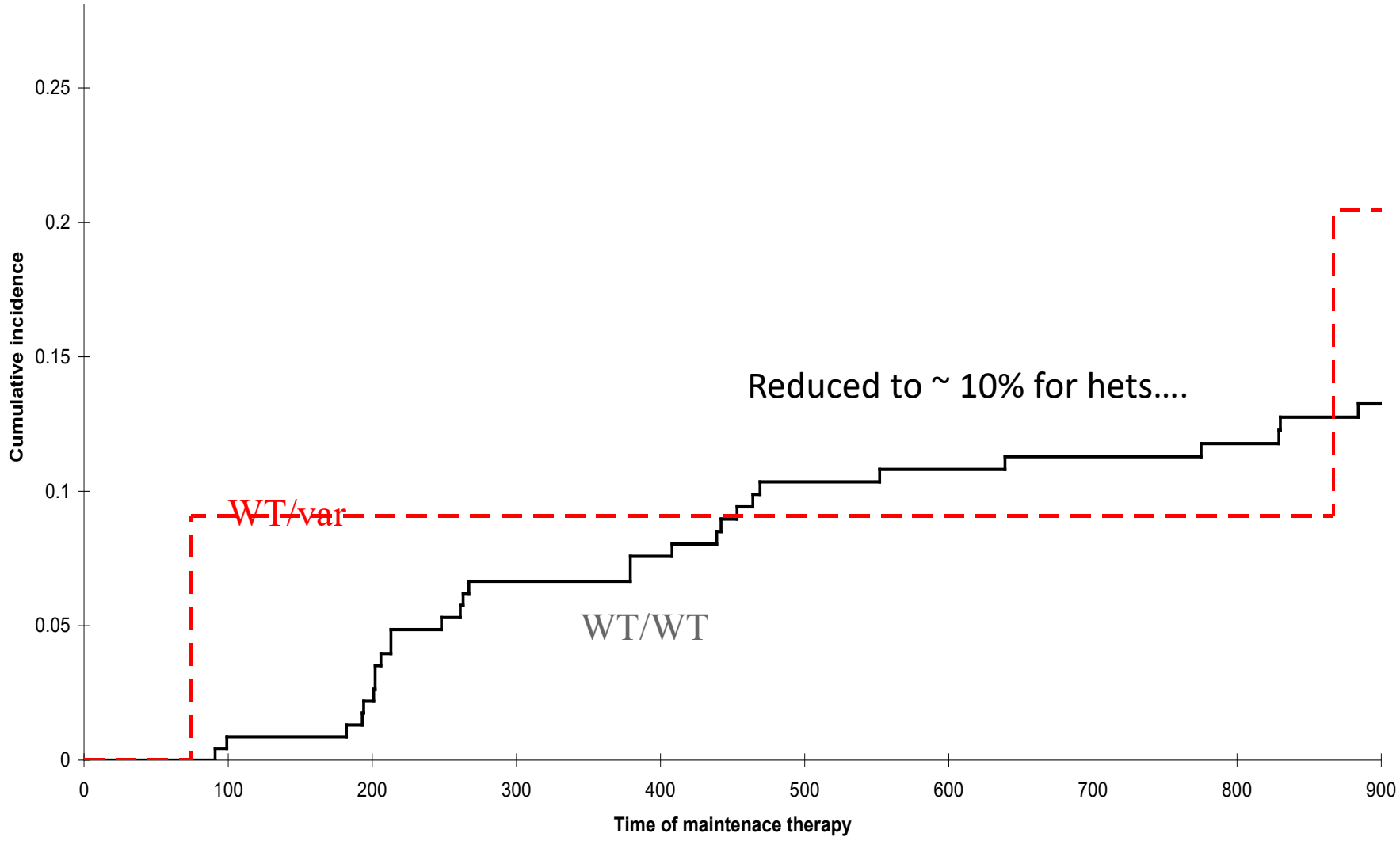
Myelosuppression was related to TPMT genotype on Total XII
(BEFORE we started adjusting doses based on TPMT testing)



Relling et al JNCI, 1999

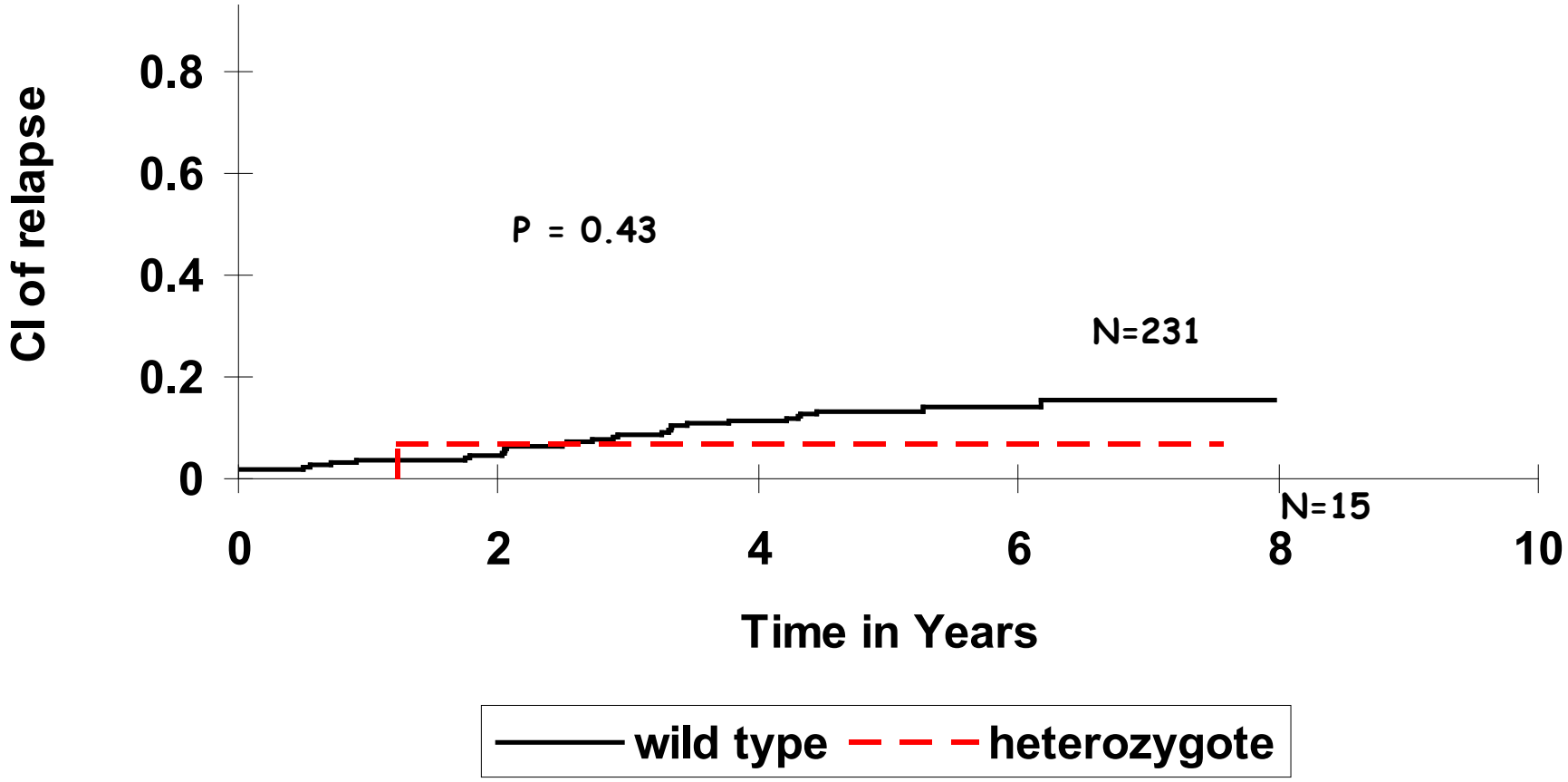
Myelosuppression was not related to TPMT genotype on Total XIII

(AFTER we started adjusting doses based on TPMT testing)



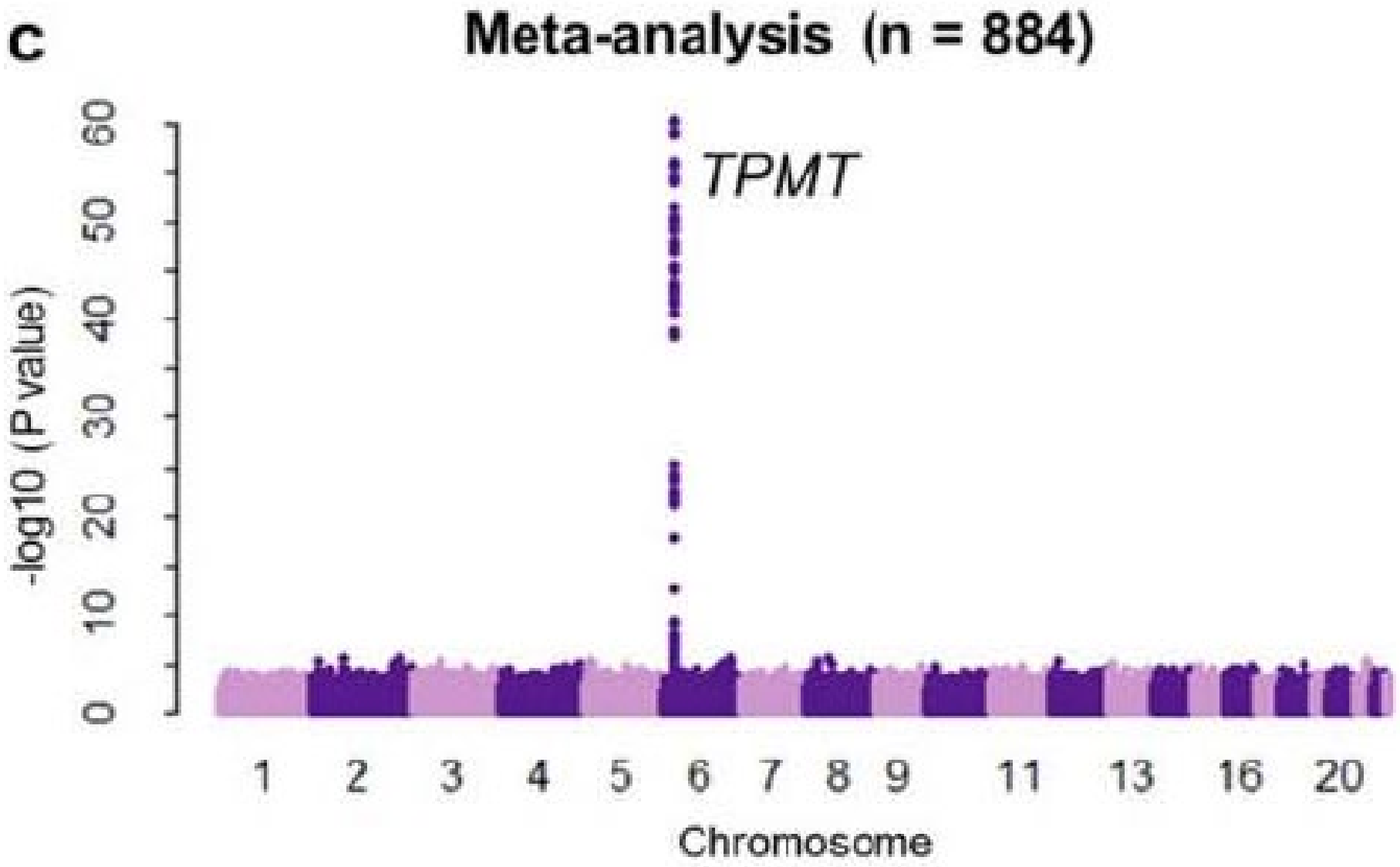
Stocco et al *Clin Pharm Ther* 2009

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



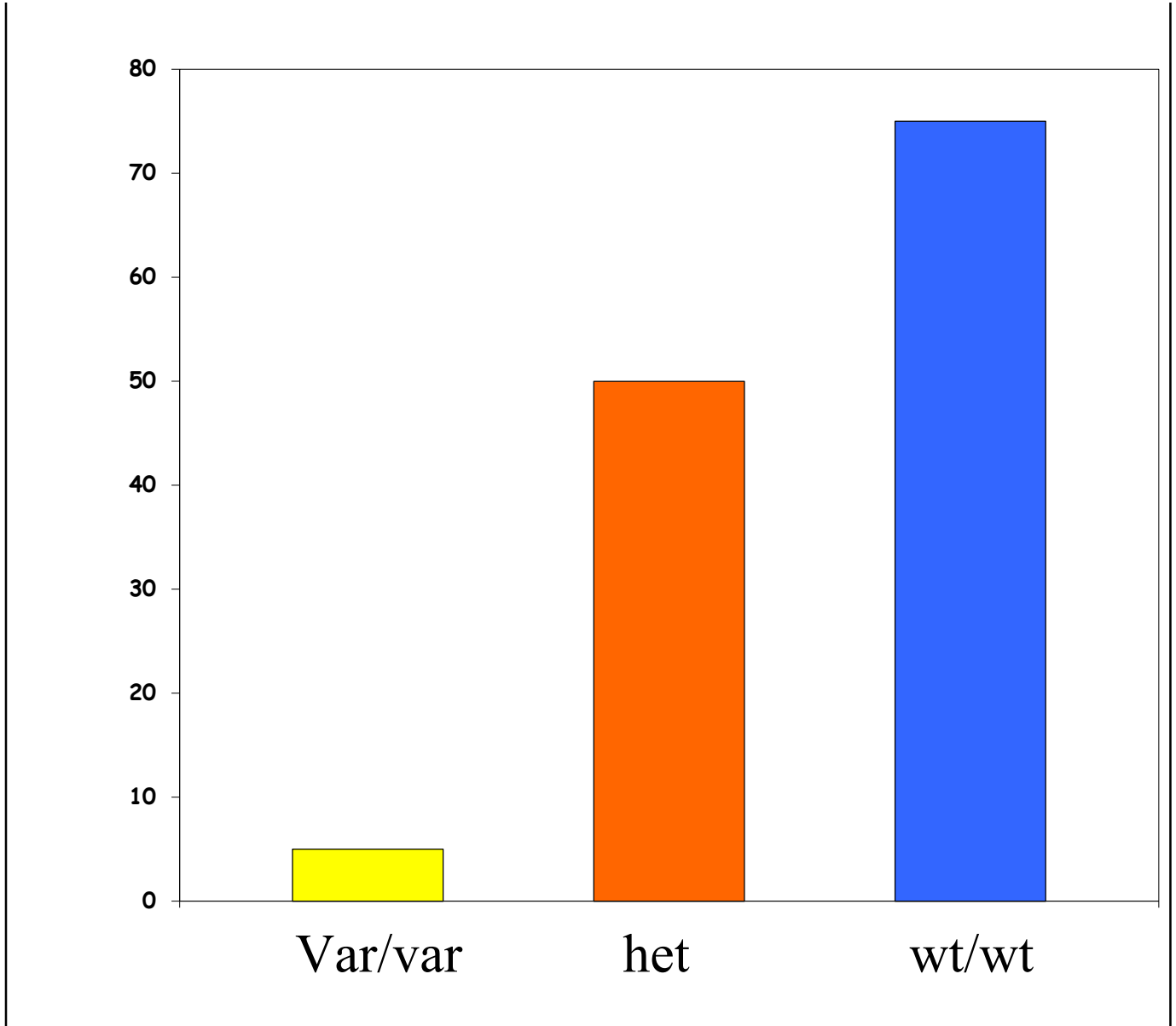
Relling et al, *Blood*, 2006

TPMT activity is a monogenic trait; a handful of variants account for > 95% of low activity variants

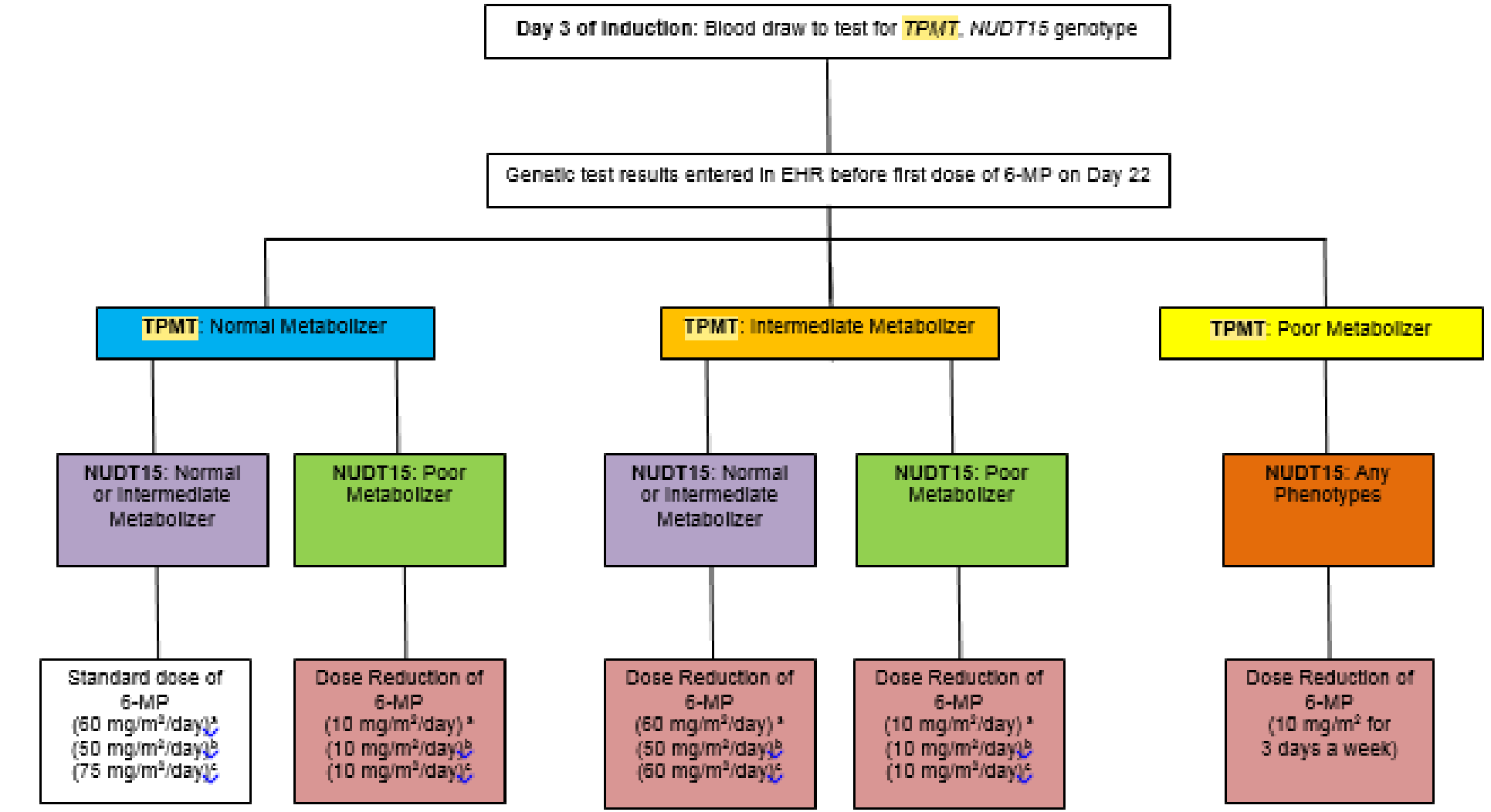


Liu et al, CPT, 2017

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



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[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]

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT*15 Genotypes: 2018 Update

Mary V. Relling[1], Matthias Schwab[2,3,4], Michelle Whirl-Carrillo[5], Guilherme Suarez-Kurtz[6], Ching-Hon Pui[7], Charles M. Stein[8], Ann M. Moyer[9], William E. Evans[1], Teri E. Klein[4], Federico Guillermo Antillon-Klussmann[10,11], Kelly E. Caudle[1], Motohiro Kato[12], Allen E.J. Yeoh[13,14], Kjeld Schmiegelow[15,16] and Jun J. Yang[1]

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?

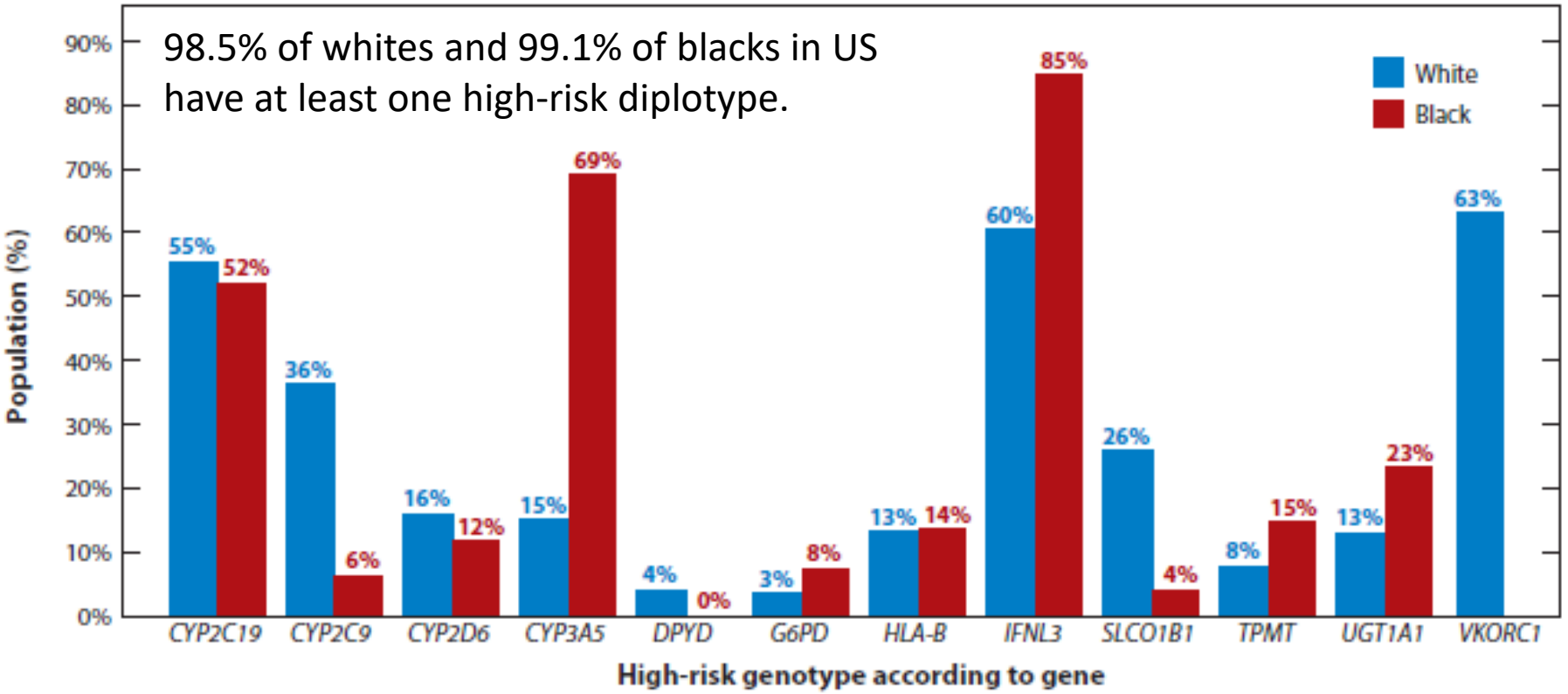
- There are multiple high-evidence gene drug pairs ready for clinical implementation
- All patients are at reasonably high risk to receive at least one high risk drug for at least one of those loci --- especially over a lifetime—so the chance that genotype data will be used is high
- Preemptive genotyping 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….

Use of 33 “Pharmacogenetically High Risk” Drugs in St. Jude patients (11 CPIC genes)

Abacavir	Methylene blue
Amitriptyline	Metoprolol
Aripiprazole	Nitrofurantoin
Aspirin	Olanzapine
Azathioprine	
Capecitabine	
Clopidogrel	
Codeine	
Dapsone	Risperidone
Fluorouracil	Sertraline
Fluoxetine	Sulfamethoxazole-trimethoprim
Haloperidol	Sulfasalazine
Hydroxychloroquine	Thioguanine
Irinotecan	Tramadol
Lidocaine	Voriconazole
Menthol	Warfarin

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



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

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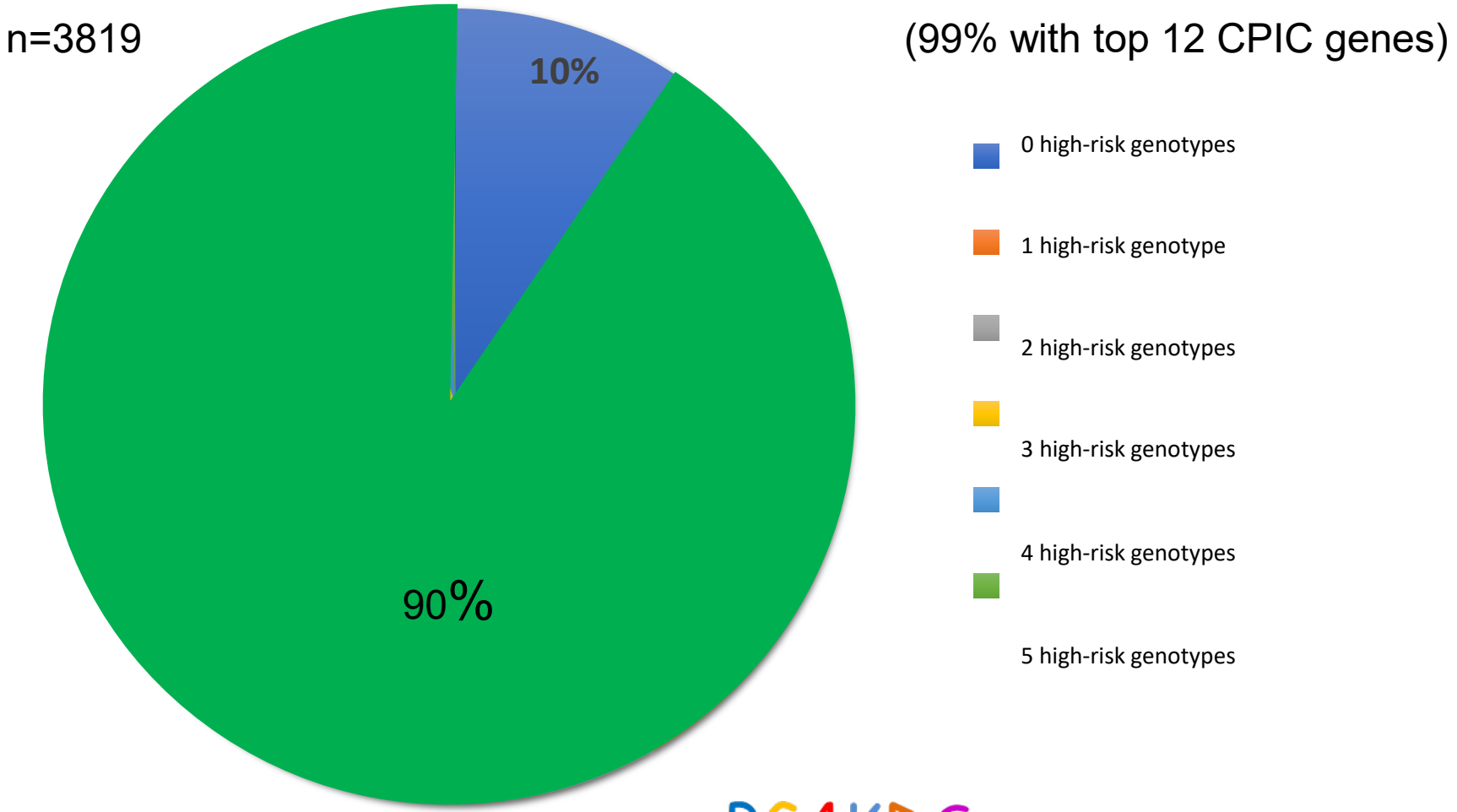
90% of patients have at least one high-risk genotype in their EHR (9 genes)



PG4KDS

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

Clin Pharmacol Ther. 2011 89:464-7; updated 2017.

- 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

PharmGKB

PGRN

Research Directions in the Clinical Implementation of Pharmacogenomics: An Overview of US Programs and Projects

Simona Volpi[1], Carol J. Bult[2], Rex L. Chisholm[3], Patricia A. Deverka[4], Geoffrey S. Ginsburg[5], Howard J. Jacob[6], Melpomeni Kasapi[1], Howard L. McLeod[7], Dan M. Roden[8], Marc S. Williams[9], Eric D. Green[1], Laura Lyman Rodriguez[1], Samuel Aronson[10], Larisa H. Cavallari[11], Joshua C. Denny[12], Lynn G. Dressler[13], Julie A. Johnson[11], Teri E. Klein[14], J. Steven Leeder[15], Micheline Piquette-Miller[16], Minoli Perera[17], Laura J. Rasmussen-Torvik[18], Heidi L. Rehm[19], Marylyn D. Ritchie[20], Todd C. Skaar[21], Nikhil Wagle[22], Richard Weinshilboum[23], Kristin W. Weitzel[24], Robert Wildin[25], John Wilson[26], Teri A. Manolio[1] and Mary V. Relling[27]

Volpi et al Clin Pharm Ther 2018

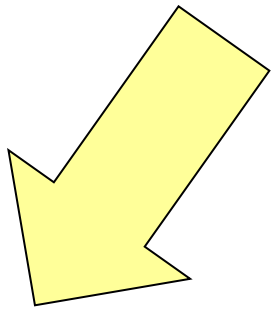
Resources used by implementers: 34/36 use CPIC

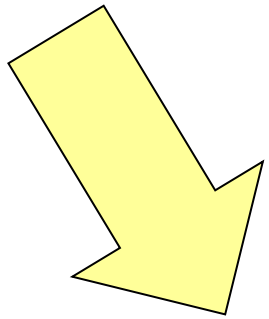
Table 1 Resources of value for PGx implementation

Resource	Description	URL
Pharmacogenomics Research Network (PGRN)	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.	http://www.pgrn.org/
PharmGKB	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.	https://www.pharmgkb.org/
PharmCAT	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.	https://github.com/PharmGKB/PharmCAT
Clinical Pharmacogenetics Implementation Consortium (CPIC)	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.	https://cpicpgx.org/

Volpi et al Clin Pharm Ther 2018

We are approaching implementation on 2 fronts at St. Jude





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St. Jude Children's Research Hospital
PG4KDS Protocol

STANFORD UNIVERSITY

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

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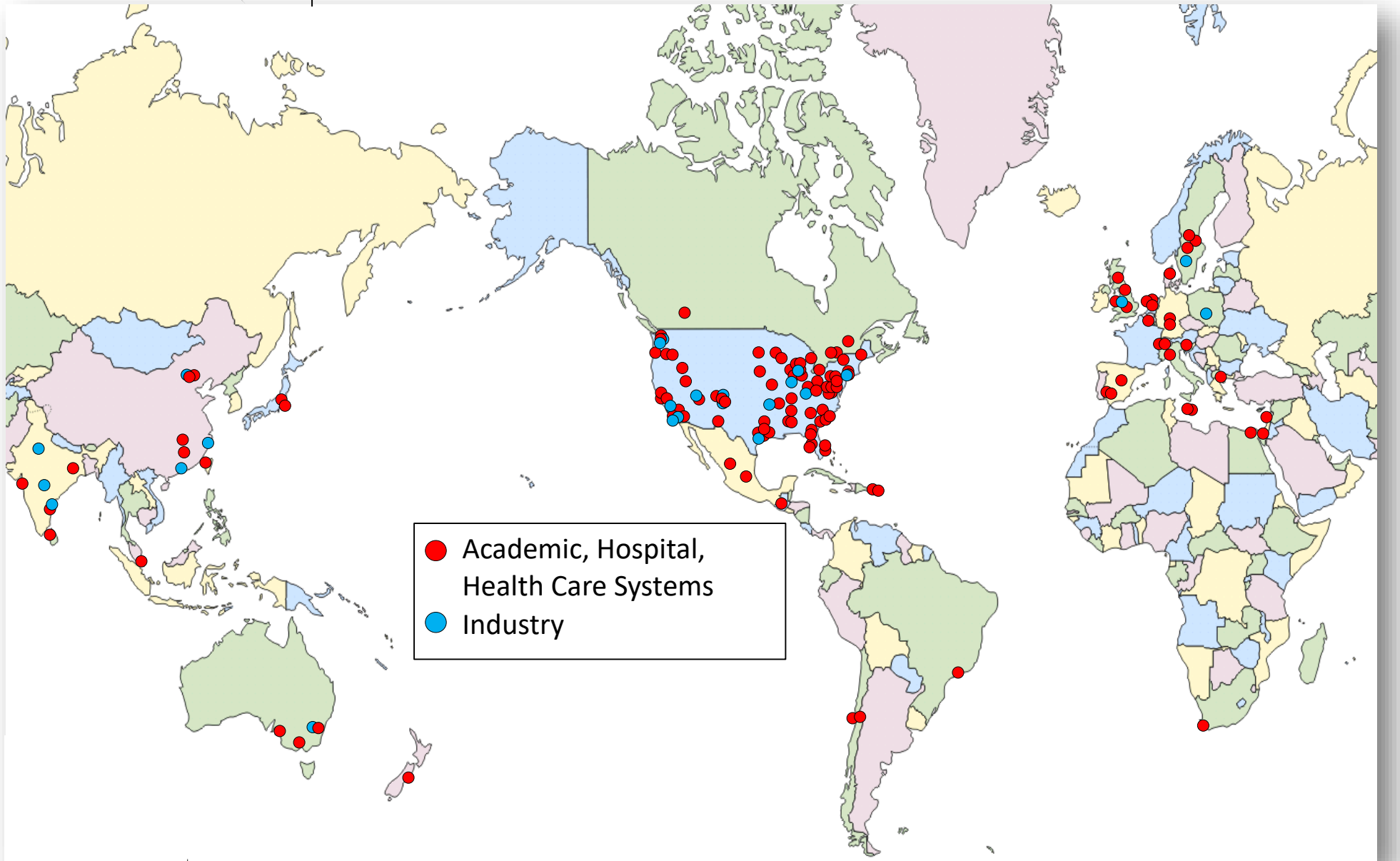
>300 members



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

MS Hershfield[1,2], JT Callaghan[3,4,5], W Tassaneeyakul[6], T Mushiroda[7], CF Thorn[8], TE Klein[8] and MTM Lee[9,10,11]

Clin Pharmacol Ther. 2013 Feb;93(2):153-8

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks[1], JJ Swen[2], CF Thorn[3], K Sangkuhl[3], ED Kharasch[4], VL Ellingrod[5,6], TC Skaar[7], DJ Müller[8], A Gaedigk[9] and JC Stingl[10]

Clin Pharmacol Ther. 2013 May;93(5):402-8.

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

SG Leckband[1,2], JR Kelsoe[1,2], HM Dunnenberger[3], AL George Jr[4], E Tran[1], R Berger[1], DJ Müller[5,6], M Whirl-Carrillo[7], KE Caudle[3] and M Pirmohamed[8]

Clin Pharmacol Ther. 2013 Sep;94(3):324-8.

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

MV Relling[1], EE Gardner[2], WJ Sandborn[3], K Schmiegelow[4,5], C-H Pui[6], SW Yee[7], CM Stein[8], M Carrillo[9], WE Evans[1], JK Hicks[1], M Schwab[10,11] and TE Klein[9]

Clin Pharmacol Ther. 2013 Apr;93(4):324-5.

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update

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

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 Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12]

CPIC™
Clinical Pharmacogenetics Implementation Consortium

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update

JA Johnson[1], KE Caudle[2], L Gong[3], M Whirl-Carrillo[3], CM Stein[4], SA Scott[5], MT Lee[6], BF Gage[7], SE Kimmel[8,9], MA Perera[10], JL Anderson[11], M Pirmohamed[12], TE Klein[3], NA Limdi[13], LH Cavallari[1] and M Wadelius[14]

CPIC® Guideline for Clopidogrel and CYP2C19

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 update (September 2013)

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 figure 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 figure provided in the main manuscript of the guideline:

Table 1. Assignment of likely phenotypes based on diplotypes
Table 2. Dosing recommendations for tricyclic antidepressants based on CYP2D6 phenotype
Table 3. Dosing recommendations for the tertiary amines amitriptyline, 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 figure provided in the main manuscript of the guideline:

Table 1. Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes
Table 2. Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype
Figure 3. Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism or see PharmGKB Codeine and Morphine Pathway, Pharmacokinetics

CPIC® Guideline for Fluoropyrimidines and DPYD

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing (December 2013)

Updates since publication:

May 2014: The CPIC authors recommend that the *DPYD*4, *5, *6* and **9A* alleles be categorized as "normal" activity, in part based upon the recent publication Comparative Functional Analysis of DPYD Variants of Potential Clinical Relevance to Dihydropyrimidine Dehydrogenase Activity.

Tables provided in the main manuscript of the guideline:

Table 1. Assignment of likely DPD phenotype based on genotype
Table 2. Recommended dosing of fluoropyrimidines by DPD phenotype

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, VKORC*1 – 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

https://cpicpgx.org/guidelines/

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, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

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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

2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – 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

https://cpicpgx.org/guidelines/

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, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

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2017

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

2018

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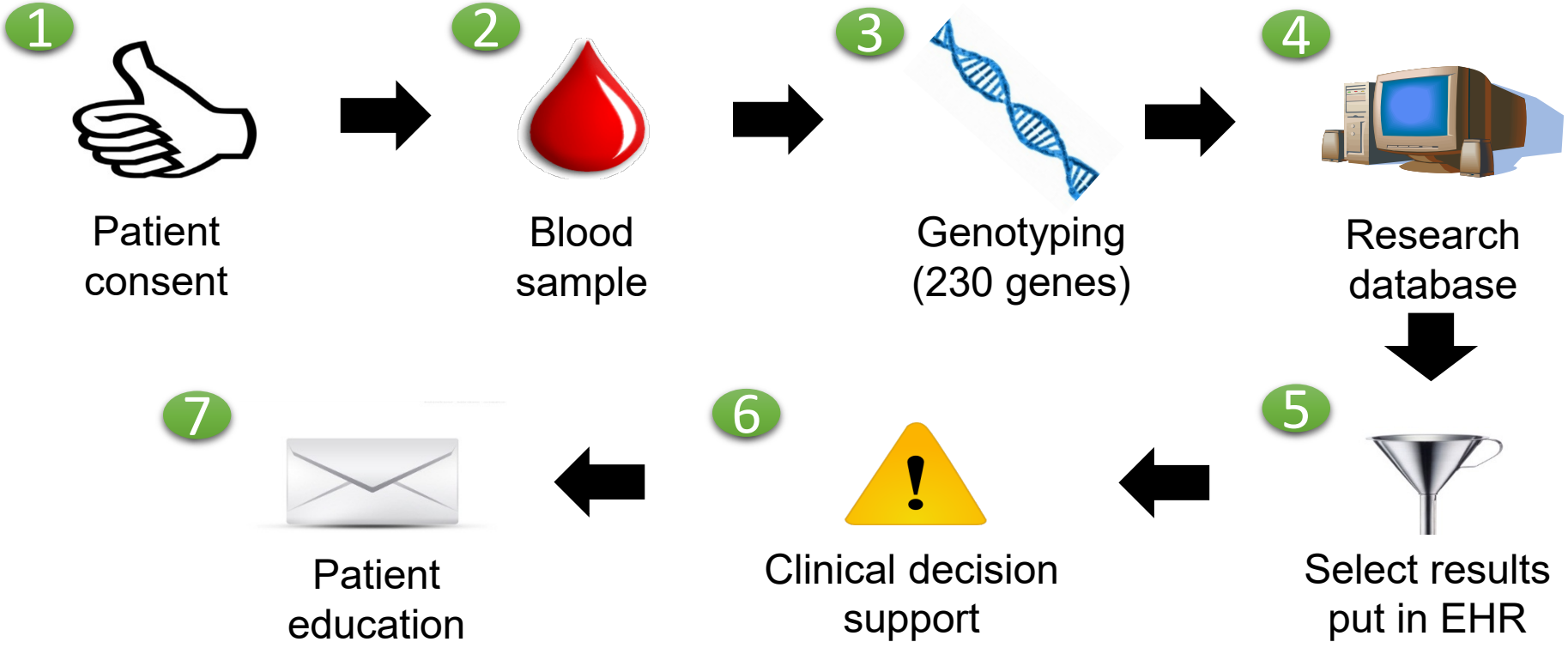
- *CYP2C19*/PPI
- *CYP2C9*/HLA-phenytoin—UPDATE
- *CYP2C9*/celecoxib
- CYP2D6/codeine-UPDATE

PG4KDS: The Process



Hoffman JM, et al. *Am J Med Genet C Semin Med Genet*. 2014;166C:45.

PG4KDS

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

Genotyping at Medical College of Wisconsin, now RPRD

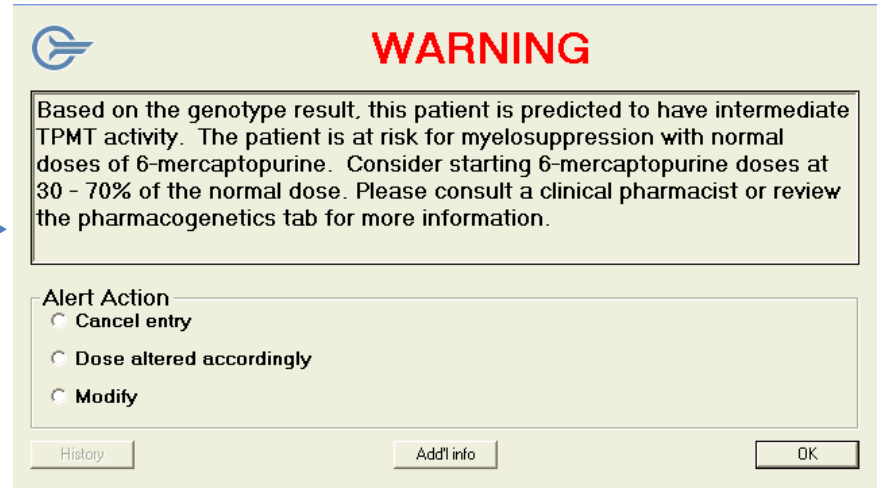
Pharmaceutical Sciences Research database (>225 genes parsed into separate files)

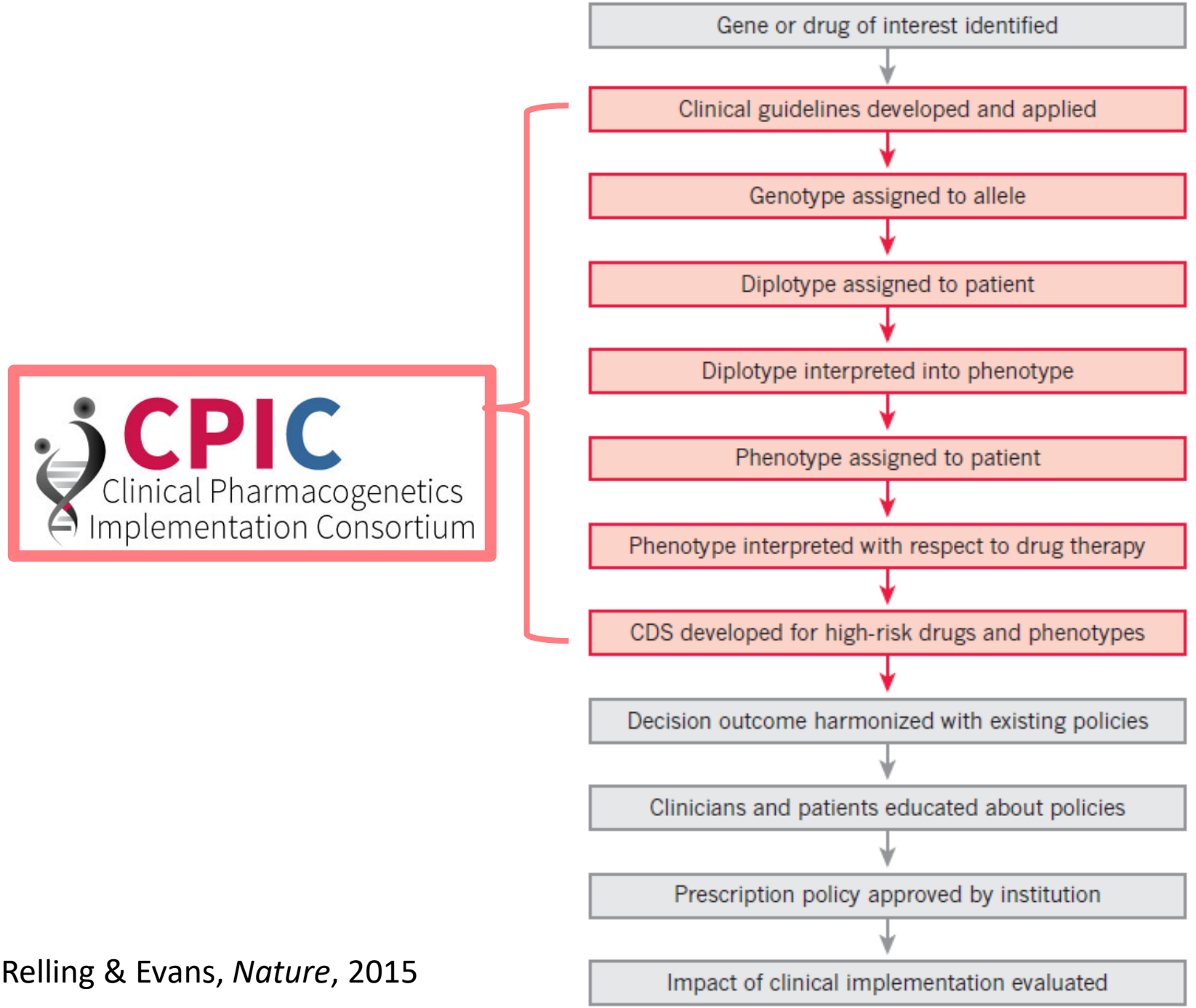
TPMT	*DPYD*	*CYP3A4*	*GSTT1*	*CYP4B1*
CYP2C19	*VKORC1*	*CYP2F1*	*NAT1*	*CYP1A1*
CYP2D6	*SLCO1B1*	*CYP2J2*	*FMO3*	*CYP2C18*
CYP2C9	*G6PD*	*UGT1A1*	*CYP4F2*	*ABCC1*

- *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





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

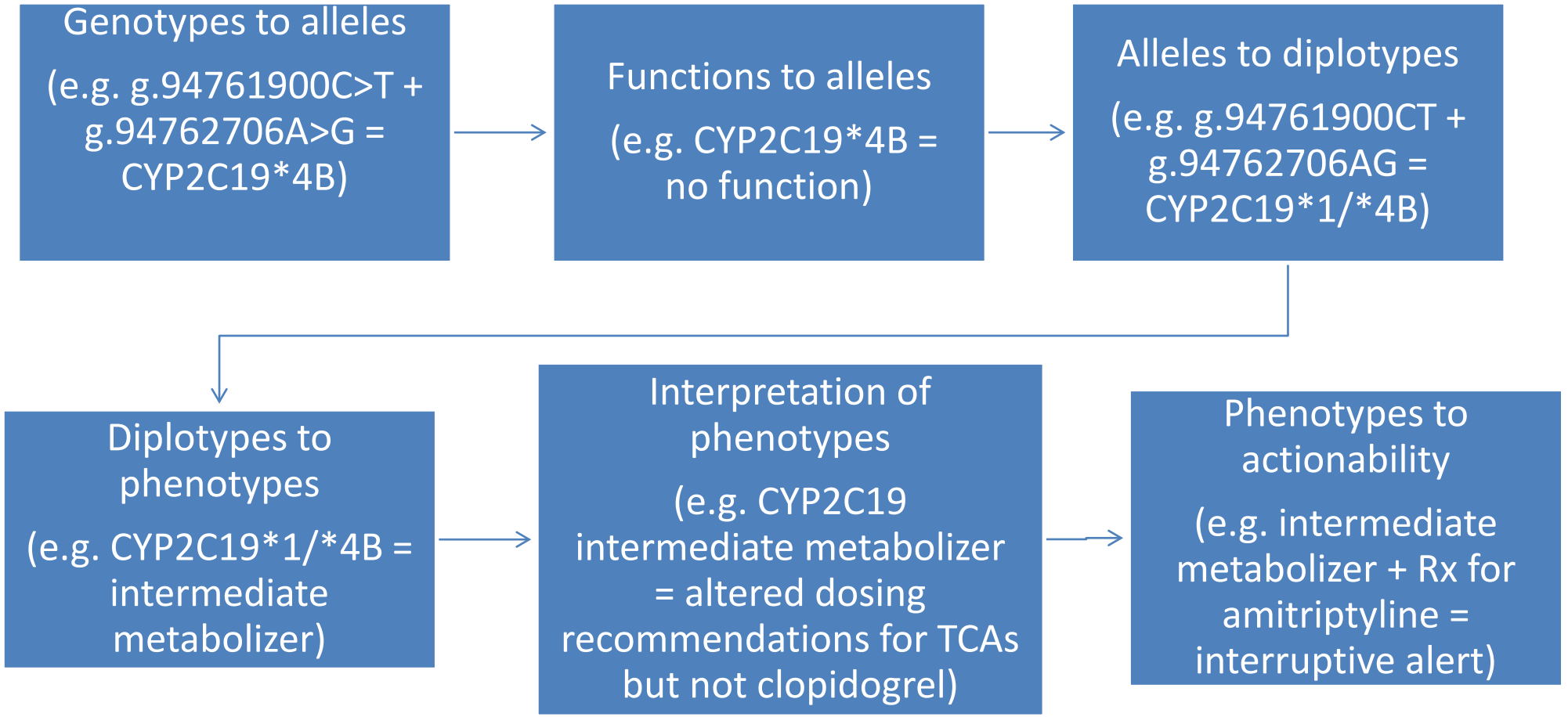
Table 1. Assignment of likely CYP2C29 phenotype based on genotypes
Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients
Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

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[a]

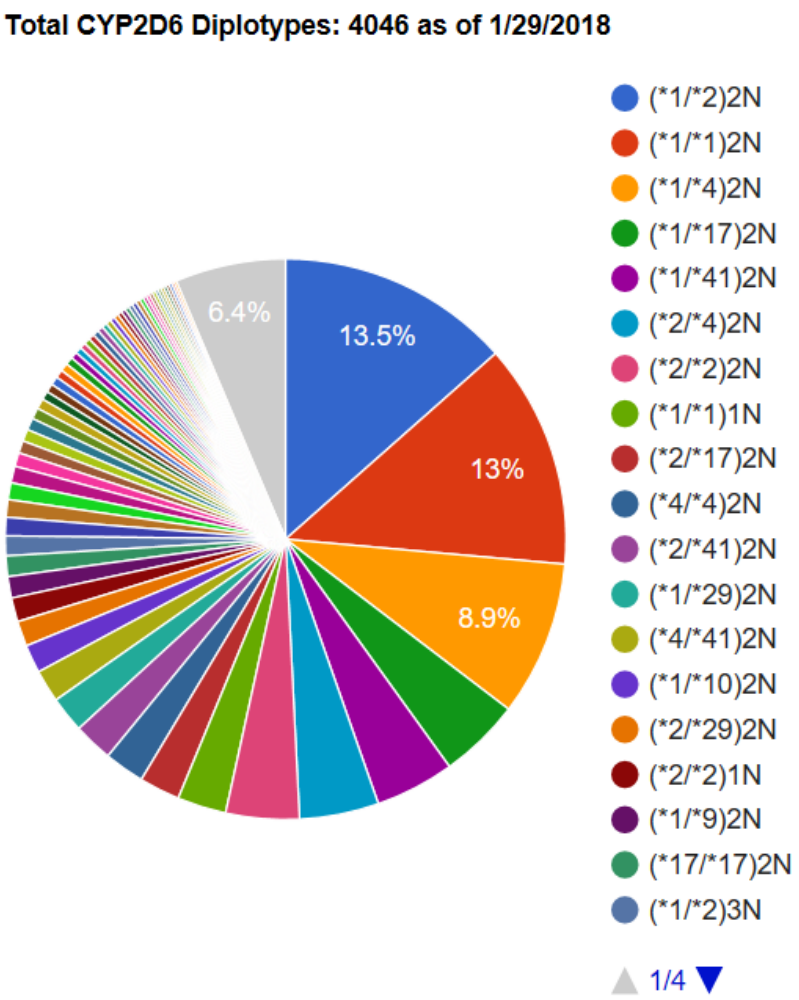
Levels of Evidence Linking Genotype to Phenotype
CYP2C19 Allele Definition Table
CYP2C19 Allele Functionality Table
CYP2C19 Frequency Table
CYP2C19 Diplotype-Phenotype Table
Gene Resource Mapping *CYP2C19* Gene Resource Mappings

CPIC tables allow translation of genetic test results to actionability

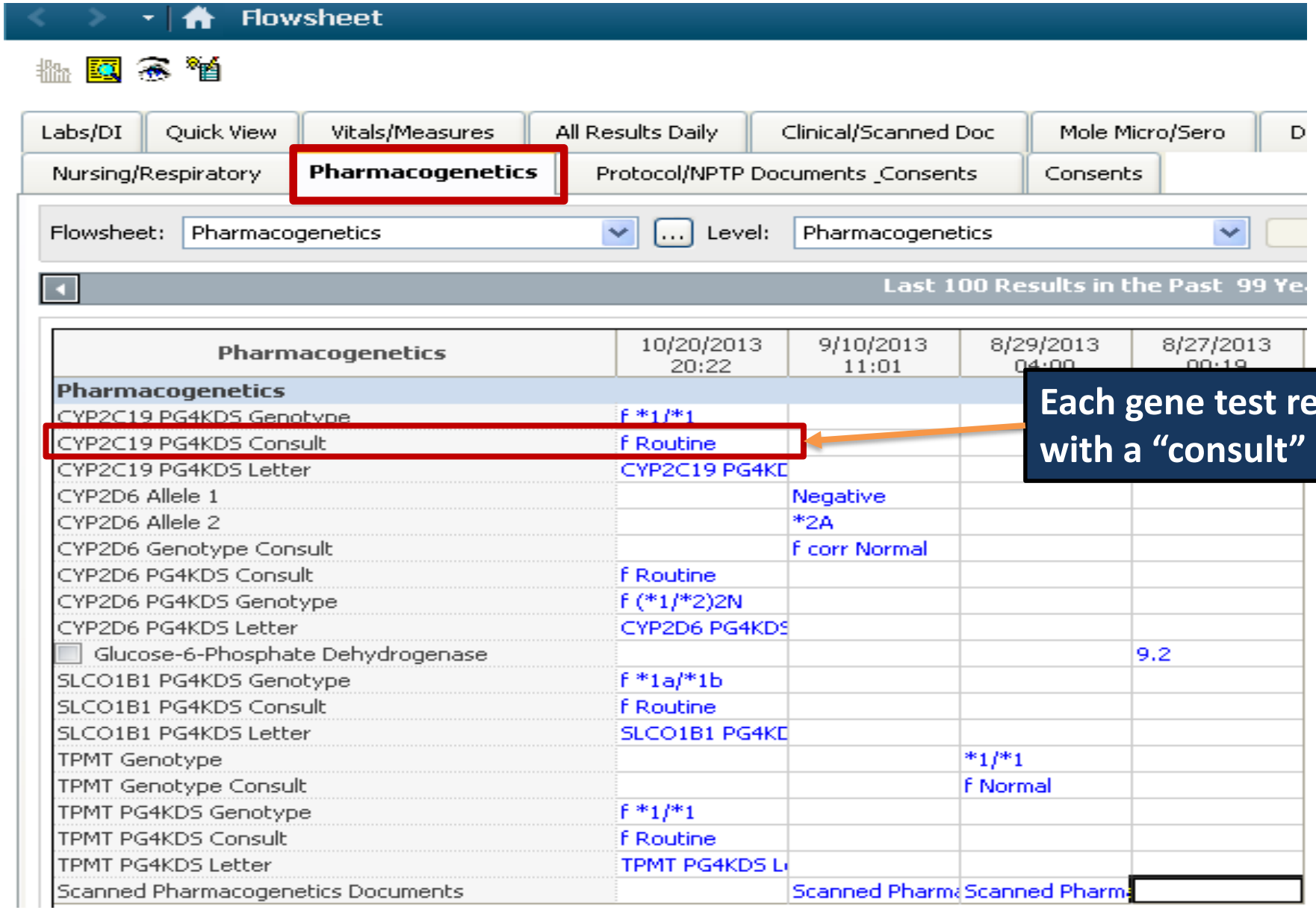


https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials

CYP2D6: 207 diplotypes observed in first 4046 pts on PG4KDS

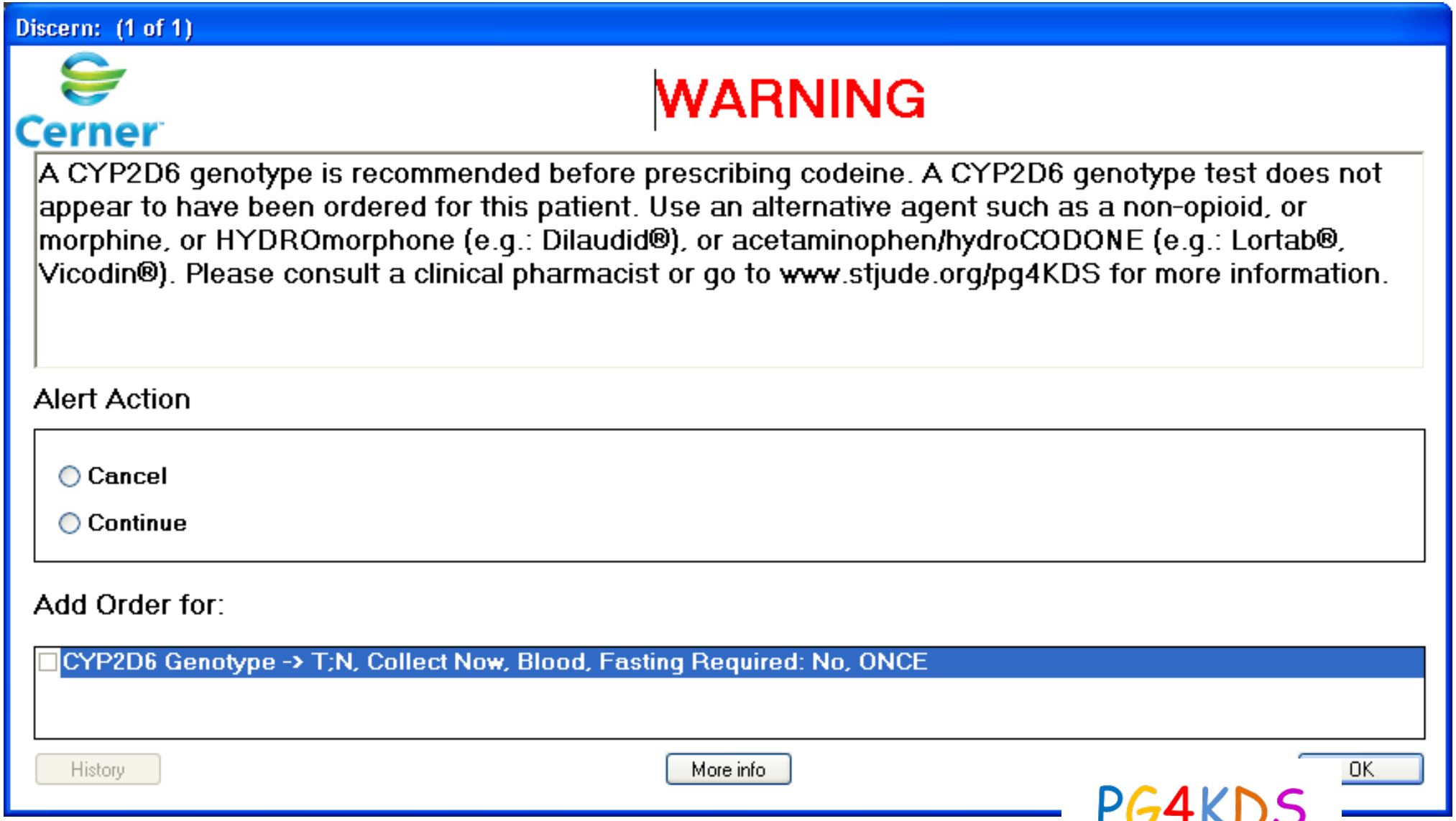


Dedicated Pharmacogenetics Section in EHR: not encounter-specific

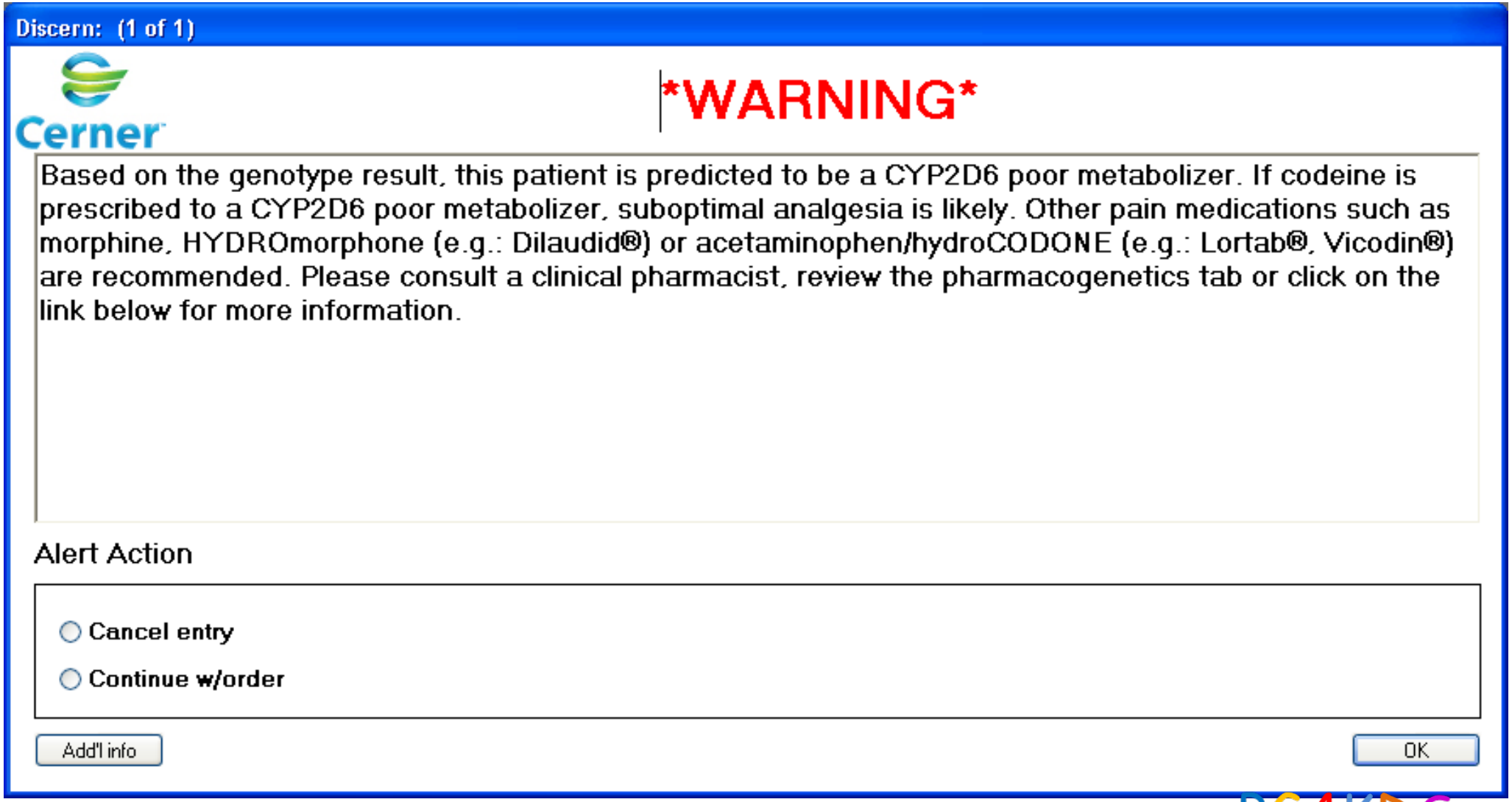


Pharmacogenetics	10/20/2013 20:22	9/10/2013 11:01	8/29/2013 04:00	8/27/2013 00:19
Pharmacogenetics				
CYP2C19 PG4KDS Genotype	f *1/*1			
CYP2C19 PG4KDS Consult	f Routine			
CYP2C19 PG4KDS Letter	CYP2C19 PG4KD			
CYP2D6 Allele 1		Negative		
CYP2D6 Allele 2		*2A		
CYP2D6 Genotype Consult		f corr Normal		
CYP2D6 PG4KDS Consult	f Routine			
CYP2D6 PG4KDS Genotype	f (*1/*2)2N			
CYP2D6 PG4KDS Letter	CYP2D6 PG4KDS			
Glucose-6-Phosphate Dehydrogenase				9.2
SLCO1B1 PG4KDS Genotype	f *1a/*1b			
SLCO1B1 PG4KDS Consult	f Routine			
SLCO1B1 PG4KDS Letter	SLCO1B1 PG4KD			
TPMT Genotype			*1/*1	
TPMT Genotype Consult			f Normal	
TPMT PG4KDS Genotype	f *1/*1			
TPMT PG4KDS Consult	f Routine			
TPMT PG4KDS Letter	TPMT PG4KDS L			
Scanned Pharmacogenetics Documents		Scanned Pharma	Scanned Pharm	

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

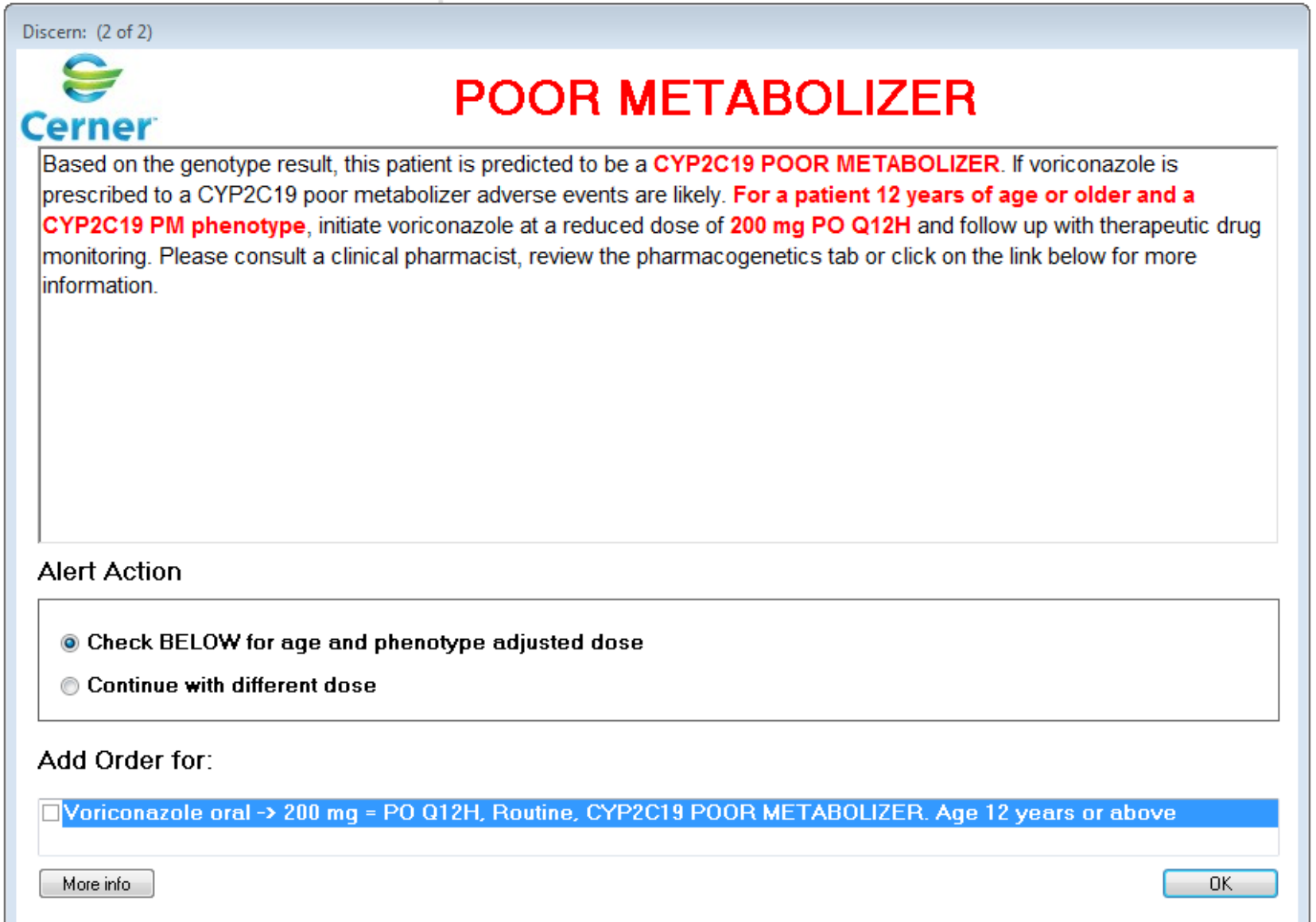


Post-test alerts contain prescribing recommendations based on the PRESENCE of a high risk test result



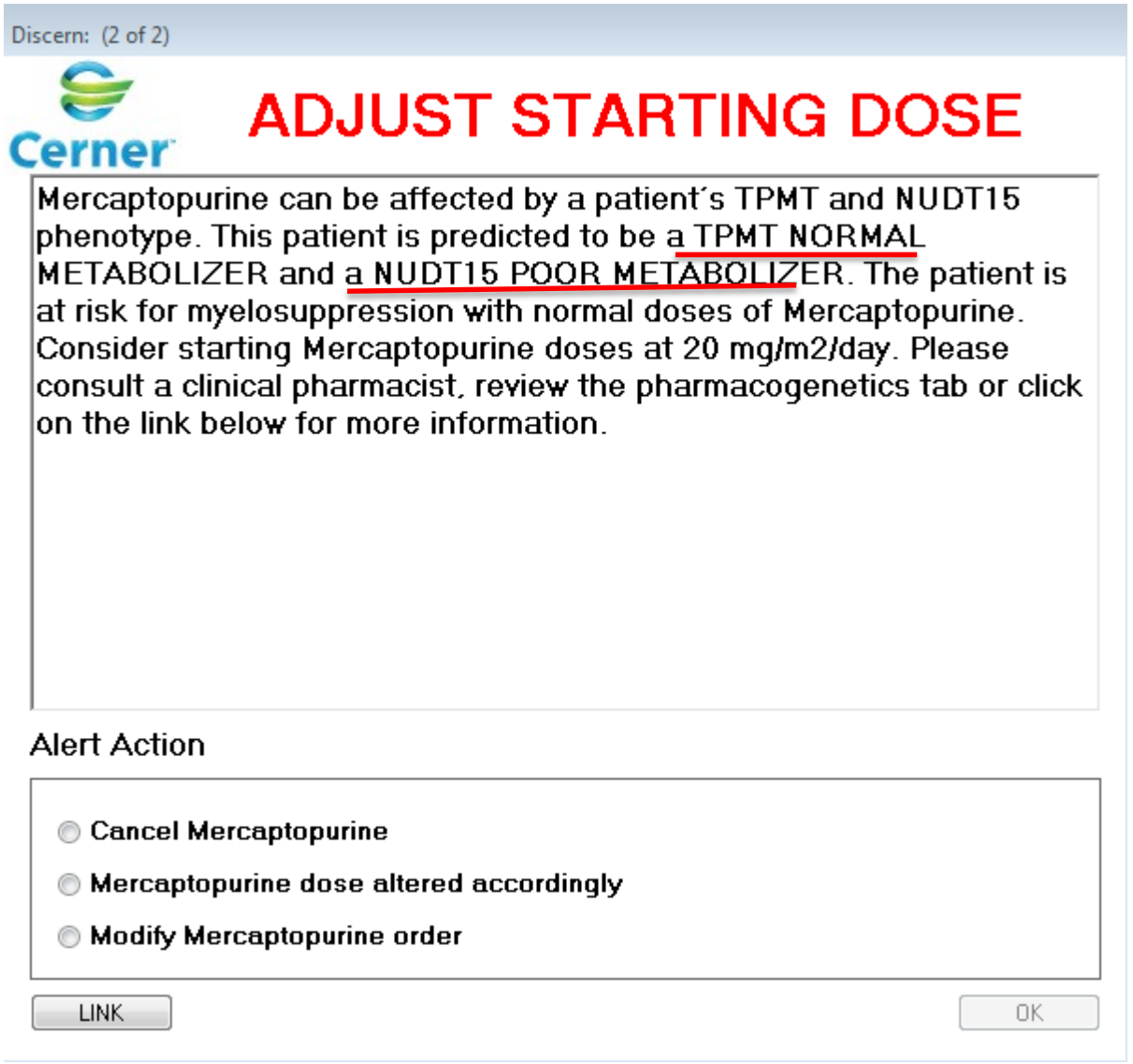
PG4KDS

Post-test alert can incorporate non-genetic info too: based on CYP2C19 phenotype, route of administration, age



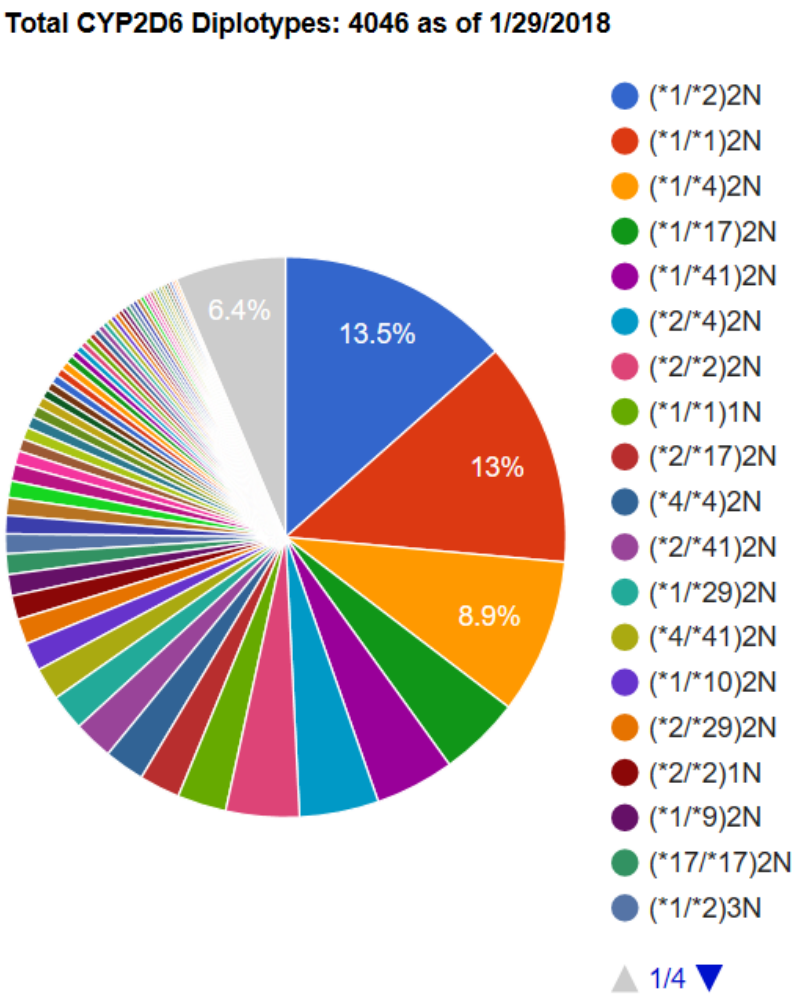
PG4KDS

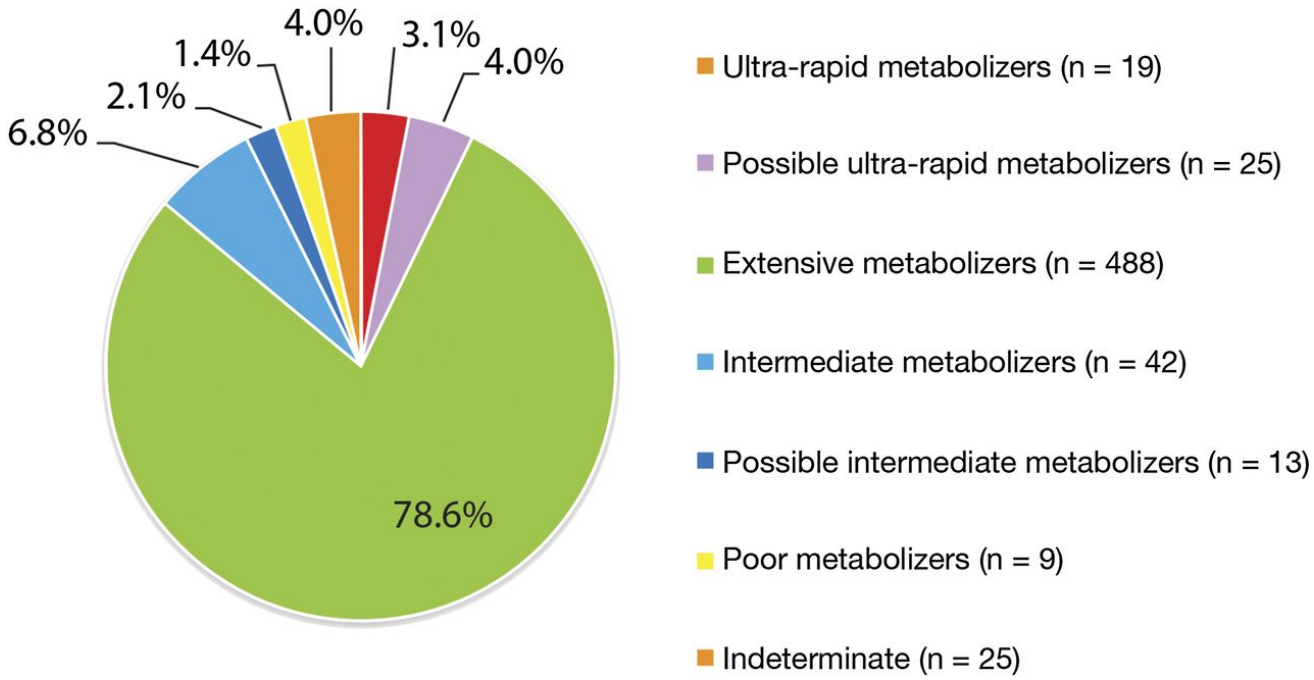
Post-test alert: based on 2 genes affecting same drug



PG4KDS

Phenotypes drive CDS and allow for interoperability, portability of results





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

Open

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

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

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 laboratorians, 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

Standardized Terms-Allele function

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

Standardized Terms-Phenotype

Term/Gene Category	Final Term*	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Phenotype-Drug Metabolizing Enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultra-rapid Metabolizer	Increased enzyme activity compared to rapid metabolizers.	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
	Rapid Metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers.	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal Metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate Metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor Metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*
Phenotype-Transporters (SLCO1B1)	Increased Function	Increased transporter function compared to normal function.	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal Function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased Function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor Function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype-High risk genotype status (HLA-B)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High risk-allele not detected	No copies of high-risk allele	

Working with SNOMED to match codes to standardized phenotype terms: SNOMED CT International Browser

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)

February 2008 · Vol. 10 · No. 2

The incidence of duplicate genetic testing

Douglas L. Riegert-Johnson, MD[1], Daniela Macaya, MQC[2], Timothy W. Hefferon, PhD[3], and Lisa A. Boardman, MD[1]

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 cer **Results:** The percentage of patients having the same genetic test more than once in 2006 was 3.3% (253/7 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 2(an all-time records review was performed on a subset of internal patients and found the all-time incidence of for *TPMT, HFE,* and *CYP450 2D6* testing to be 6.9%, 1.9%, and 0.9%, respectively. No case of DGT witl appropriate indication for duplicate testing was found. A system in place to decrease *HFE* DGT is estimated to h 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 systems-ba process to limit DGT. ***Genet Med* 2008:10(2):114–116.**

Can't detect duplicate testing unless standardized test names are adopted

Table 1

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

		Percentage of patients with DGT (patients with DGT/patients in group)	
Test	Cohort	In 2006 only	At anytime in the past[a]
TPMT	All	3.3% (253/7710)	—
	Internal	2.5% (25/996)	6.9% (17/246)
	External	3.4% (228/6714)	—
HFE	All	0.3% (24/7851)	—
	Internal	0.6% (4/681)	1.9% (4/207)
	External	0.3% (20/7170)	—
CYP2D6	Internal	0.9% (4/433)	0.9% (4/433)

[a]Incidence of DGT at anytime in the past determined for consecutive series of internal patients only.

9 Genes and 25 Drugs Implemented

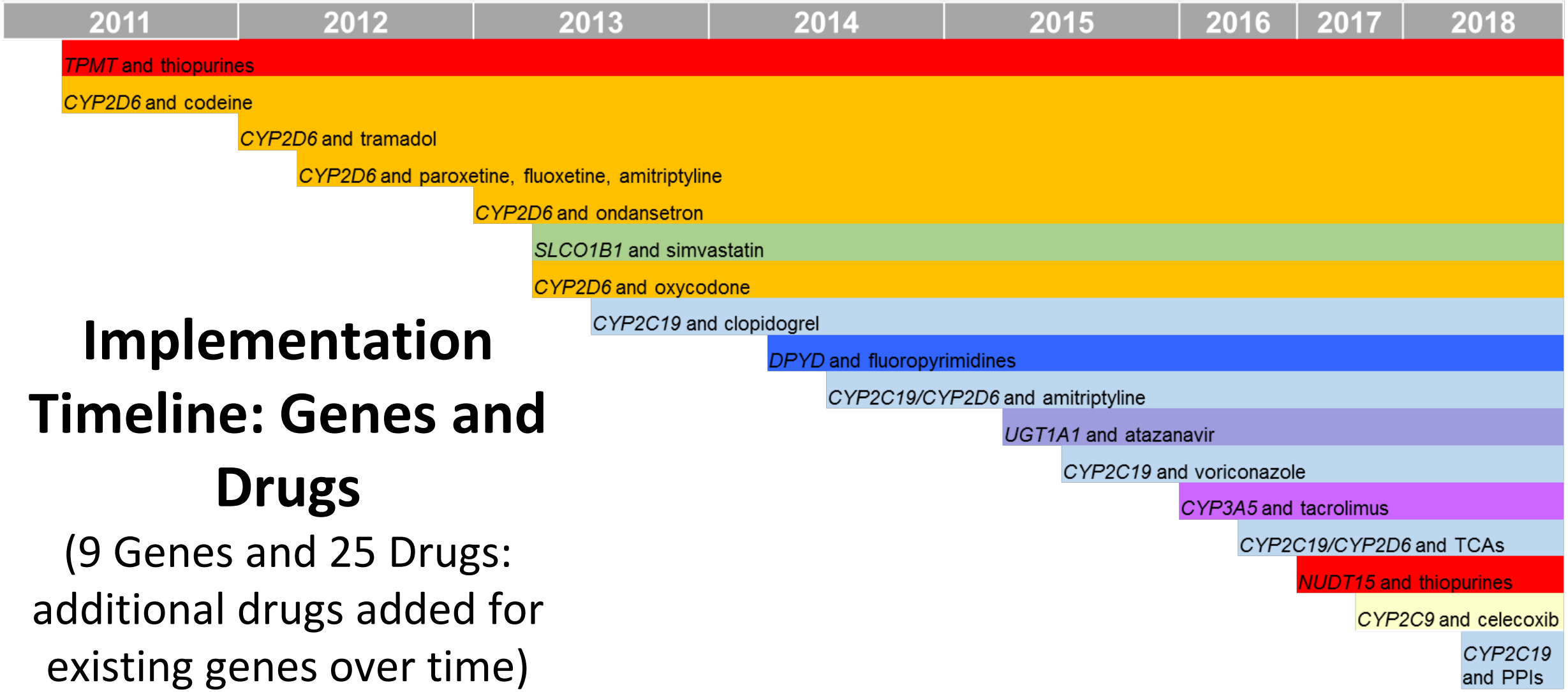
- ***CYP2D6*** *(17%)*
  - Codeine
  - Oxycodone
  - Tramadol
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Fluoxetine
  - Paroxetine
  - Ondansetron
- ***CYP2C19*** *(62%)*
  - Clopidogrel
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - PPIs
  - Voriconazole
- ***CYP3A5*** *(41%)*
  - Tacrolimus
- ***SLCO1B1*** *(13%)*
  - Simvastatin
- ***TPMT/NUDT15*** *(11%)*
  - Mercaptopurine
  - Thioguanine
  - Azathioprine
- ***DPYD*** *(0.4%)*
  - Fluorouracil
  - Capecitabine
- ***UGT1A1*** *(28%)*
  - Atazanavir
- ***CYP2C9*** *(32%)*
  - Celecoxib

PG4KDS

% indicate the %of patients enrolled on PG4KDS who have a high-risk genotype for that gene.

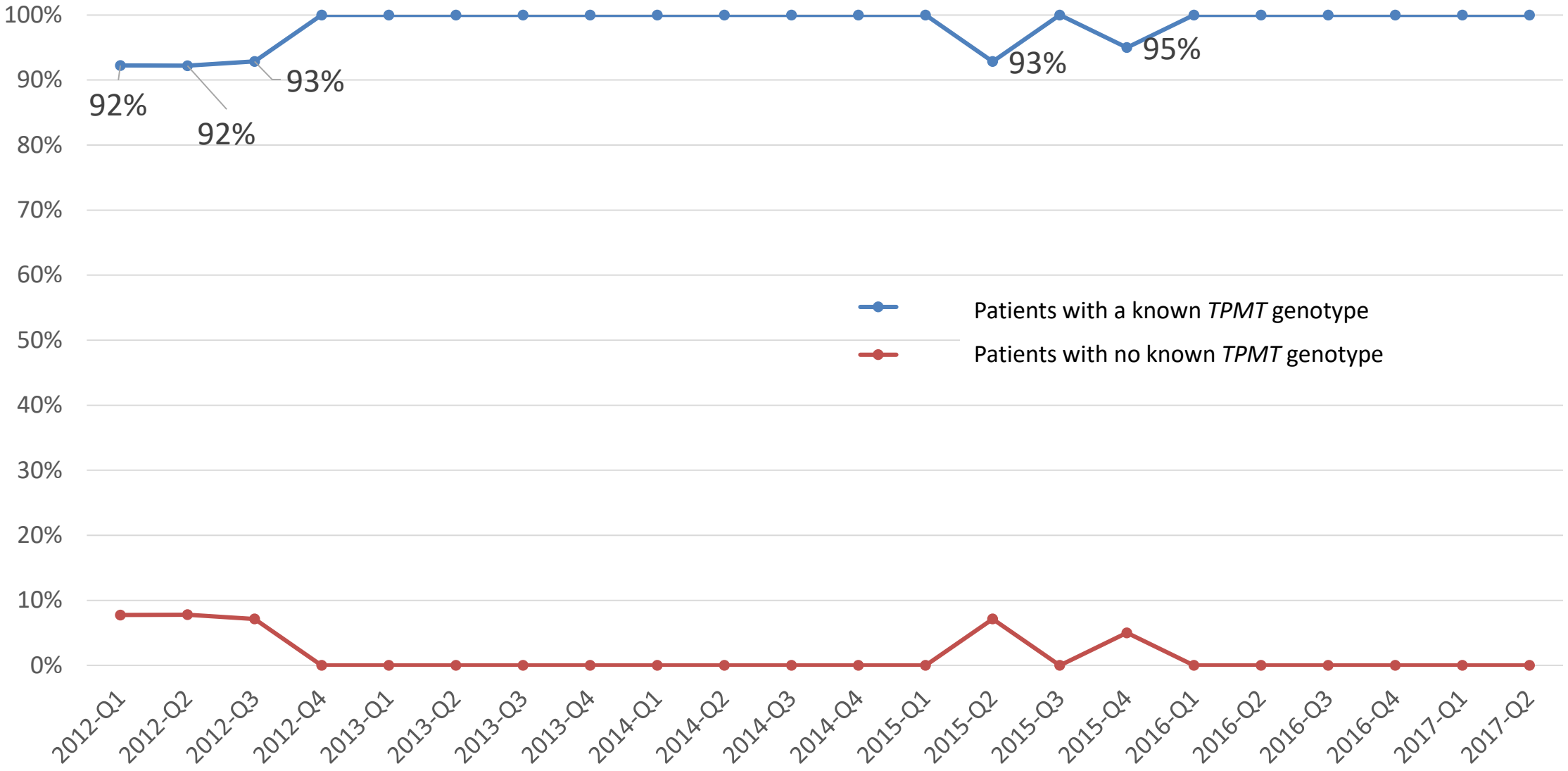
Implementation Timeline: Genes and Drugs

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



www.stjude.org/pg4kds/implement

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

JJ Swen[1], M Nijenhuis[2], A de Boer[3], L Grandia[2], AH Maitland-van der Zee[3], H Mulder[3,4], GAPJM Rongen[5,6,7], RHN van Schaik[8], T Schalekamp[3], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

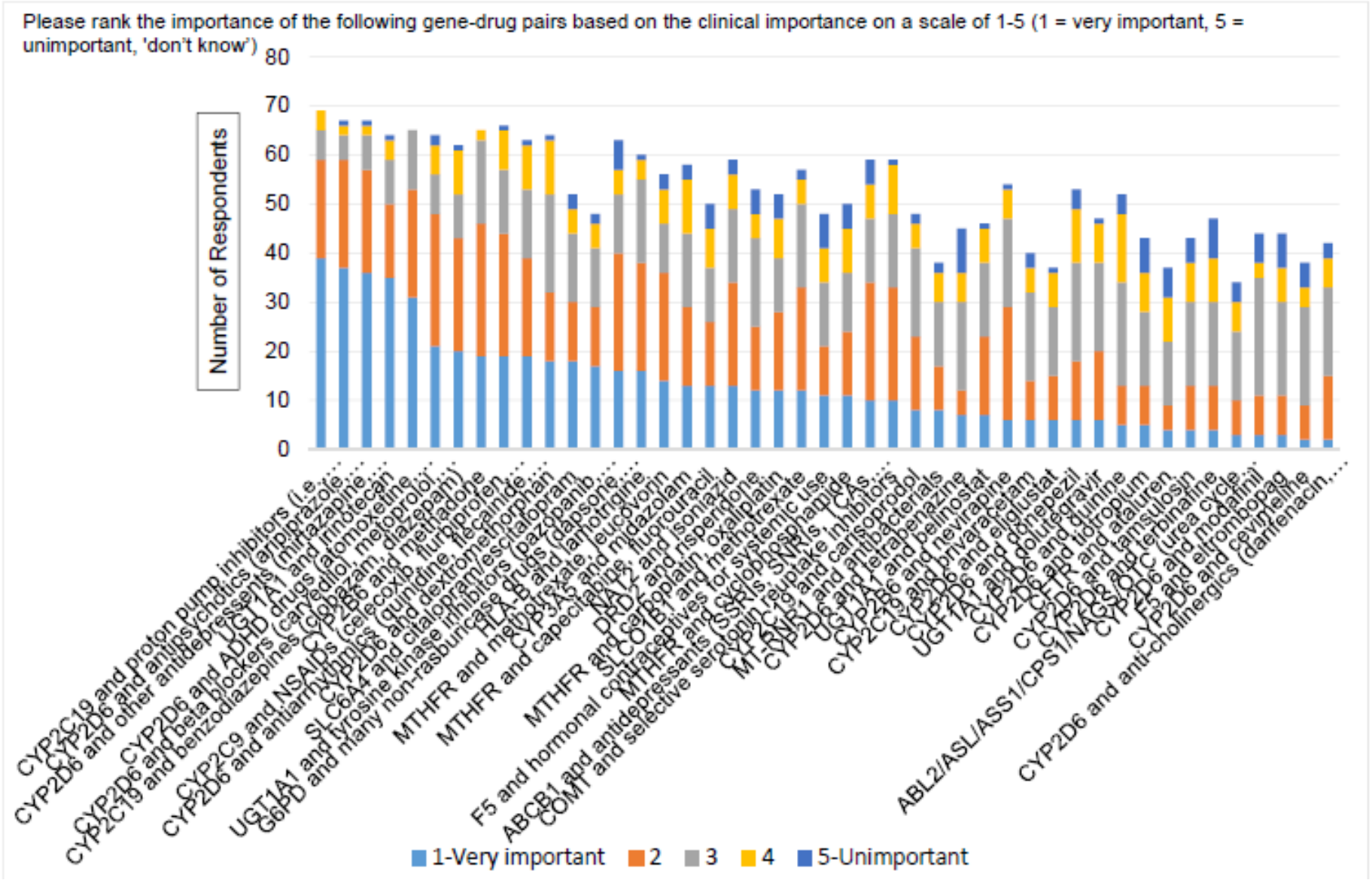
Omeprazole	2,522	PM	4	AA#	Yes	No	331, 353, 355, 358, 359, 361, 364, 375–389
		IM	4	AA#	Yes	No	331, 353, 355, 358, 359, 361, 364, 371, 375–379, 381–385, 387–390
		UM	3	A	Yes	*H. pylori* eradication: increase dose by 100–200%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 100–200%	391–393

Swen JJ et al 662 VOLUME 89 NUMBER 5 | MAY 2011 | www.nature.com/cpt

PG4KDS

CPIC
Clinical Pharmacogenetics Implementation Consortium

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

PG4KDS Anecdotes

- 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

Characterizing Pharmacogenomic-Guided Medication Use With a Clinical Data Repository

PC Mathias[1], N Hendrix[2], W-J Wang[2], K Keyloun[2], M Khelifi[3], P Tarczy-Hornoch[3,4,5] and B Devine[2,3,6]

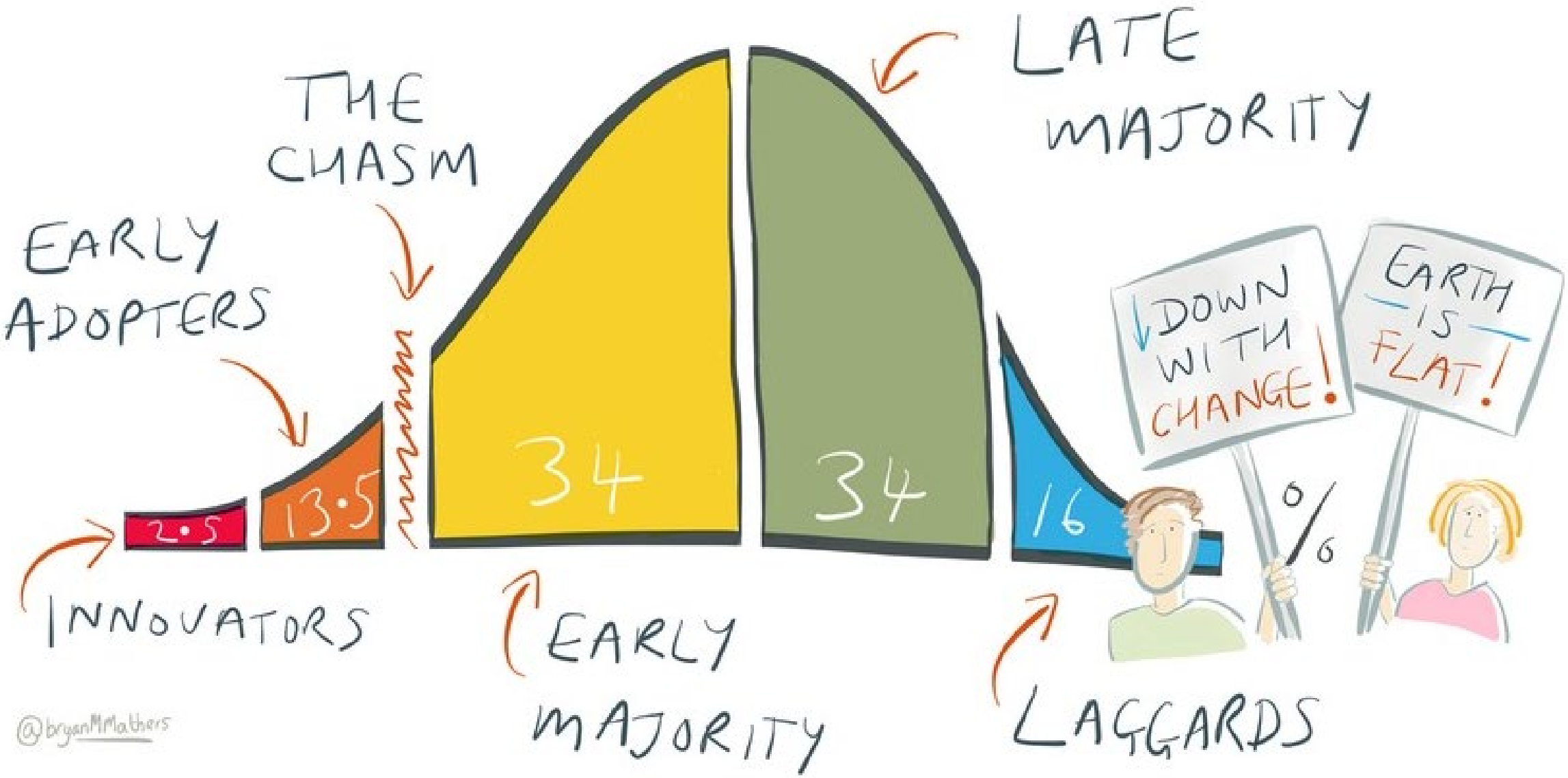
- large academic center but no directed efforts at preemptive genotyping
- 132,340 patients and 3,211,797 hospital/clinic visits,
- 268,262 medication orders for 95 drugs with germline PGEN testing mentioned in their FDA-approved drug labels (49 of which were actionable by CPIC)

- 1.5% of prescriptions for those 95 drugs accompanied by testing, even when the FDA label “recommended or required” testing

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 102 NUMBER 2 | AUGUST 2017

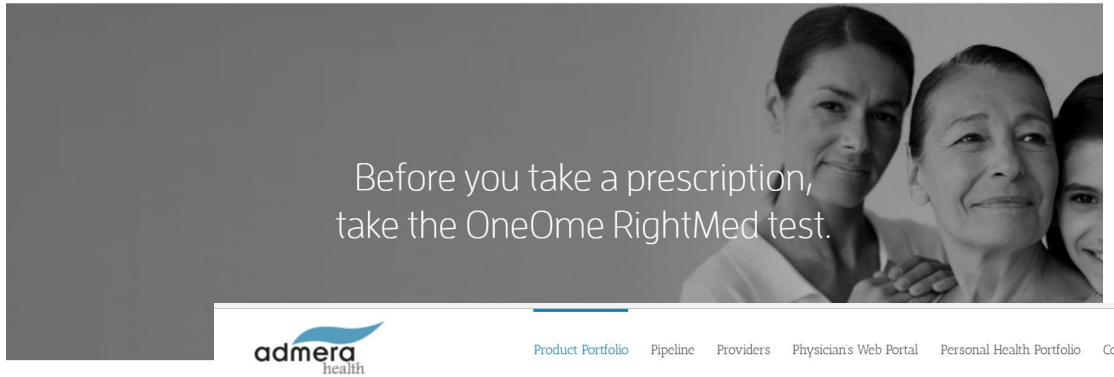
DIFFUSION OF INNOVATION

City & Guilds



@bryanMMathers

ONEOME PRODUCTS PROVIDERS PHARMACISTS PATIENTS ABOUT



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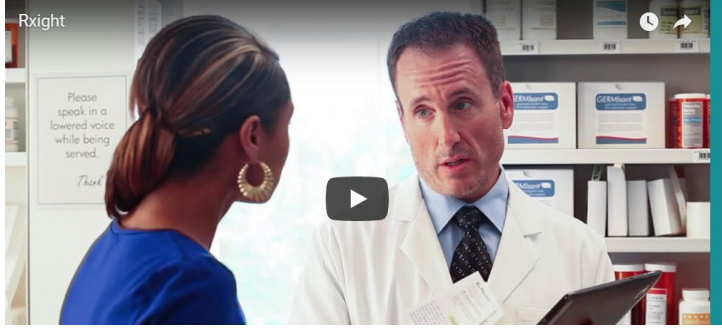

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Date Issued

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

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age

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Somatically acquired genetics: MTX

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Somatically acquired genetics: other drugs

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PK

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Clinical implementation of pgx

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adherence

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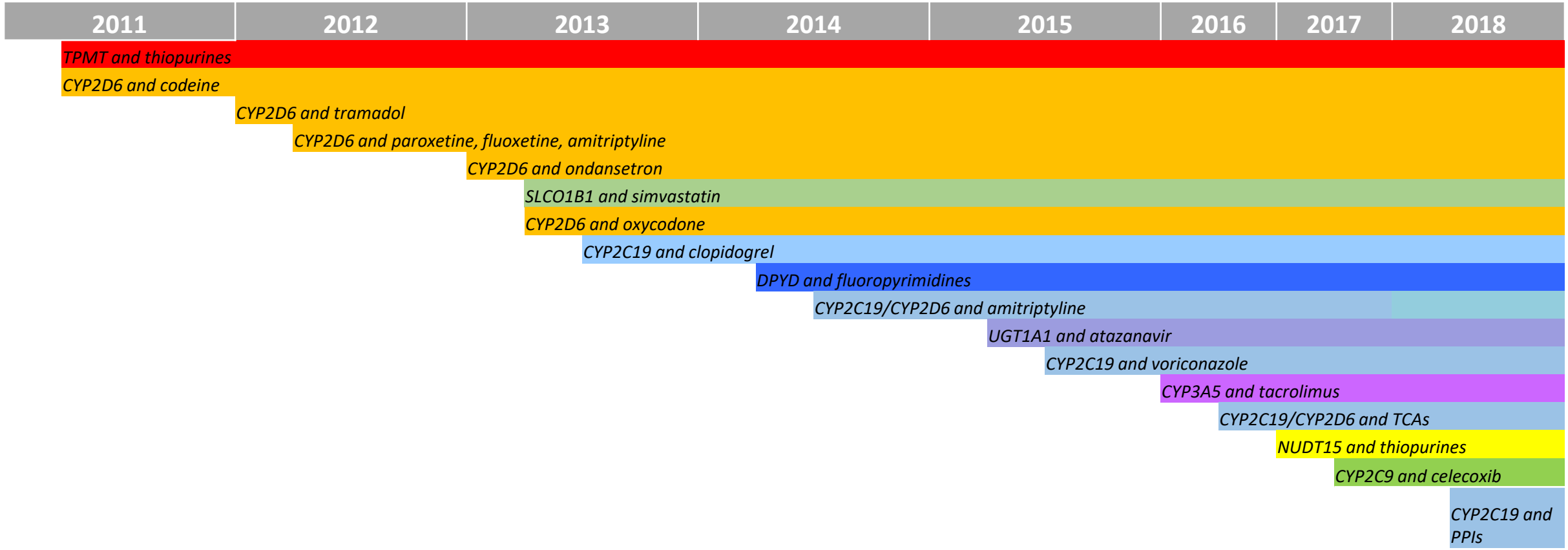
PG4KDS : Multiple steps to implement a new gene/drug pair

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- 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



www.stjude.org/pg4kds/implement

PG4KDS

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

PG4KDS

Percentages in parenthesis indicate the proportion of patients enrolled on the PG4KDS protocol who have a high-risk genotype for that gene.

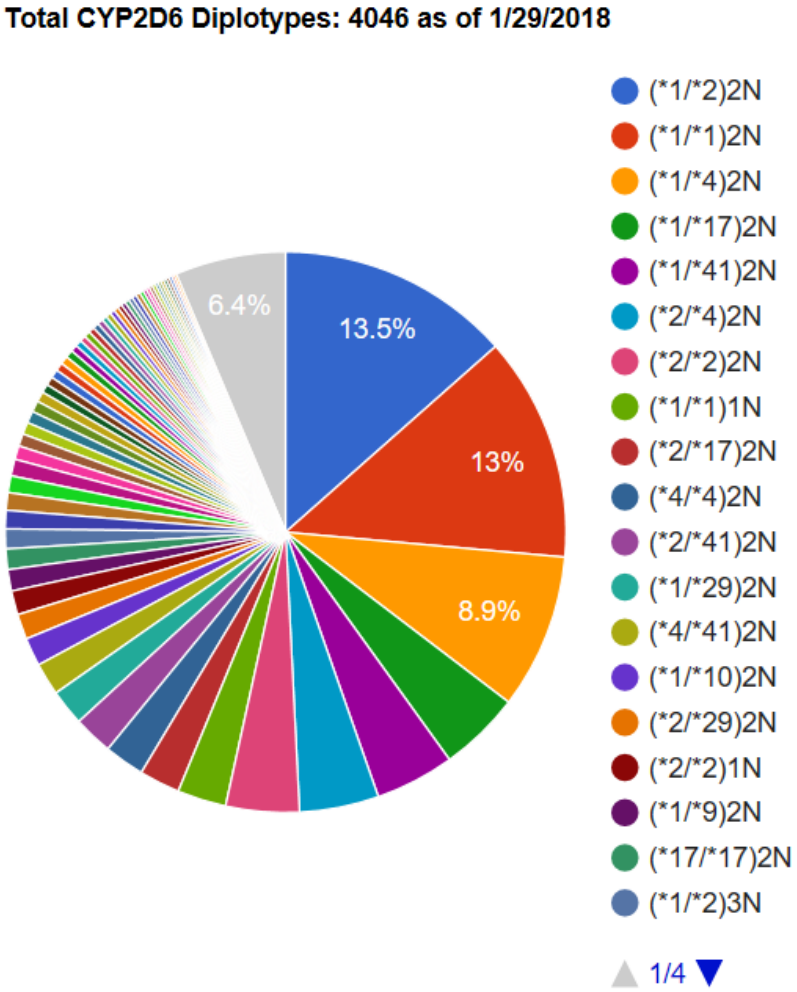
PG4KDS by numbers

	Number of patients	%
Approached for consent	4735	--
Enrolled on protocol	4471	94
Re-consented at age of majority*	535	97
Request to be informed of pharmacogenetic test result	4564	96
Incidental findings	2	0.04%

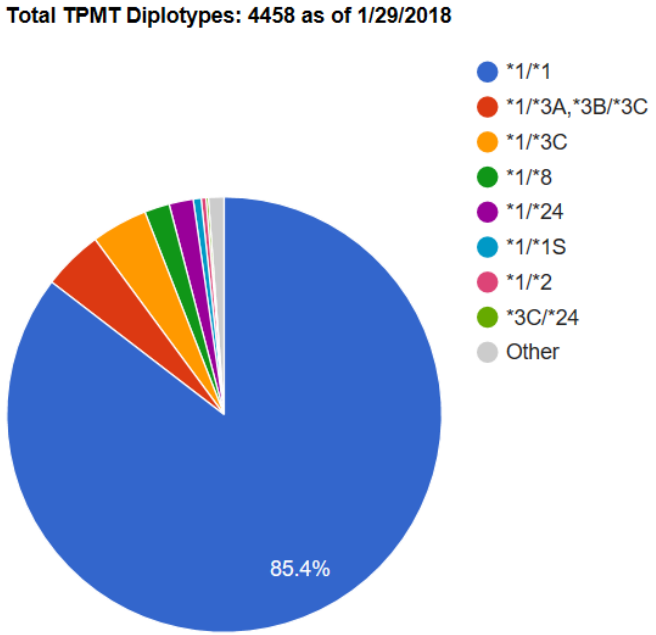
**550 patients turned 18 years old after being enrolled on the PG4KDS study*

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

DMET_8170_CYP2D6_translation.txt - Notepad

File Edit Format View Help

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#SJAccession=08-155-0435B
#PatientName=XXXXX
#DMETFile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAF
#AnnotationFile=DMET_Plus.v1.20090910.dc_annot.csv
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker list.txt
PharmGKB link    http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Independent Copy Number 2
Called Interpretation Code        UNIQ+UNK
Called Diplotypes Possible        *1/*41
Called Novel Diplotypes Possible        *2/UNK
Copy Number Corrected Alleles    NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Description
AM_12261        Y       Ch22:40853887   rs16947 C/T     Ref/Var *2,*8,*11,*12,*14A,*14B,*17,*19,*20,*21,*29,*40,*41,*42,*56A    CYP2D6_285
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       Ch22:40858512   rs1080983       G/A     Ref/Var -       CYP2D6_-1770G>A
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        Y       Ch22:40852557   rs1135840       G/C     Ref/Var S486T   CYP2D6_4180G>C(S486T)
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Description
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_1758G>A>T(G169RorX)
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

Result History

Value	Valid From	Valid U
Priority	5/25/2016 18:04	Curren
Priority	5/25/2016 17:58	5/25/2

Passive CDS: interpretation of pgen test results always available

Result | Specimen | **Comments** | Action List

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

PG4KDS

PHARMACOGENETICS CONSULT FOR
DPYD GENOTYPE

Sample for DPYD Genotype Obtained: $SAMPLE_DT_TM
PG4KDS DPYD Genotype Result: $EMR_RESULT
DPYD Phenotype Assignment: DPYD Intermediate Metabolizer

This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a no function allele (*2). Based on the genotype result, this patient is predicted to be an intermediate metabolizer of DPYD. This patient may be at higher risk for toxicity from medications that are affected by DPYD (e.g. fluoropyrimidines such as 5-fluorouracil). To minimize toxicity, dose decreases or alternative therapy regimens may be necessary for medications affected by the DPYD enzyme pathway. For more specific information about how DPYD metabolizer status influences drug dosing, please go to www.stjude.org/pg4kds.

Kristine Crews, Pharm.D., pager 2256.

$CONSULT_TITLE $VERSION-$APPROVAL_DT_TM

Templates based on deconstructing the consult into sections: scalable

Phenotype Assignment

Diplotype Interpretation

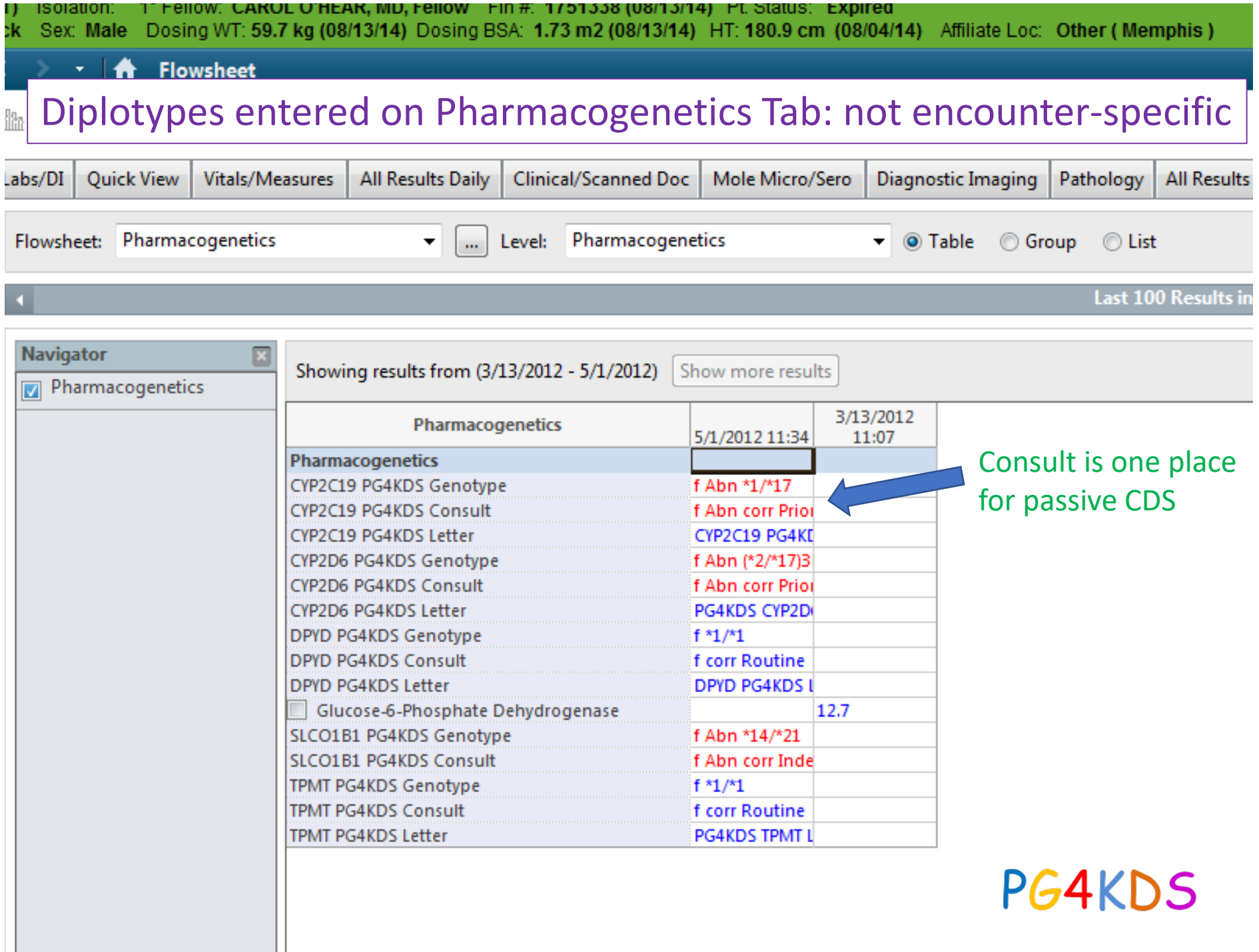
Phenotype interpretation, medications

Prescribing Recommendations

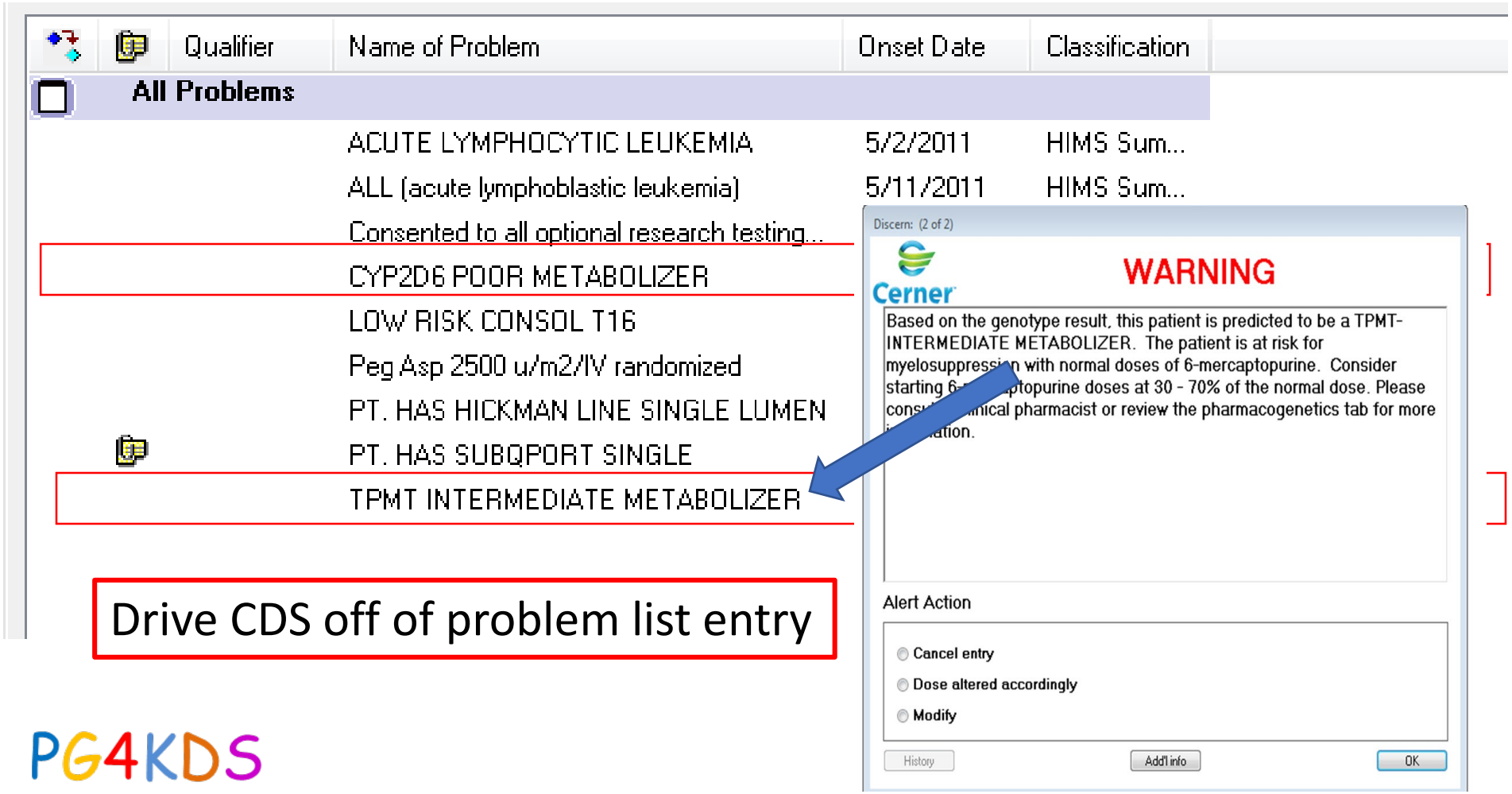
Educational Link

PG4KDS

Consult Builder
Hicks et al (*CPT* 2012)


Isolation: 1° Fellow: CAROL O'HEAR, MD, Fellow Fin #: 1751338 (08/13/14) Pt. Status: Expired
Sex: Male Dosing WT: 59.7 kg (08/13/14) Dosing BSA: 1.73 m2 (08/13/14) HT: 180.9 cm (08/04/14) Affiliate Loc: Other (Memphis)
Flowsheet
Diplotypes entered on Pharmacogenetics Tab: not encounter-specific
Labs/DI
Quick View
Vitals/Measures
All Results Daily
Clinical/Scanned Doc
Mole Micro/Sero
Diagnostic Imaging
Pathology
All Results
Flowsheet: Pharmacogenetics
Level: Pharmacogenetics
Table
Group
List
Last 100 Results in
Navigator
Pharmacogenetics
Showing results from (3/13/2012 - 5/1/2012)
Show more results
Pharmacogenetics
5/1/2012 11:34
3/13/2012 11:07
Pharmacogenetics
CYP2C19 PG4KDS Genotype
f Abn *1/*17
CYP2C19 PG4KDS Consult
f Abn corr Prior
CYP2C19 PG4KDS Letter
CYP2C19 PG4KD
CYP2D6 PG4KDS Genotype
f Abn (*2/*17)3
CYP2D6 PG4KDS Consult
f Abn corr Prior
CYP2D6 PG4KDS Letter
PG4KDS CYP2D
DPYD PG4KDS Genotype
f *1/*1
DPYD PG4KDS Consult
f corr Routine
DPYD PG4KDS Letter
DPYD PG4KDS L
Glucose-6-Phosphate Dehydrogenase
12.7
SLCO1B1 PG4KDS Genotype
f Abn *14/*21
SLCO1B1 PG4KDS Consult
f Abn corr Inde
TPMT PG4KDS Genotype
f *1/*1
TPMT PG4KDS Consult
f corr Routine
TPMT PG4KDS Letter
PG4KDS TPMT L
Consult is one place for passive CDS
PG4KDS

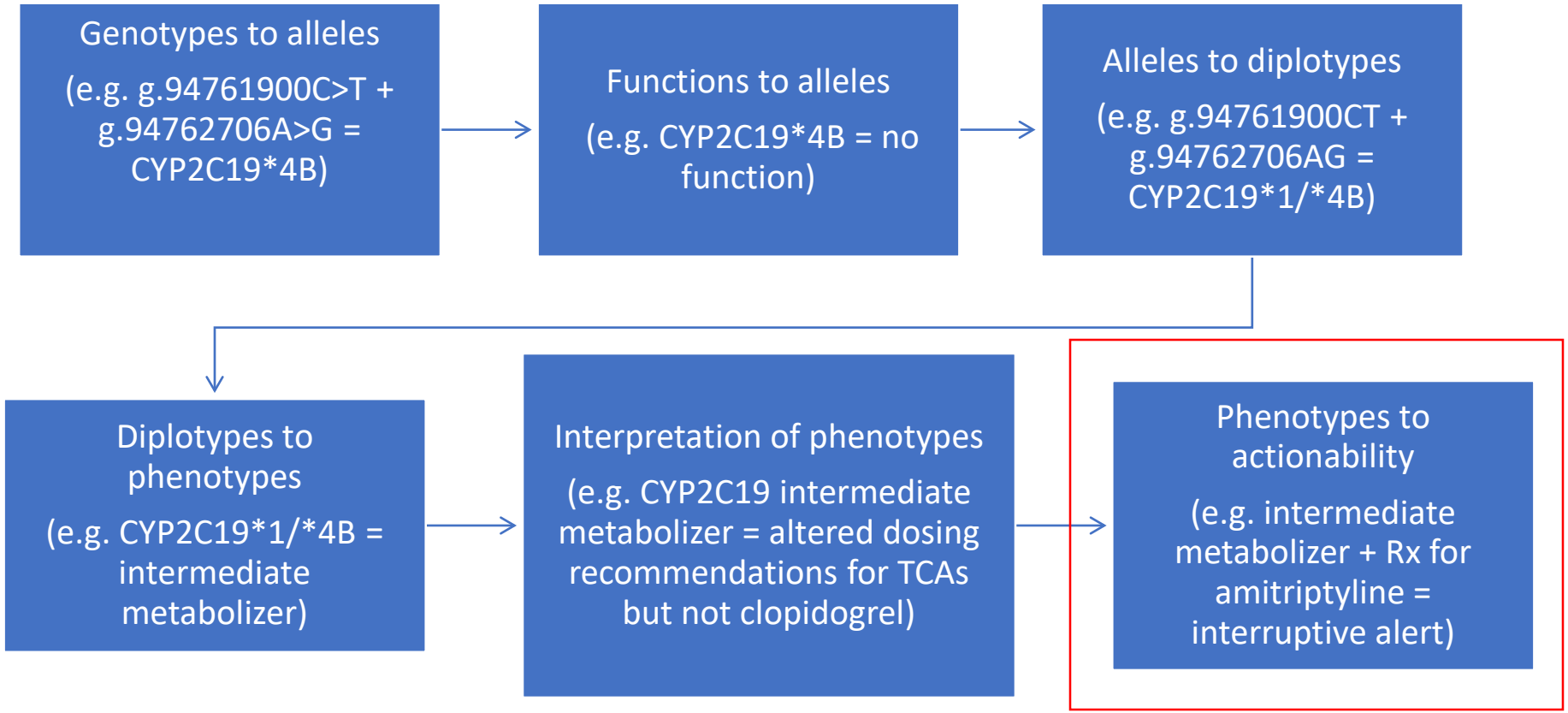
High risk phenotypes automatically populate the “Problem List”; can also manually enter also



Drive CDS off of problem list entry

PG4KDS

CPIC tables allow translation of genetic test results to actionability

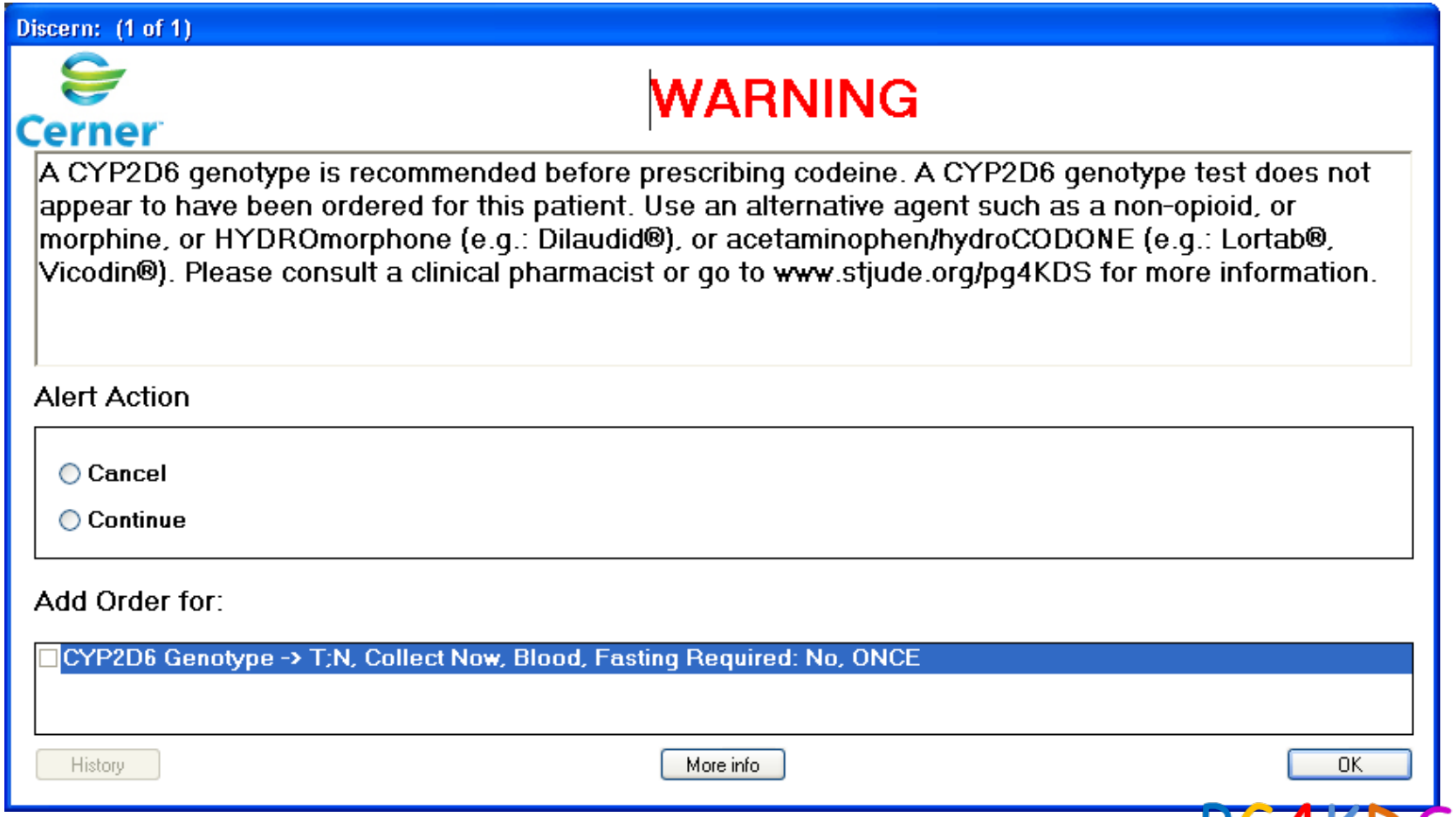


https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials

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 contains prescribing and testing recommendations if a patient has not been genotyped: driven off the ABSENCE of a test result



PG4KDS

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

Open

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

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

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 laboratorians, 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.

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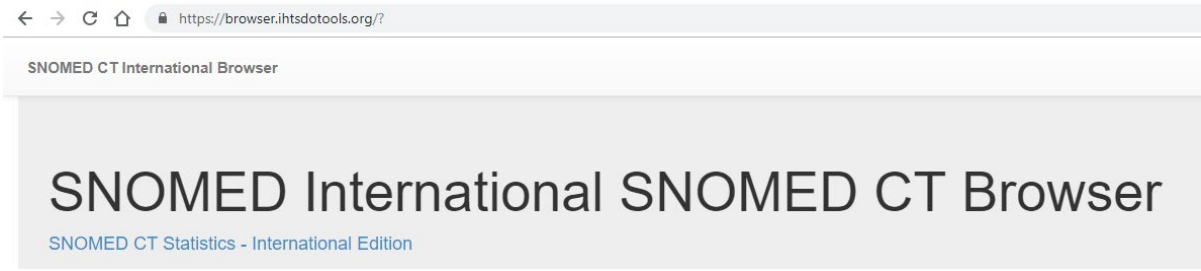
Key Words: CPIC; nomenclature; pharmacogenetics; pharmacogenomics; terminology

Working with SNOMED to match codes to standardized phenotype terms

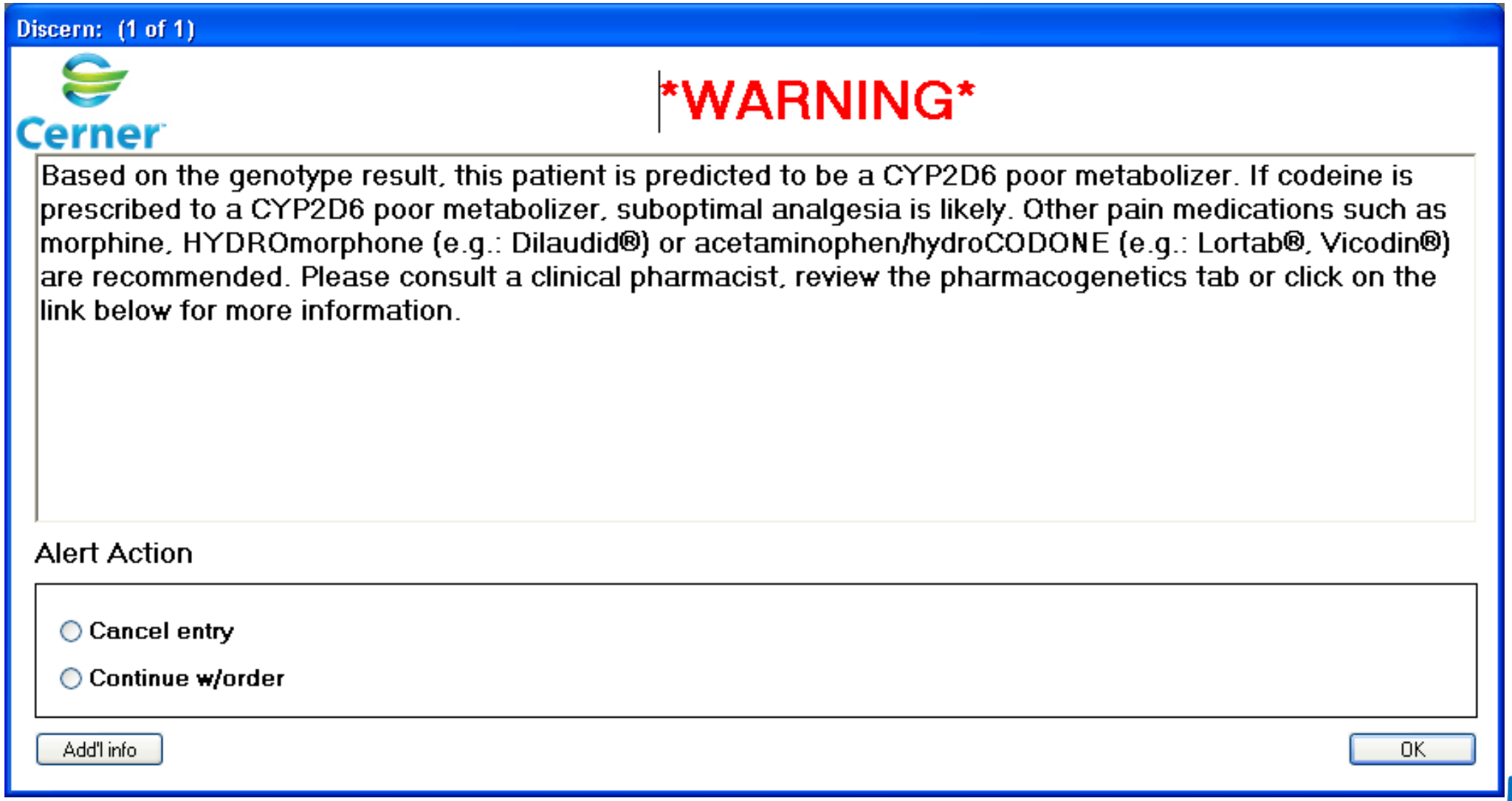


TPMT – SNOMED CT Code
Thiopurine methyltransferase deficiency

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



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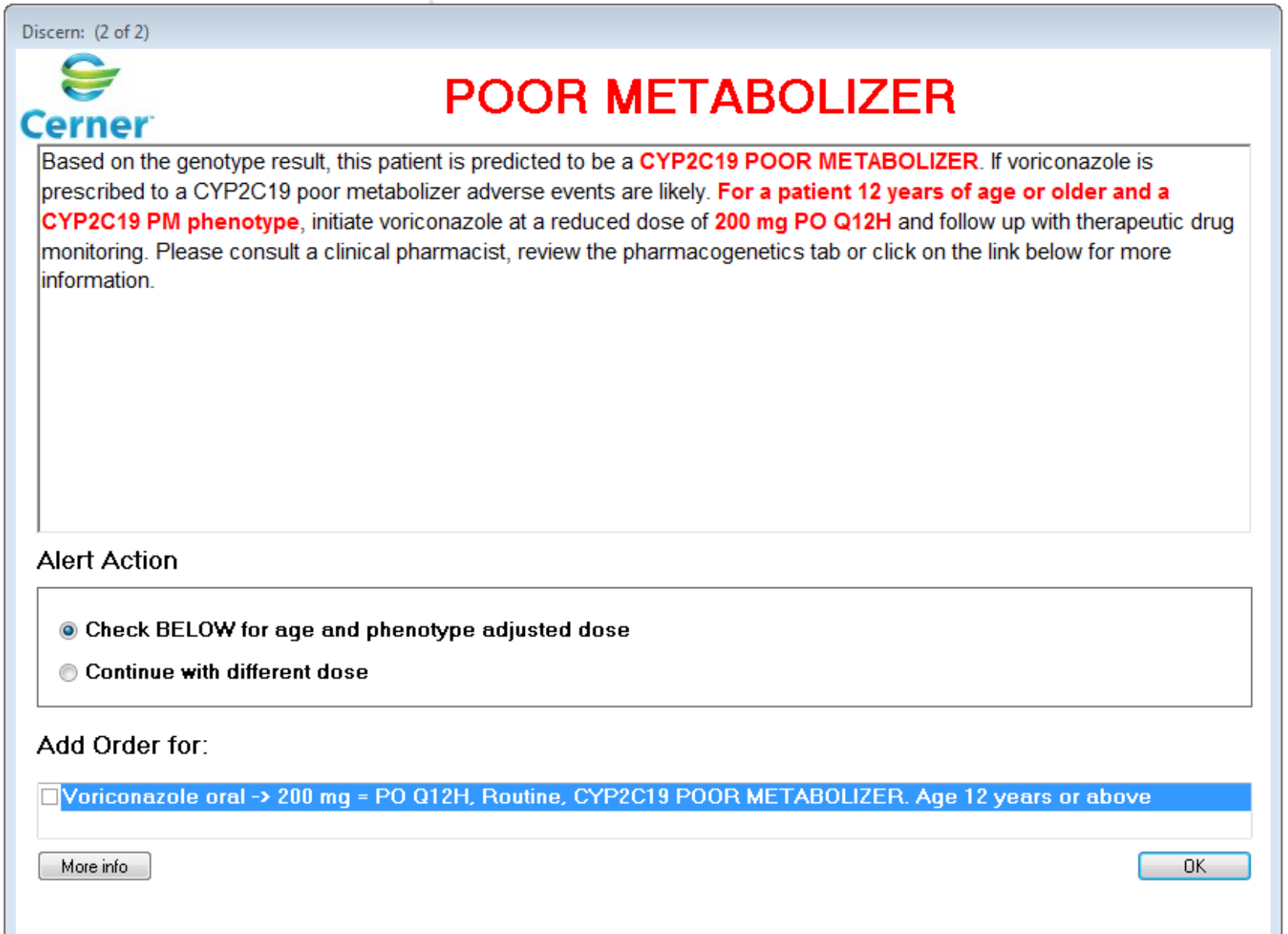
Post-test alert can incorporate non-genetic info too: based on CYP2C19 phenotype, route of administration, age



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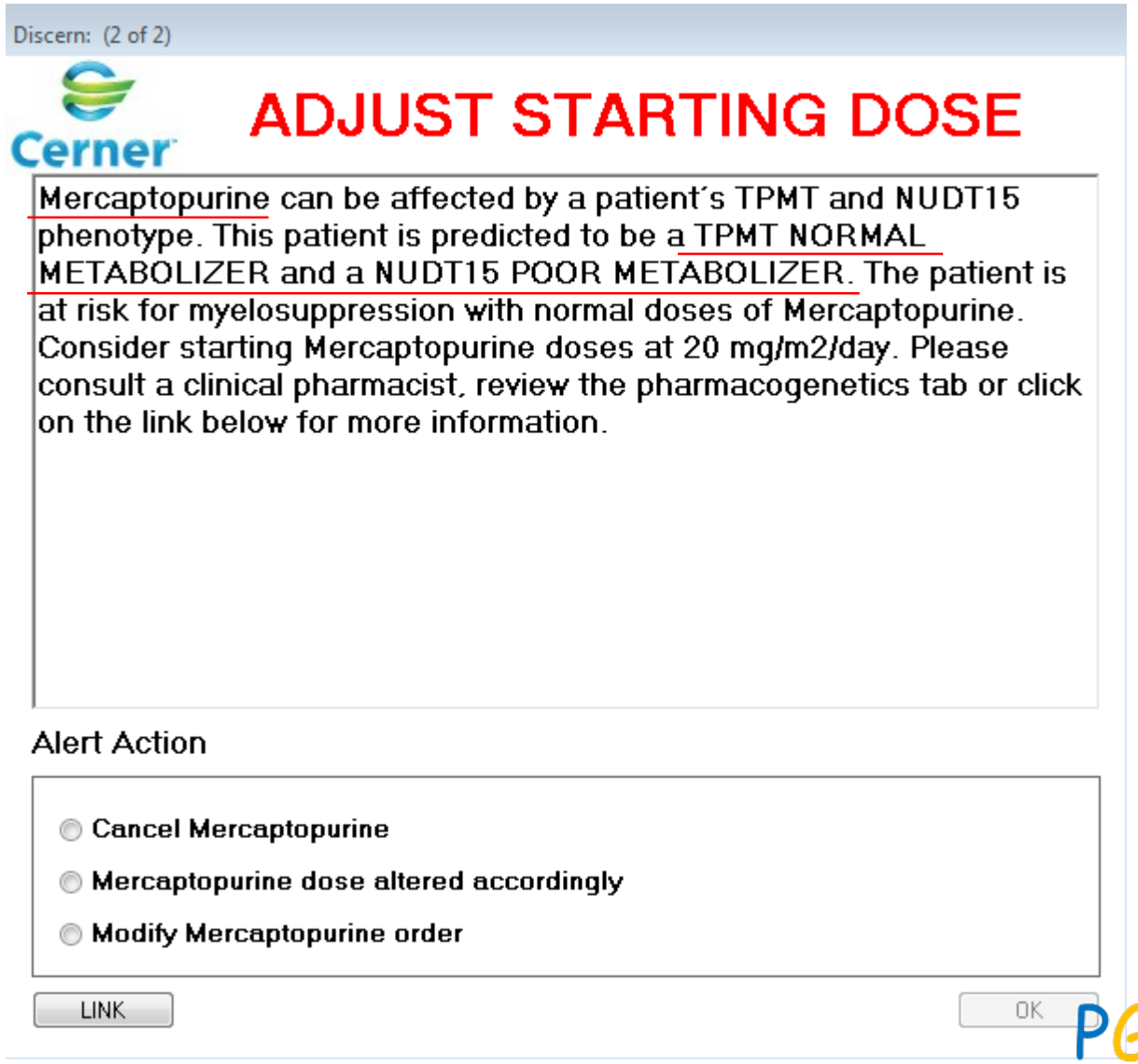
Post-test alert: based on 2 genes affecting same drug



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