Moving Beyond Single Gene-Drug Pairs in Clinical Pharmacogenomics Testing

Yuan Ji, PhD, DABCP, FACMG

Gwendolyn McMillin, PhD, DABCC

Learning Objectives

- Describe the strengths and limitations of pharmacogenomic testing.
- List examples of single gene-drug associations with the strongest levels of evidence for clinical implementation.
- Discuss cautions when considering the use of multi-gene drug associations to inform drug therapy decisions.

Disclosure

- None

Outline

- Singe gene-drug based pharmacogenomics (PGx) testing
  - An introduction
  - Evidence and examples
  - Considerations for developing and evaluating clinical PGx laboratory developed tests (LDTs)
- Multi-gene PGx panels
  - Evidence and examples
  - PROs and CONs for utilizing PGx panels
  - Considerations for successful PGx implementation

Single Gene-Drug Based PGx Testing

Yuan Ji, PhD, DABCP, FACMG

Medical Director of Genomics and Genetics; PGx, ARUP Laboratories

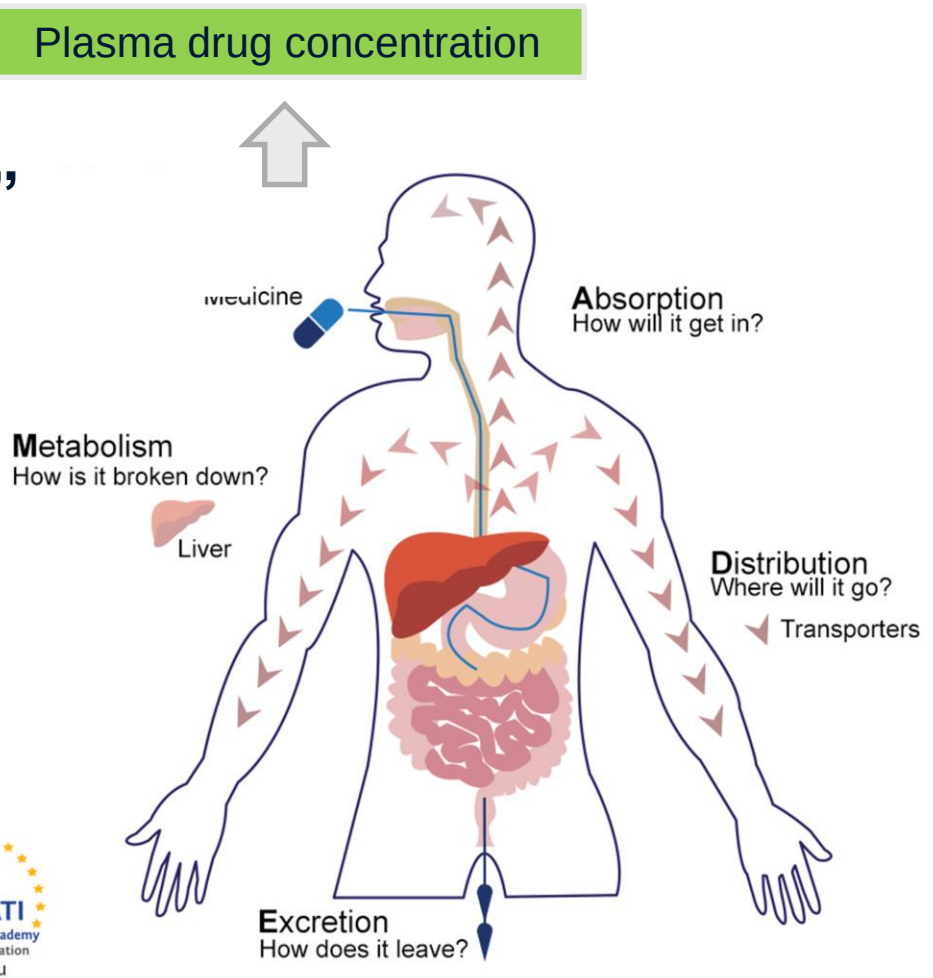
Associate Professor (Clinical) of Pathology, University of Utah

Medications: Myths and Facts

- ~30% people take at least one medication within a 30-day period
- Most medications cause adverse drug events (ADEs)
- Some medications like antibiotics may do more harm than good
- CDC statistics:
  - ~ 200,000 ADEs-related ER visits in pediatric population (17 years or younger)
  - ~ 450,000 ADEs-related ER visits in older adults (65 years or older)
  - Medications, e.g., anticoagulant warfarin
- Many ADEs are preventable by closely supervising of dosing, blood tests (therapeutic drug monitoring, TDM), or PGx test

Pharmacogenomics or Pharmacogenetics is the study of inheritance or acquired genomic changes on drug response phenotypes

Pharmacokinetics (PK)
"What the body does to a drug"



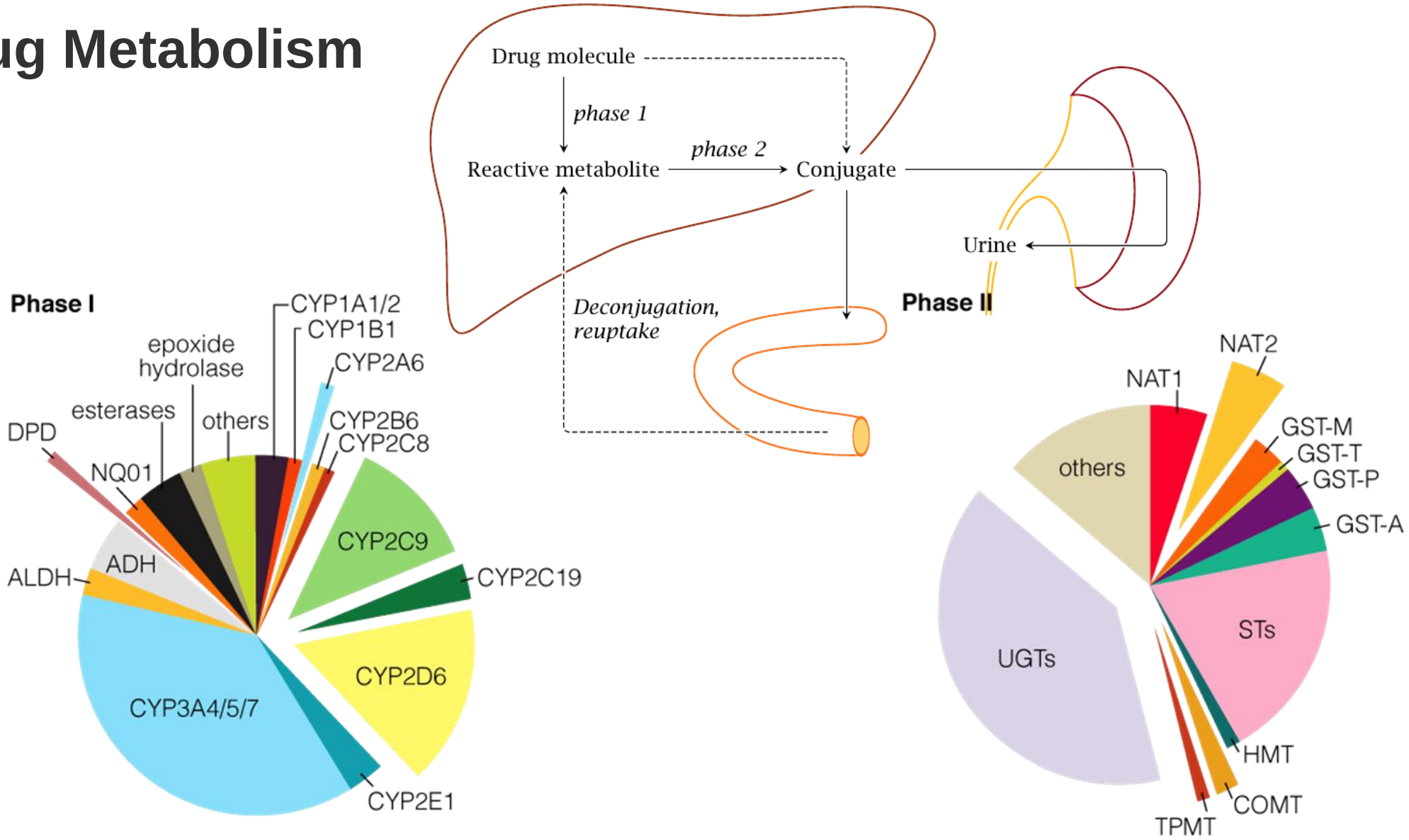
Pharmacodynamics (PD)
"What a drug does to the body"

- Target organ/tissue
- Receptor, protein
- Signaling pathway
- Physiologic effects
- Mechanism of action

EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

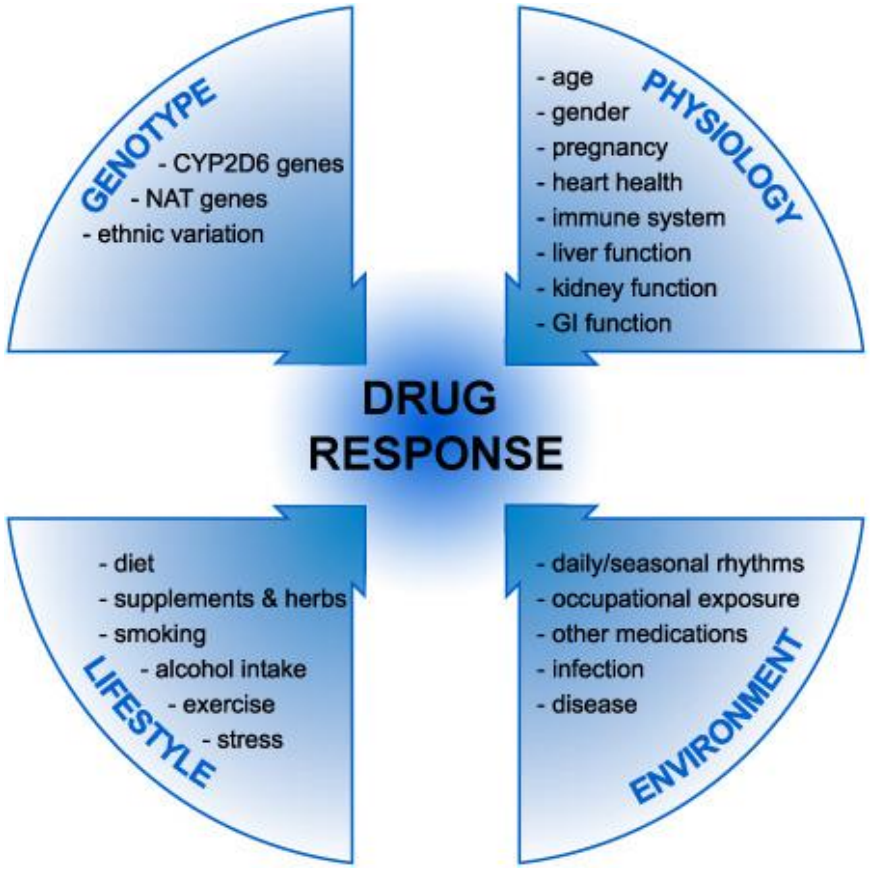
Dose response

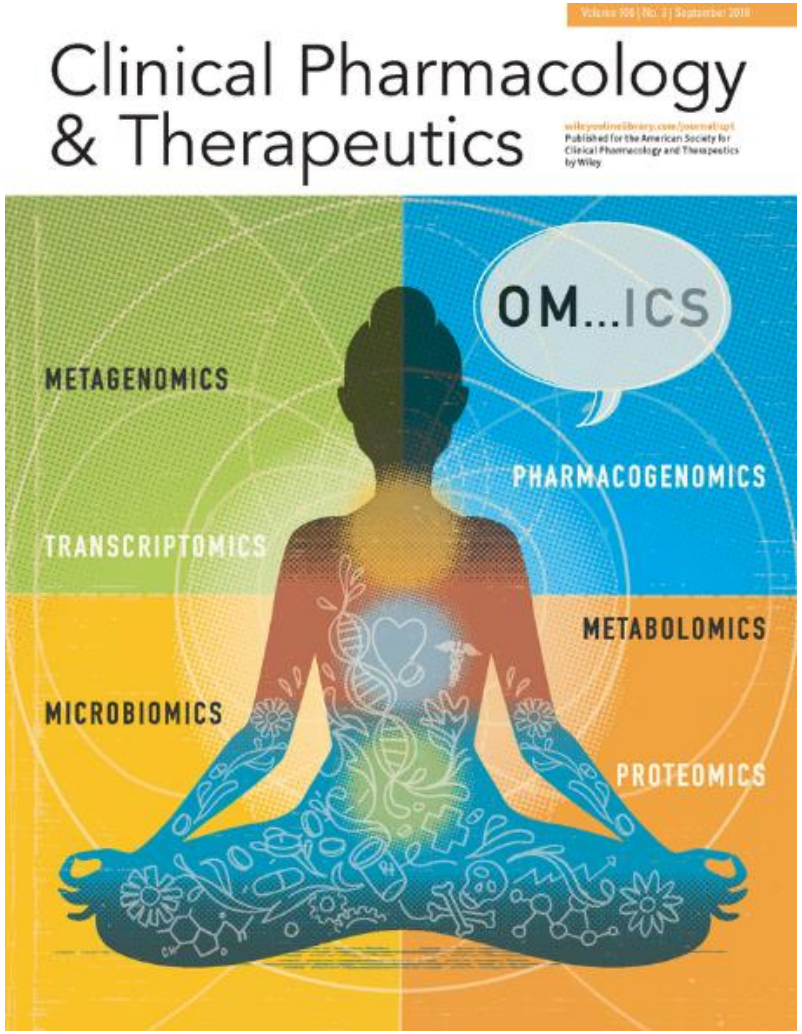
Drug Metabolism



http://www.cyprotex.com/admepk/polymorphic-and-non-cyp-mediated-metabolism

Factors Influencing Drug Response Phenotypes





Utilities of Clinical PGx Testing

- Patient selection
  - Identify patient at high risk for a serious ADE
  - Identify patient not likely to respond
  - Identify patient likely to be sensitive or resistant to a drug, and require non-standard dosing
- Optimize therapy
  - Optimize dosing to a specific drug for maximum efficacy and minimum toxicity
  - Avoid toxicity and drug-drug interaction
  - Reduce medical expense

ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
6120 Executive Blvd., Suite 700, Rockville, MD 20852
Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

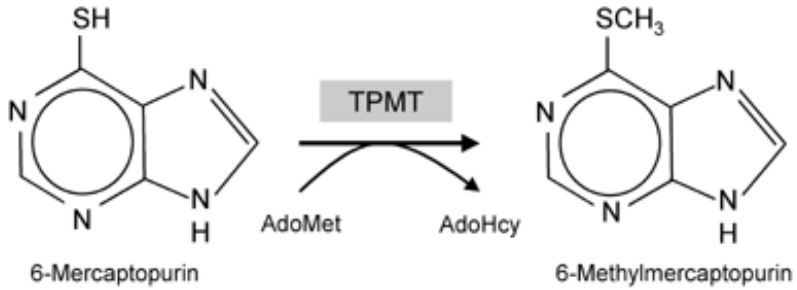
Association for Molecular Pathology Position Statement:
Best Practices for Clinical Pharmacogenomic Testing – September 4, 2019

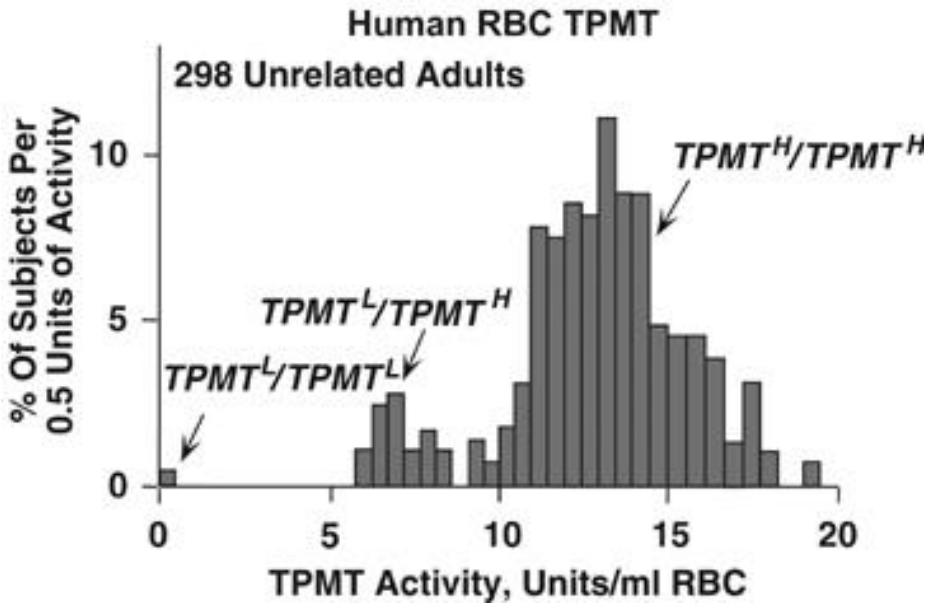
The field of pharmacogenomics is steadily growing, and the FDA has already approved the inclusion of pharmacogenomic information in the labels of hundreds of medications[2]. As the prevalence of pharmocogenetic testing continues to increase, so will the need for laboratory professionals to translate genetic laboratory results to healthcare providers who make prescribing decisions for patient care. Pharmacogenomic tests that are offered clinically should demonstrate evidence of clinical validity before being offered to patients, the same standard as for other practices of medicine. Such evidence may be established and/or demonstrated through peer-reviewed literature, clinical practice guidelines, and/or FDA drug labels.

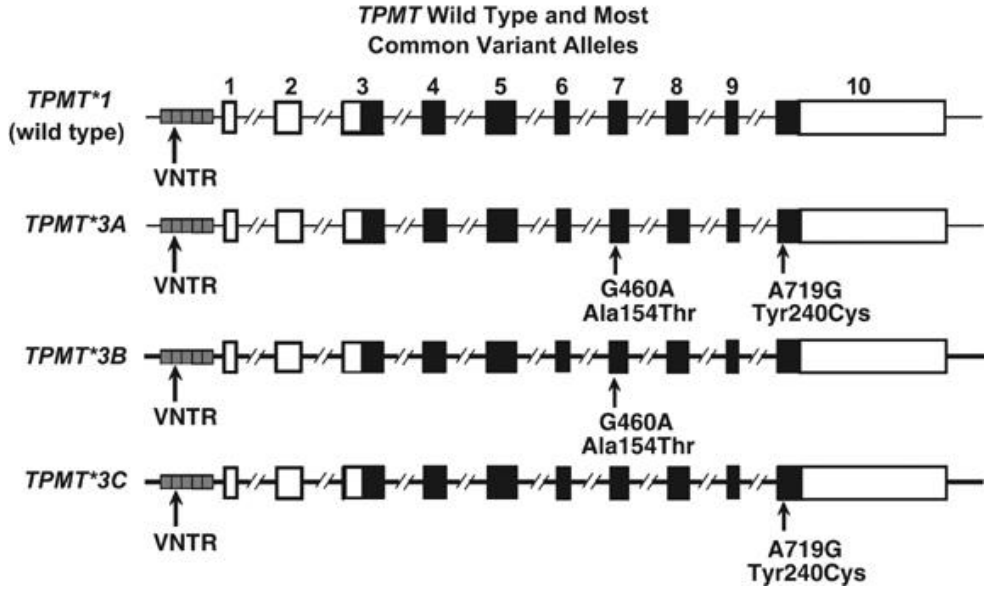
Single Gene-drug Based PGx Testing

- Drug-gene pairs: strongest evidence
- Many guidelines are single gene-drug pair based
  - Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) etc.
- FDA drug label information
- Evidences and examples:
  - *TPMT* and 6-mercaptopurine
  - *CYP2C19* and clopidogrel
  - *HLA-B*5701* and abacavir
  - *UGT1A1* and irinotecan
  - *CYP2D6* and codeine
  - *CYP2D6* and tamoxifen
- Most LDTs use a targeted genotyping approach

TPMT and Thiopurines







Weinshilboum and Sladek, 1980

Evidence Supporting *TPMT*-Thiopurines Associations

TABLE S1. EVIDENCE LINKING *TPMT* GENOTYPE WITH THIOPURINE PHENOTYPE

Type of experimental model (in vitro, in vivo, preclinical or clinical)	Major findings	References	Level of evidence[a]
In vitro	MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from TPMT homozygous deficient individuals	Weinshillboum, et al. (1980) (65) Van Loon, et al. (1982) (66) Van Loon, et al. (1990) (67) Szumlanski, et al. (1992) (68)	High
In vitro	TG's catabolism to methylthioguanine	Moore, et al. (1958) (69)	High
In vitro	Mechanisms of functional inactivation for TPMT *2, *3A, *3B, *3C, *4 demonstrated by expression of specific variant alleles	Tai, et al. (1997) (70) Tai, et al. (1999) (71) Wang, et al. (2003) (72)	High
In vitro	Heterologous expression of TPMT catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthioguanine, and TIMP to methylTIMP	Hill, et al. (1971) (73) Krynestki, et al. (2003) (74)	High
In vitro	TPMT deficiency could lead to chronic exposure to thiopurine and could be linked to development of brain cancer (astrocytomas).	Hosni-Ahmed, et al. (2011) (75)	Low
In vitro	TPMT knock-down cells are more sensitive to 6-TG, and in some cases 6-MP, than wild type	Karim, et al. (2013) (76)	High
Clinical	TPMT genotype correlates with TPMT activity measured by biochemical assay (variant genotypes have lower activity in general than *1/*1), but activity cannot be explained by genotype alone because the *1/*1 and variant (het) activities overlap	Relling, et al. (1999) (83) Ansari, et al. (2002) (118) Gearry, et al. (2005) (90) Schmiegelow, et al. (2009) (119) Booth, et al. (2011) (94) Fangbin, et al. (2012) (96) Wennerstrand, et al. (2013) (120) Ben-Salah, et al. (2013) (101) Liang, et al. (2013) (121) Demlova, et al. (2014) (122) Chen, et al. (2014) (104) Farfan, et al. (2014) (123) Chouchana, et al. (2014) (124) Karas-Kuzelicki, et al. (2014) (125) Coelho, et al. (2016) (126) Liu, et al. (2017) (6) Tamm, et al. (2017) (7)	High
	TPMT variant genotype is associated with increased TGN levels and/or lower MMPN levels	Lennard, et al. (2013) (127) Stocco, et al. (2014) (128) Uchiyama, et al. (2014) (105) Chouchana, et al. (2014) (124) Kim, et al. (2014) (106) Lee, et al. (2015) (129) Lee, et al. (2015) (130) Fangbin, et al. (2016) (111)	High
	TPMT variant genotype associated with incidence of gastrointestinal ADRs	Hlavaty, et al. (2013) (98) Ben Salah, et al. (2013) (101) Liu, et al. (2015) (44) Liu, et al. (2015) (43)	Weak

https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/

Evidence and Clinical Utility for PGx Testing: the RCT Approach

Randomized Controlled Trials

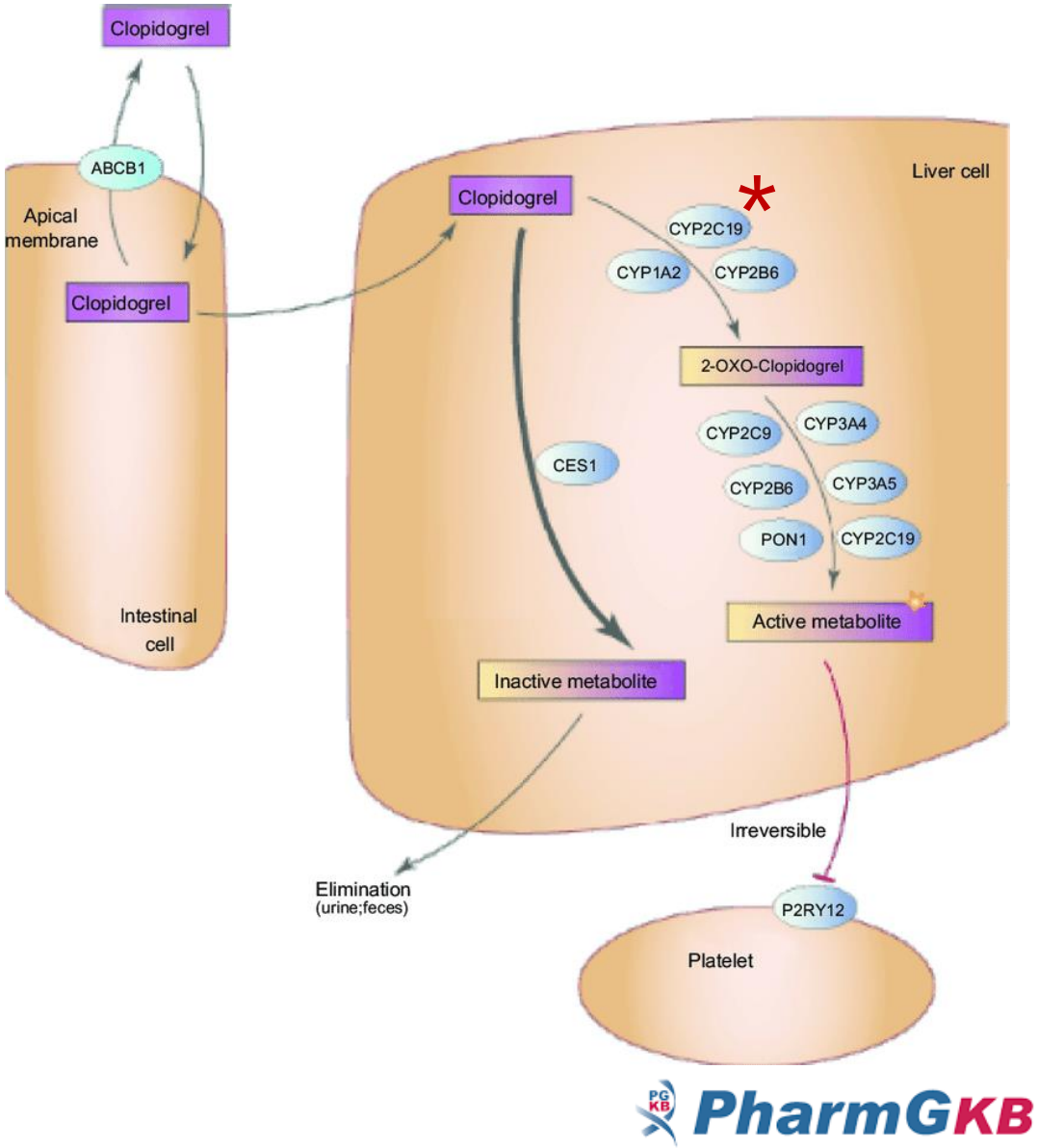
- *HLA-B*5701* - abacavir, PREDICT-1 trial, 1956 patients with HIV randomized to prospective genetic screening with avoidance of abacavir in patients with screening positive or to abacavir without screening (Mallal et al, NEJM, 2008)
- *TPMT* - thiopurines, TOPIC trial, 783 patients with inflammatory bowel disease randomized to pre-treatment screening with thiopurine dose reduction in *TPMT* carriers (one or more *TPMT* functional alleles) to usual dosing without preemptive genotyping (Coenen et al, Gastroenterology, 2015)
- *CYP3A5* - tacrolimus, 280 renal transplant recipients randomized to *CYP3A5*-guided tacrolimus dosing vs. standard dosing regimen (Thervet et al, CPT, 2010)
- *CYP2C9*/*VKORC1* - warfarin, several trials including COAG, EU-PACT, and GIFT (Kimmel, et al, NEJM, 2013; Pirmohamed et al, NEJM, 2013; Gage, et al, JAMA, 2017)

Evidence for Clinical Utility of PGx Testing: Other Approaches

- Evidence for supporting clinical utility is important
- **RCTs**: the gold standard
  - Expensive
  - Ethic issues, e.g., *HLA*1502* allele-related ADE, Stevens-Johnson syndrome
  - Well controlled setting with strict eligibility criteria
- **Pragmatic studies**: to gather evidence of in the context of clinical practice
  - More generalizable, selection biases/confounding factors minimized
  - Less rigorous to conduct

CYP2C19 and Clopidogrel

- Antiplatelet clopidogrel is a prodrug to prevent heart attacks and strokes in persons with heart disease or after certain procedures
- CYP2C19 enzyme is a major enzyme for its bioactivation
- Increased risk for cardiovascular adverse events in patients after percutaneous coronary intervention (PCI)
- Nonfunctional alleles are common, i.e., ~30% in Caucasian and African Americans, ~60% in Asians



CYP2C19 and Clopidogrel: Clinical Studies

- **TAILOR-PCI trial** (May 2013 – March 2020)
  - A multi-site (41 locations), open label, prospective, randomized trial, n=5300
  - Hypothesis tested: post-PCI patients using ticagrelor is superior to clopidogrel in reducing rate of major adverse cardiovascular events in *CYP2C19* reduced function allele (**2* or **3*) patients
  - PI: Naveen L. Pereira, Mayo Clinic
- **POPular Genetics** (June 2011 – April 2019)
  - A multi-site (10 locations, 8 in Netherland, Italy, and Belgium), randomized, parallel assignment-based intervention study, n=2488
  - To compare clinical outcomes (adverse events, safety endpoint of using alternative drugs, pharmacoeconomics) between intervention and non-intervention groups
  - The intervention group: genotyped for *CYP2C19* nonfunctional allele variants within 48 hours after primary PCI. Carriers will receive either ticagrelor or prasugrel instead of clopidogrel; Non-carriers will be treated with clopidogrel
  - The control group receives either ticagrelor or prasugrel, according to local standards at the same dosage as the *CYP2C19*2* or **3* carriers in the intervention group

POPular Genetics Trial

Sep 3, 2010 NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

Daniel M.F. Claassens, M.D., Gerrit J.A. Vos, M.D., Thomas O. Bergmeijer, M.D., Renicus S. Hermanides, M.D., Ph.D., Arnoud W.J. van 't Hof, M.D., Ph.D., Pim van der Harst, M.D., Ph.D., Emanuele Barbato, M.D., Ph.D., Carmine Morisco, M.D., Ph.D., Richard M. Tjon Joe Gin, M.D.

CONCLUSIONS

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Organization for Health Research

Factors to Consider When Developing and Evaluating a Clinical PGx LDT

- Understand the reasons for ordering PGx tests
  - Preemptive testing or reactive (post-event)
- Evaluate the test contents not only at the gene level but also at the variant level
  - Not two PGx tests are the same
  - More genes ≠ better
- Test technical performance and workflow
- Genotypes ≠ phenotypes
- Apply guidelines when appropriate
- Testing results should be interpreted by clinicians/pharmacists
- Testing results should be utilized together with patients' other clinical information

Contents of Single-Gene PGx Tests: Variants

No two clinical PGx assays testing the same variants and/or haplotypes

Table 1 Loci and Alleles Detected by Each Assay

Assay (sample sets tested)	Affymetrix DMET (tier 1)	GenMark eSensor† (tier 1)	Luminex xTAG (tier 1)	LifeTech Taqman laboratory-developed tests (tiers 1 and 2)	Agena Bioscience iPLEX ADME PGx Pro (tiers 1 and 2)	Agena Biosciend *CYP2D6*, *CYP2C9*, *VKORC1*, *CYP2C1*, *UGT1A1* (tiers 1 and 2)
CYP2C9	*2, *3, *4, *5, *6, *9, *10, *11, *12, *13, *14, *15, *16, *25, Y358C	*2, *3	*2, *3, *4, *5, *6	*2, *3, *5, *6, *8, *11	*2, *3, *4, *5, *6, *8, *9, *10, *11, *12, *13, *15, *25, *27	*1A, *1B, *1C, *1D, *2A, *2B, *2C, *3A, *3B, *4, *5, *6, *7, *8, *9, *10, *11A, *11B, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35
CYP2C19	*2A, *2B, *3, *4, *5, *6, *7, *8, *9, *10, *12, *13, *14, *15, *17, 439FS, 241FS, V331I	*2, *3, *4, *5, *6, *7, *8, *9, *10, *13, *17	*2, *3, *4, *5, *6, *7, *8, *9, *10, *17	*2, *3, *4, *4B, *6, *8, *17	*1B, *2, *3, *4, *5A, *5B, *6, *7, *8, *12, *17	*1A, *1B, *1C, *2, *2B, *3A, *3B (*20), *4A, *4B, *5A, *5B, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18,

Pratt VM, et al., 2016 (GeT-RM)

AMP Recommendations for Clinical PGx Laboratories: Allele/Variant Selection (*CYP2C19*, *CYP2C9*…)

The Journal of Molecular Diagnostics, Vol. 20, No. 3, May 2018

AMP Association for Molecular Pathology

ELSEVIER

the Journal of Molecular Diagnostics
jmd.amjpathol.org

SPECIAL ARTICLE

Recommendations for Clinical *CYP2C19* Genotyping Allele Selection

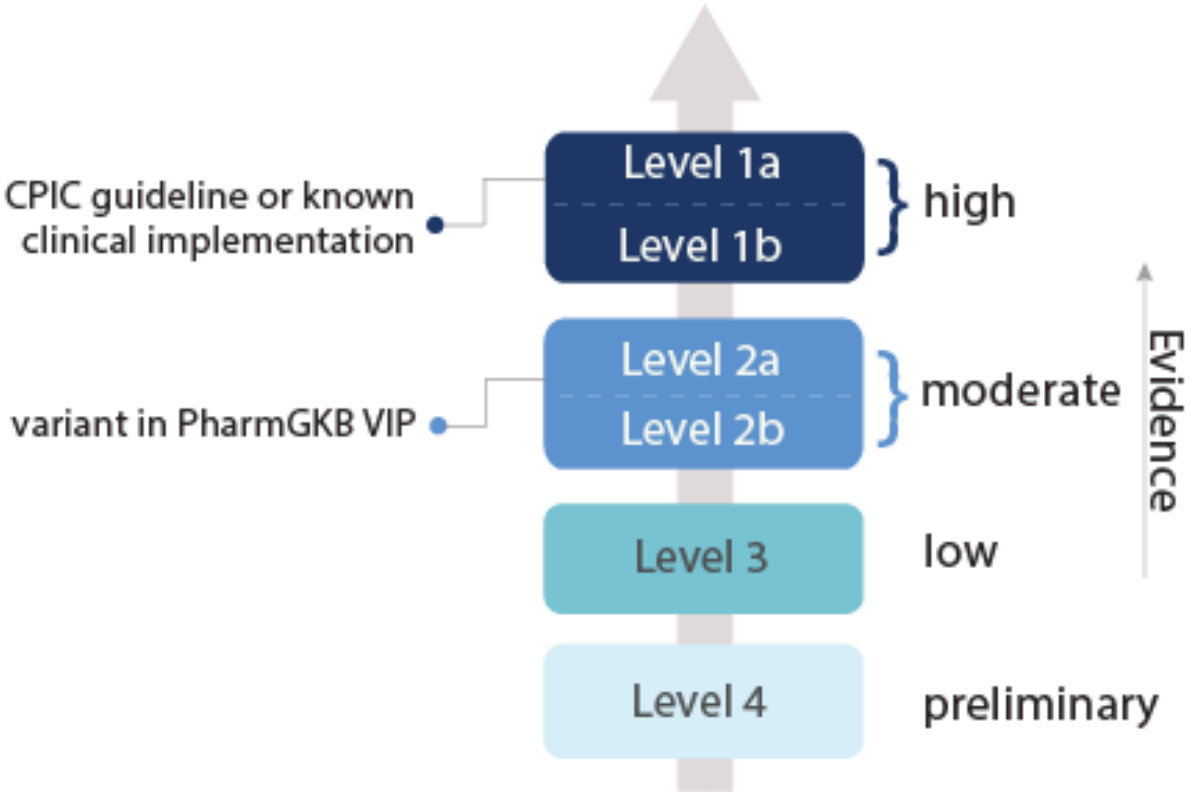
A Report of the Association for Molecular Pathology

Victoria M. Pratt,[*†] Andria L. Del Tredici,[*‡] Houda Hachad,[*§] Yuan Ji,[*¶] Lisa V. Kalman,[*‖] Stuart A. Scott,[*,**††] and Karen E. Weck[*‡‡§§]

From the Pharmacogenomics Working Group of the Clinical Practice Committee, Association for Molecular Pathology, Bethesda, Maryland; the Department of Medical and Molecular Genetics,† Indiana University School of Medicine, Indianapolis, Indiana; Millennium Health, LLC,‡ San Diego, California; Translational Software,§ Bellevue, Washington; the Department of Pathology and ARUP Laboratories,¶ University of Utah School of Medicine, Salt Lake City, Utah; the Division of Laboratory Systems,‖ Centers for Disease Control and Prevention, Atlanta, Georgia; the Department of Genetics and Genomic Sciences,** Icahn School of Medicine at Mount Sinai, New York, New York; Sema4, a Mount Sinai Venture,†† Stamford, Connecticut; and the Departments of*

Professional Guidelines/Regulations for Clinical PGx Practice

PharmGKB

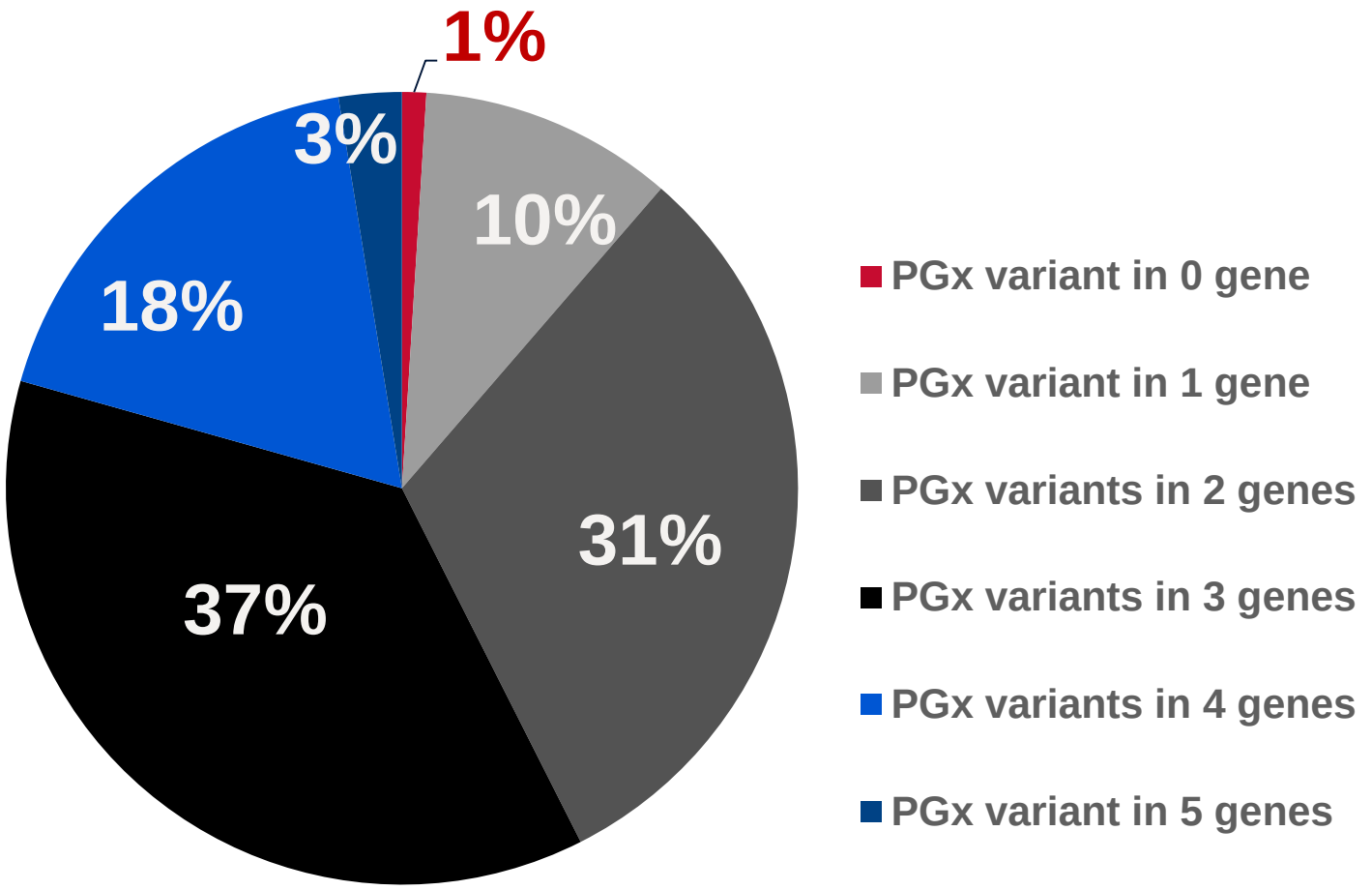


CPIC®
Clinical Pharmacogenetics Implementation Consortium

AMP Association for Molecular Pathology

FDA

the Journal of Molecular Diagnostics



The fraction of 1013 RIGHT subjects among groups carrying actionable PGx variants in 0 to 5 of the PGx genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *VKORC1*, and *SLCO1B1*)

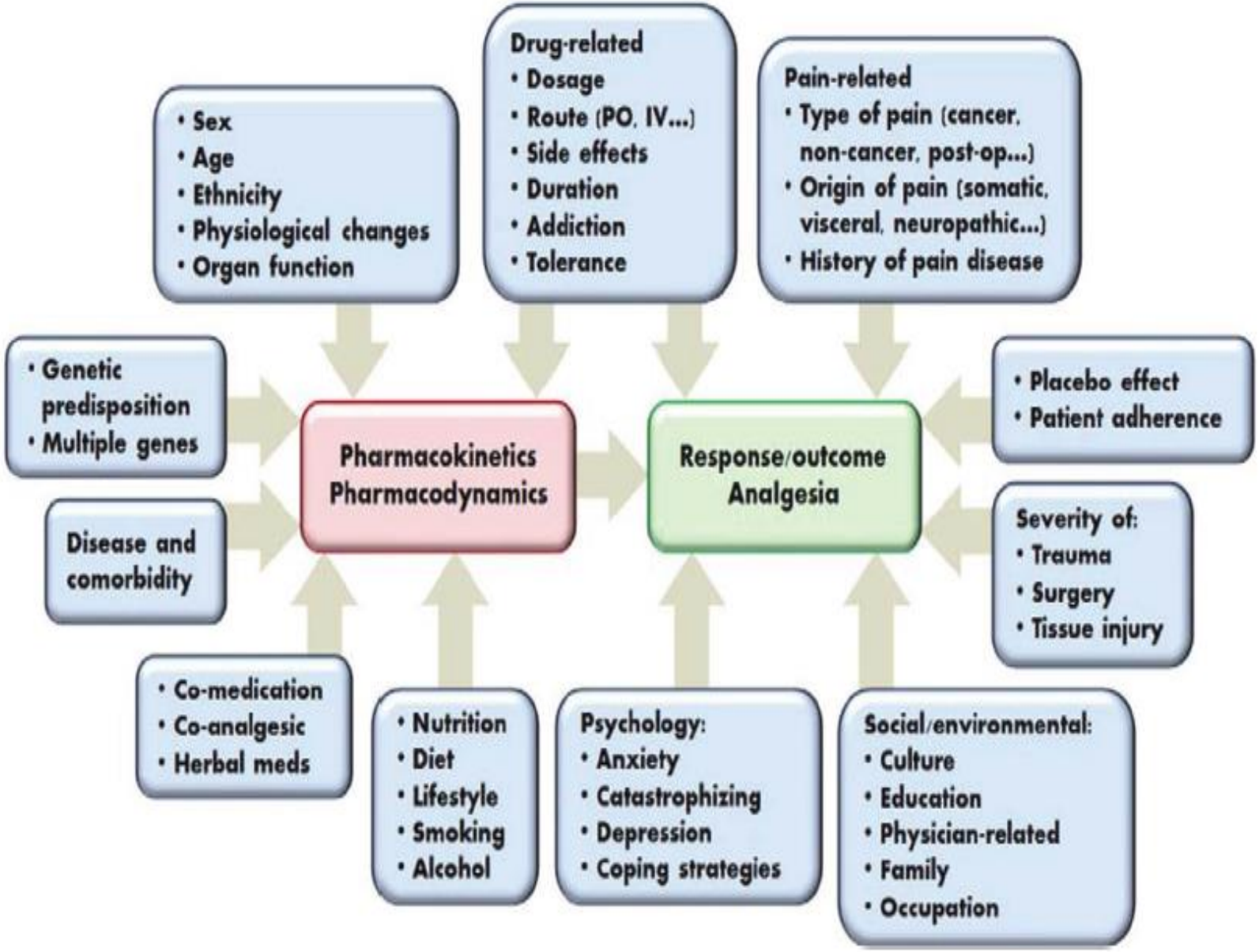
Ji et al. J. Mole Diagn. 2016

Multi-Gene PGx Panels

Gwen McMillin, PhD, DABCC(CC,TC)

Medical Director of Toxicology and PGx, ARUP Laboratories

Professor (Clinical) of Pathology, University of Utah



Clarke NJ, *Clin Chem* 62:70-6, 2016

FDA Drug Labels that Contain PGx (n=362 entries in August, 2019)

18 clinical indications

Top 10:

- Oncology (n=140)
- Infectious Disease (n=35)
- Psychiatry (n=35)
- Neurology (n=25)
- Anesthesiology (n=23)
- Hematology (n=20)
- Cardiology (n=17)
- Gastroenterology (n=16)
- Pulmonary (n=9)
- Rheumatology (n=9)

77 genes

Top 10:

- *CYP2D6* (n=66)
- *G6PD* (n=39)
- *CYP2C19* (n=22)
- *ESR, PGR* (n=15)
- *ERBB2* (n=14)
- *IFNL3* (n=12)
- *BCR-ABL1* (n=10)
- *CYP2C9* (n=10)
- *RYR1* (n=10)
- *UGT1A1* (n=9)

https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Examples of Drugs with Multiple Germline PGx Associations

Cardiology / Coagulation

Drug (generic name)	Gene
carvedilol	CYP2D6
clopidogrel	CYP2C19
flecainide	CYP2D6
lidocaine	G6PD
metoprolol	CYP2D6
phenprocoumon	CYP4F2
propafenone	CYP2D6
propranolol	CYP2D6
quinidine	CYP2D6
tamsulosin	CYP2D6
timolol	CYP2D6
warfarin	CYP2C9
warfarin	CYP4F2
warfarin	VKORC1

Behavioral Health

Drug (generic name)	Gene	Drug (generic name)	Gene
amitriptyline	CYP2C19	iloperidone	CYP2D6
amitriptyline	CYP2D6	imipramine	CYP2C19
aripiprazole	CYP2D6	imipramine	CYP2D6
brexpiprazole	CYP2D6	methylphenidate	CYP2D6
brivaracetam	CYP2C19	midazolam	CYP3A5
carbamazepine	HLA-A*31:01	mirtazapine	CYP2D6
carbamazepine	HLA-B*15:02	modafinil	CYP2D6
carvedilol	CYP2D6	nortriptyline	CYP2D6
cevimeline	CYP2D6	olanzapine	CYP2D6
citalopram	CYP2C19	oxcarbazepine	HLA-A
clobazam	CYP2C19	oxcarbazepine	HLA-B*15:02
clomipramine	CYP2C19	paroxetine	CYP2D6
clomipramine	CYP2D6	phenytoin	CYP2C9
clozapine	CYP2D6	phenytoin	HLA-B*15:02
desipramine	CYP2D6	protriptyline	CYP2D6
diazepam	CYP2C19	risperidone	CYP2D6
doxepin	CYP2C19	sertraline	CYP2C19
doxepin	CYP2D6	sertraline	CYP2D6
duloxetine	CYP2D6	timolol	CYP2D6
escitalopram	CYP2C19	trimipramine	CYP2C19
flibanserin	CYP2C19	trimipramine	CYP2D6
flibanserin	CYP2C9	tropisetron	CYP2D6
flibanserin	CYP2D6	venlafaxine	CYP2D6
fluoxetine	CYP2D6	vortioxetine	CYP2D6
fluvoxamine	CYP2D6		

Warfarin PGx

- PharmGKB (August, 2019)
  - 1086 variant annotations
  - 88 clinical annotations
  - 4 clinical guidance annotations (CPIC, CPNDS, DPWG)
  - 2 drug label annotations (FDA, HCSC)

- Three genes impact independent aspects of PK and PD
- Many RCTs and dosing algorithms have been published with mixed clinical results
- Barriers to adoption in routine clinical practice?

PGX LEVEL	SOURCE
Actionable PGx	U.S. Food and Drug Administration
Actionable PGx	Health Canada Santé Canada

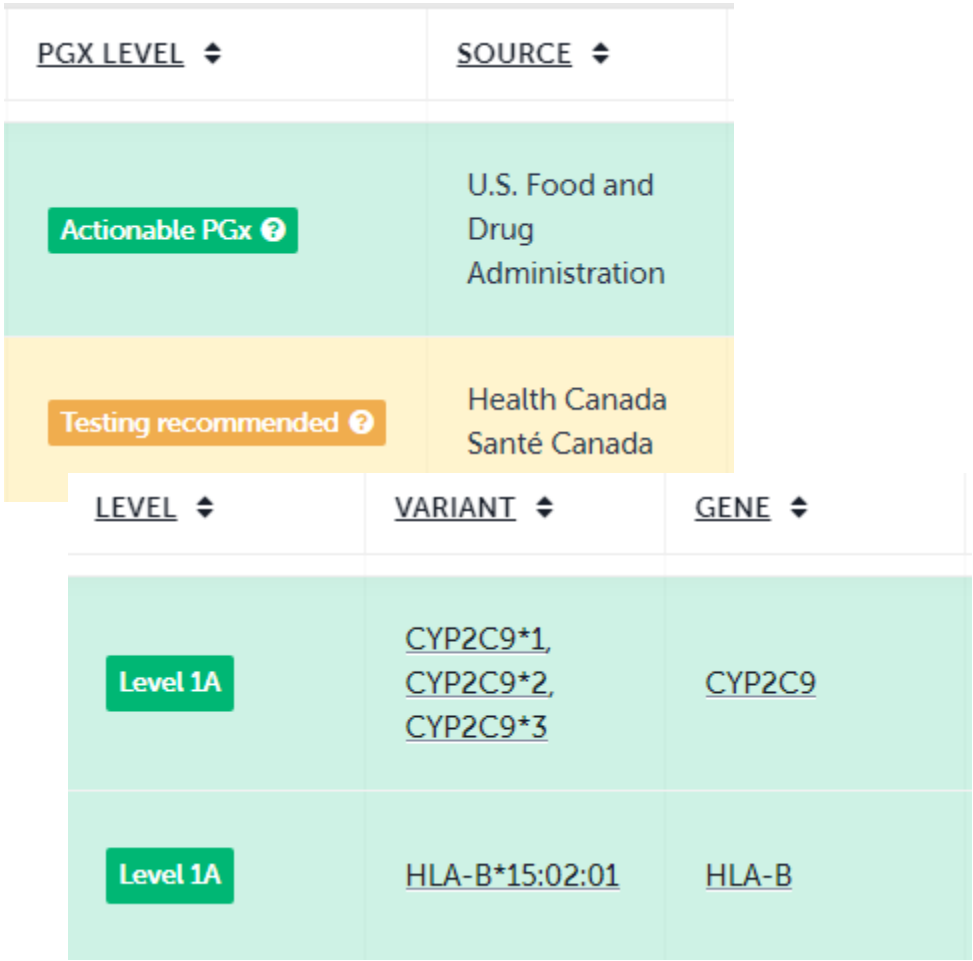
LEVEL	VARIANT	GENE
Level 1A	rs1057910	CYP2C9
Level 1A	rs9923231	VKORC1
Level 1A	rs2108622	CYP4F2

https://www.pharmgkb.org/chemical/PA451906

Phenytoin PGx

- PharmGKB (August, 2019)
  - 257 variant annotations
  - 33 clinical annotations
  - 2 clinical guidance annotations (CPIC, DPWG)
  - 2 drug label annotations (FDA, HCSC)

- Two genes impact independent aspects of PK and PD

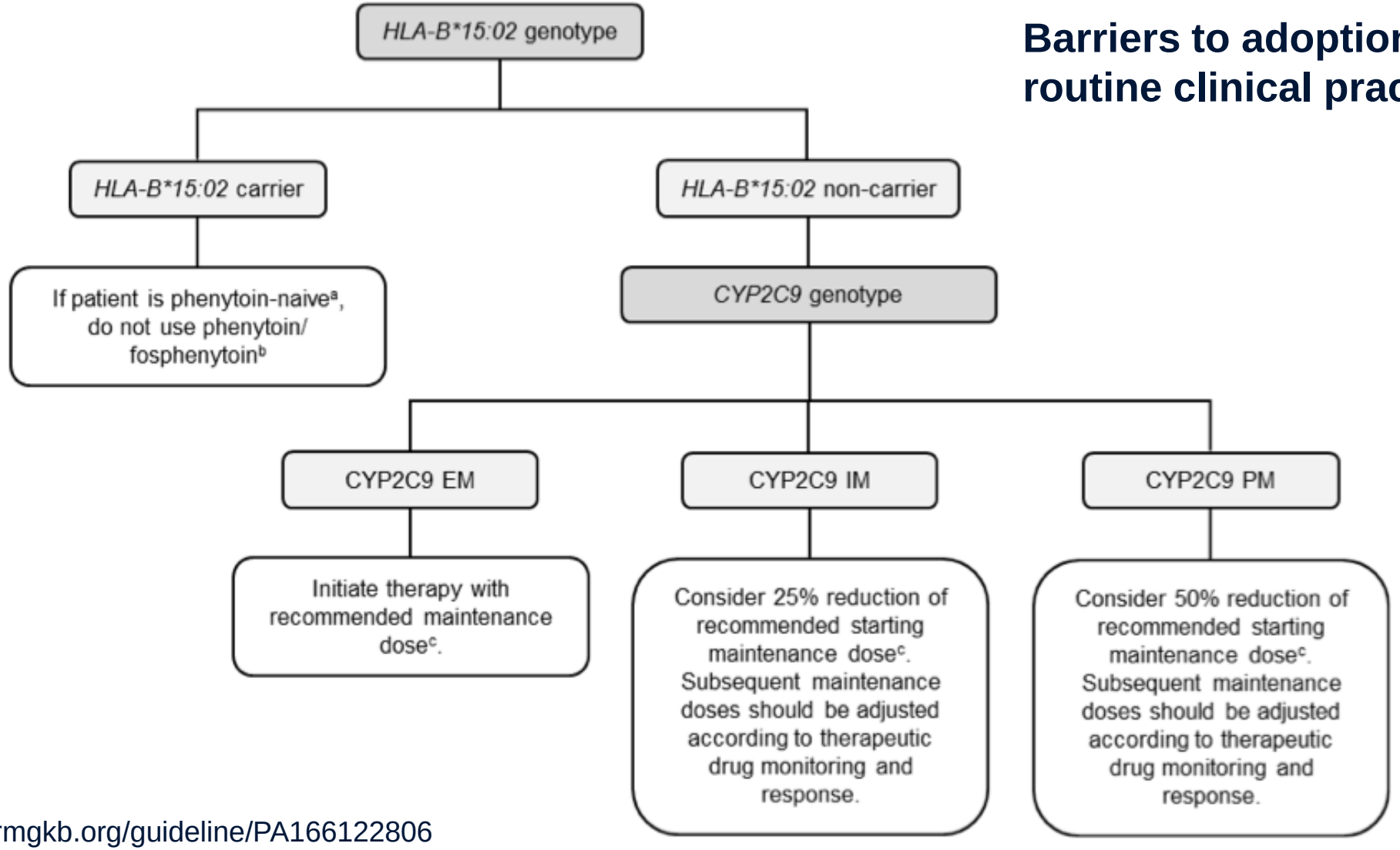


PGX LEVEL	SOURCE
Actionable PGx	U.S. Food and Drug Administration
Testing recommended	Health Canada Santé Canada

LEVEL	VARIANT	GENE
Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3	CYP2C9
Level 1A	HLA-B*15:02:01	HLA-B

https://www.pharmgkb.org/chemical/PA450947

Barriers to adoption in routine clinical practice?



https://www.pharmgkb.org/guideline/PA166122806

Examples of Positive Outcomes from Multi-gene PGx testing

- Improved antidepressant efficacy
  - 2.52-fold greater rate of remission of major depressive disorder with testing (Singh, Clin Psychopharmacology Neuroscience, 2015)
- Reduced pharmacy costs
  - $1035.60 savings over 1 yr in total medication costs with testing in cohort of psychiatric patients (Winner et al, Current Medical Research & Opinion, 2015)
- Reduced rates of hospitalization
  - 9.8% with testing versus 16.1% without testing in cohort of patients ≥65 yrs (Brixner et al, J Medical Economics, 2015)
- Improved adherence with therapy

Are more genes better?

- In a review of 22 proprietary algorithms for clinical validity, there were 46 genes represented (Bousman, Lancet Psychiatry, 2016)
  - 25 (53%) were associated with supporting evidence graded by the PharmGKB databased as preliminary or low
  - 9 (20%) were associated with high levels of evidence: *CYP2D6*, *CYP2C19,* and *HLA-B*
  - All algorithms include *CYP2D6* and *CYP2C19*; most also include *CYP2C9* and *CYP3A4/5*

- 39.1% of patients ≥65 receive at least one drug metabolized by *CYP2D6*, *CYP2C19* and/or *CYP2C9* (Kuch et al, Health Informatics, 2016)

Proposed Minimum Germline PGx Panel for Psychiatry

- Evidence based panel includes 16 variant alleles within five genes:
  - *CYP2C9*, *CYP2C19*, *CYP2D6*
  - *HLA-A*, *HLA-B*
- Relevant to antidepressants, antipsychotics, mood stabilizers

- Consistent with published CPIC guidelines:
  - Tricyclics (n=7)
  - Selective Serotonin Reuptake Inhibitors (n= 5)
  - Atomoxetine
  - Anticonvulsants (n=3)

Bousman et al, *Curr Opin Psych* 32(1):7-15, 2019

https://cpicpgx.org/guidelines/

TABLE 1. Antidepressant Drug-by-Gene Associations With Moderate to High Levels of Evidence or Included in One of the Combinatorial Pharmacogenetic Tests Evaluated Here[a]

	Pharmacodynamic										Pharmacokinetic				
Agent	ADRA2A	BDNF	COMT	CRHR1	FKBP5	GRIK4	HTR1A	HTR2A	SLC6A2	SLC6A4	ABCB1	CYP1A2	CYP2B6	CYP2C19	CYP2D6
Amitriptyline[b]											3				1A
Bupropion															
Citalopram[b]		3			2B			2B		2A	3			1A	3
Desipramine[b]		3													1A
Doxepin[b]															1A
Duloxetine[b]					3			3		2A		1A			1A
Escitalopram[b]		3		3	2B		3			3		3			3
Fluoxetine[b]		3	3				3	3			3			1A	3
Fluvoxamine[b]											3				1A
Imipramine[b]														2A	1A
Maprotiline															3
Mirtazapine					2B					3			3		
Nefazodone[b]					3						3				
Nortriptyline[b]		3									3				1A
Paroxetine[b]		3	3		2B		3			3	3	3			1A
Sertraline							3			3	3			1A	
Trimipramine[b]															1A
Venlafaxine[b]			3		2B				3		3				2A
Antidepressants, unspecified		3		3	2B	2B	3	2B			3				1A
SSRIs, unspecified	3		2B		2B		3	2B			3				
Number of variants per gene	1	6	2	2	4	2	3	5	1	3	15	9	5	8	14
Interaction type[c]	E	E,T	E	E	E,T	E	E	E,T	E	E,T	E,T	E,T	E,O	E,M,T	E,D,M,T

[a] This is not a comprehensive representation of antidepressant drug-by-gene associations; it is limited to the PharmGKB search terms "depressive disorder, major; depressive disorder; depression; [antidepressant name]"; it excludes drug-gene interactions related to "bipolar disorder; anxiety disorder"; it excludes antipsychotic and some antidepressant drugs; and it excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB. The PharmGKB knowledge base, which was used to generate this table, is not the sole source of relevant pharmacogenetic information. BDNF=brain-derived neurotrophic factor; COMT=catechol *O*-methyltransferase; SSRI=selective serotonin reuptake inhibitor.

[b] These agents have U.S. Food and Drug Administration labeling with CYP450 pharmacogenetic information.

[c] Pharmacogenetic information relevant to drug efficacy (E), dosage (D), metabolism/pharmacokinetics (M), toxicity/adverse drug reactions (T), and other (O). Values correspond to a high (1A, 1B), moderate (2A, 2B), or low (3) level of evidence according to the PharmGKB rating scale.

Zeier et al, *Am J Psychiatry* 175:873-86, 2018

Expanded PGx Panels for Behavioral Health

Possible PROs

- A broad test could provide guidance for a large number of drugs by considering multiple aspects of PK and PD
- May promote a more intensive review of medications, particularly for polypharmacy patients
- Many multi-gene tests can be consolidated to minimize time to result and costs

Possible CONs

- Inconsistencies in content among commercially available tests
- Weighted contribution of multiple gene variants to the drug response phenotype prediction may not have been well studied
- Reimbursement may be poor for genes that are not represented by FDA labeling or published gene-based dosing guidelines

Using PGx to Manage Moderate to Severe Depression

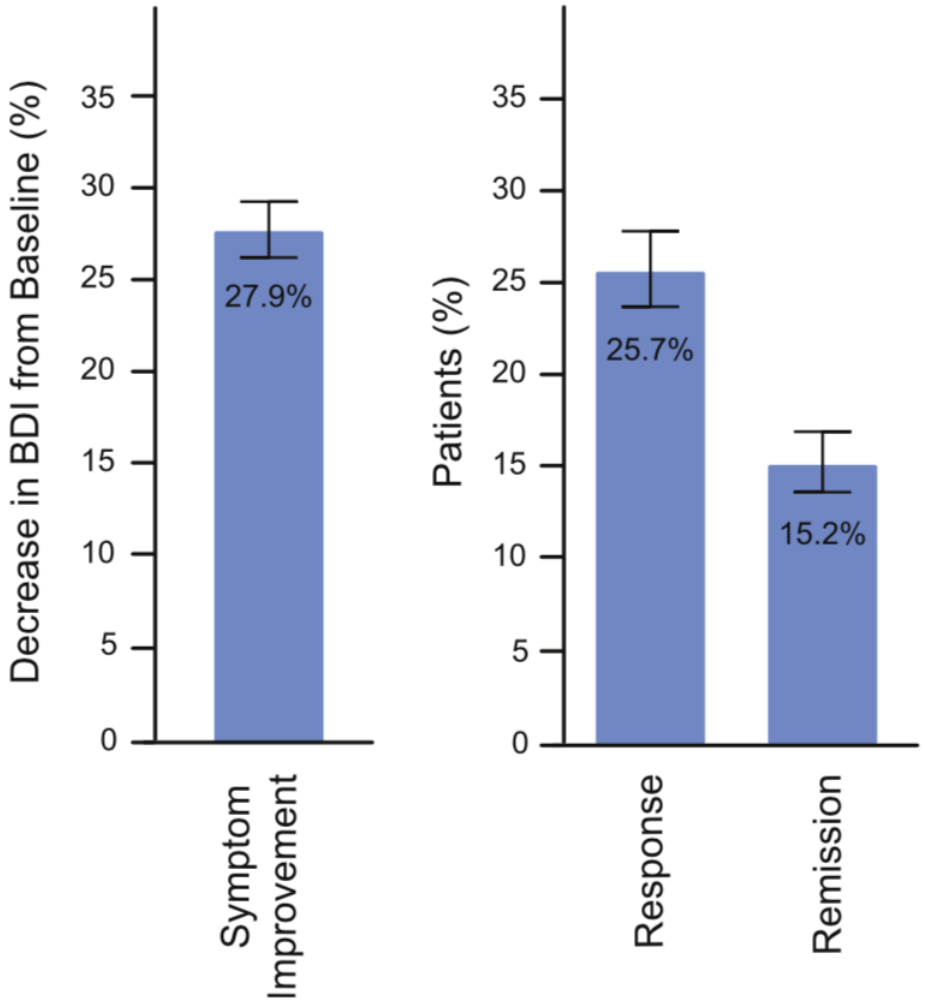


Fig. 2. Patients' symptom improvement, response rate, and remission rate from baseline to follow-up in the full cohort (N = 1871).

Tanner et al, *J Psych Res*, 104:157-62, 2018

Using PGx to Manage Moderate to Severe Depression: GUIDED Trial

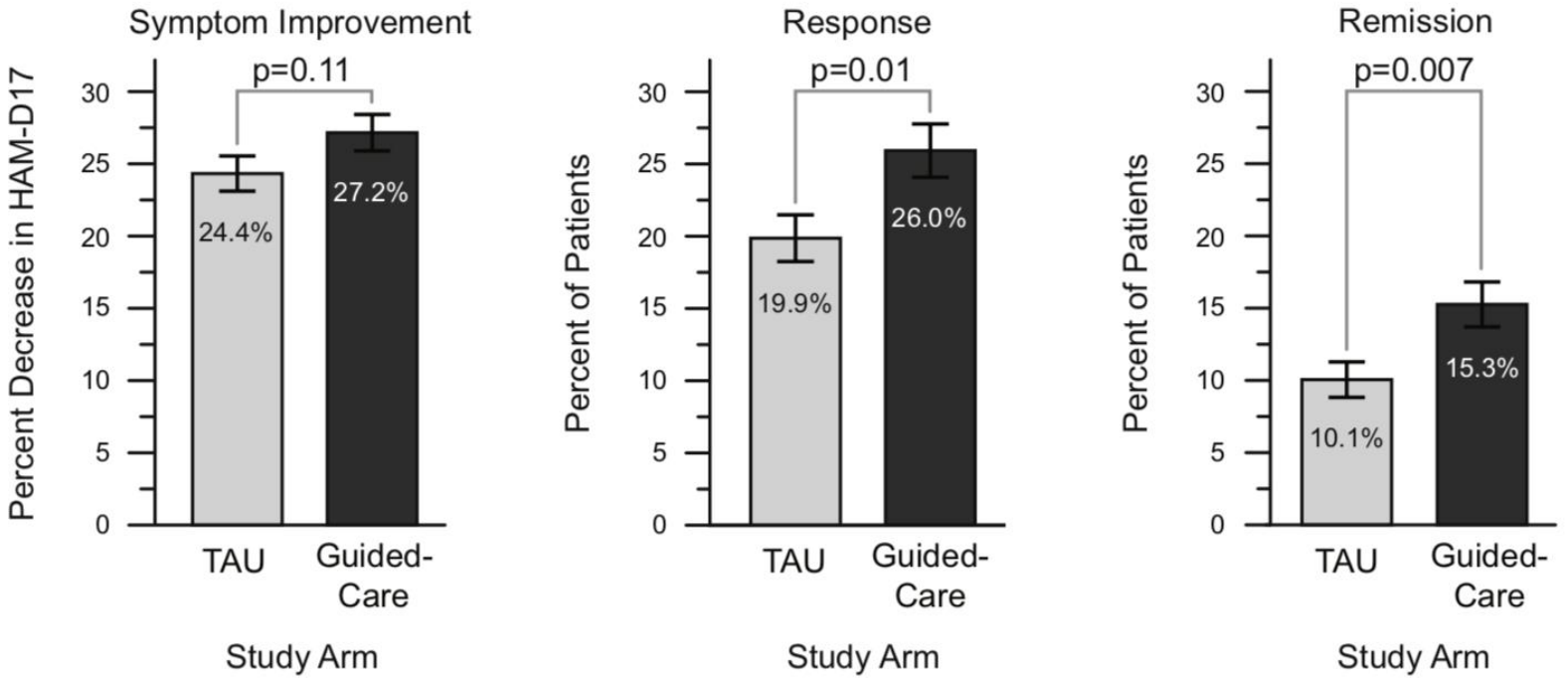


Fig. 1. Patient outcomes at week 8 in the pharmacogenomics guided-care arm (n = 560) compared to treatment as usual (n = 607). Outcomes were evaluated using the HAM-D17 depression rating scales.

Greden et al, *J Psych Res* 111:59-67, 2019

Using PGx to Manage Moderate to Severe Depression: GUIDED Trial

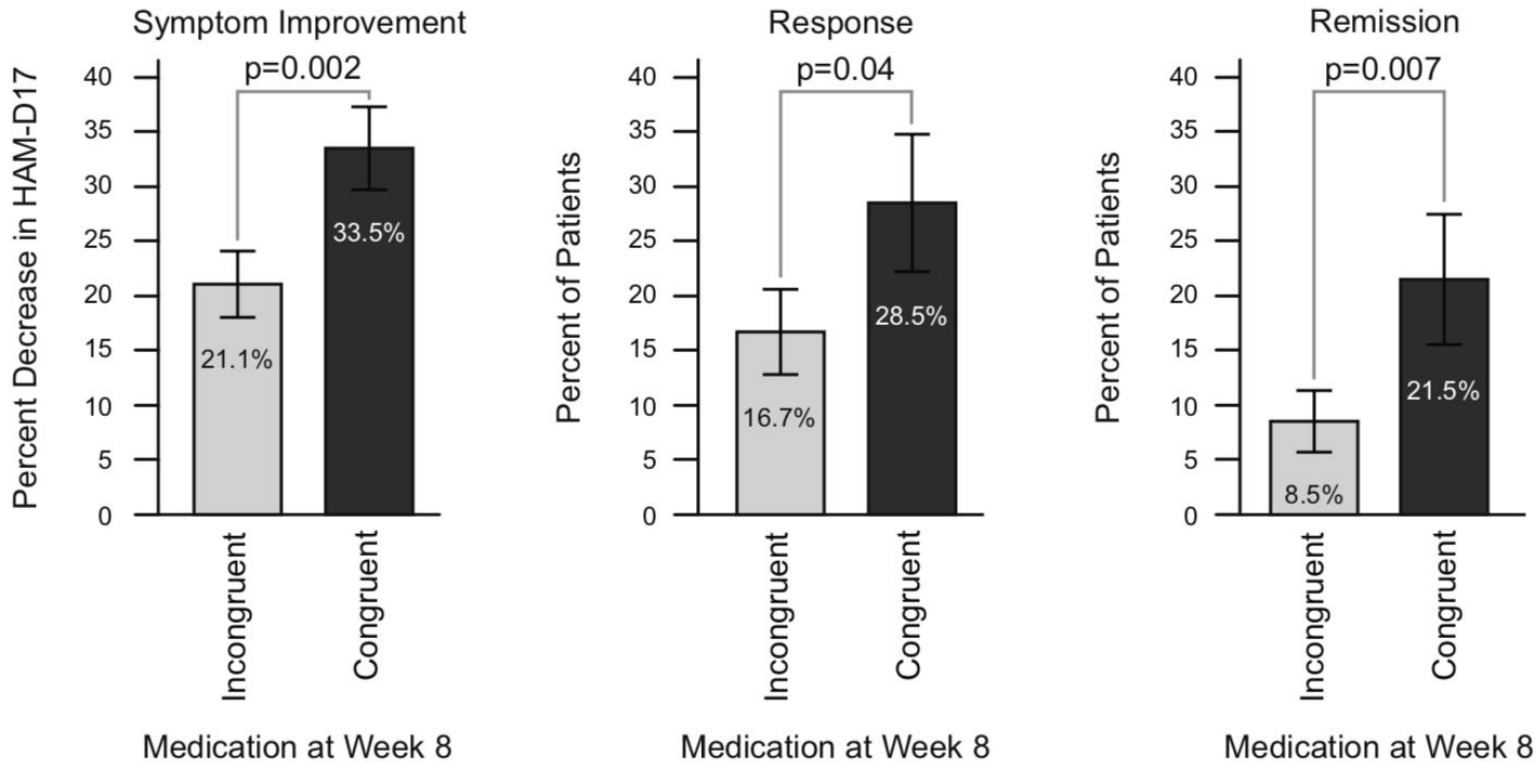


Fig. 4. Patient outcomes among those who were taking incongruent medications at baseline in both study arms (n = 213). Patients were evaluated according to whether they were prescribed congruent (n = 77) or incongruent (n = 136) medications at week 8. Outcomes were evaluated using the HAM-D17 depression rating scale.

Greden et al, *J Psych Res* 111:59-67, 2019

Published Cost Savings with PGx for Antidepressant Therapy

Table 4 Published per-patient savings using genetic testing to guide medication management (adjusted to 2016 dollars)

	Present findings 2016	Winner et al[27]	Chou et al[28]
Per-patient savings	USD$5,962	USD$6,193	USD$7,112–USD$10,667

Maciel et al, *Neuropsych Dis Treat* 14:225-30, 2018

Factors that Contribute to Successful Implementation of PGx

- Multi-disciplinary approach
  - Laboratory
  - Pharmacy
  - Providers
  - Administrators/Payers
  - Regulators
- Transparency about when to order which tests; single-gene or multi-gene panels
- Consensus on how results will be utilized
- Education

Priority should be on promoting safety and good patient care!

Conclusions

- PGx targets predict discrete aspects of pharmacology
- Clinical applications of PGx should align with needs, and consider the evidence behind any drug-gene association
- Non-genetic factors are also critical components of medication management
- No PGx test can replace the need for clinical and therapeutic monitoring
- Successful implementation requires an multi-disciplinary approach

P.A.C.E.®/FL Password:

PG91819

Go to aruplab.com/singlegene-drug
and click on the
P.A.C.E.®/FL Credit Redemption Link

Credit redemption for this webinar will be available through
October 2, 2019

This webinar can be viewed after November 1, 2019 at www.arup.utah.edu where CME/SAM, P.A.C.E.® and Florida continuing education credit will be available.

ARUP LABORATORIES

HEALTH
UNIVERSITY OF UTAH

ARUP IS A NONPROFIT ENTERPRISE OF THE UNIVERSITY OF UTAH SCHOOL OF MEDICINE, DEPARTMENT OF PATHOLOGY.