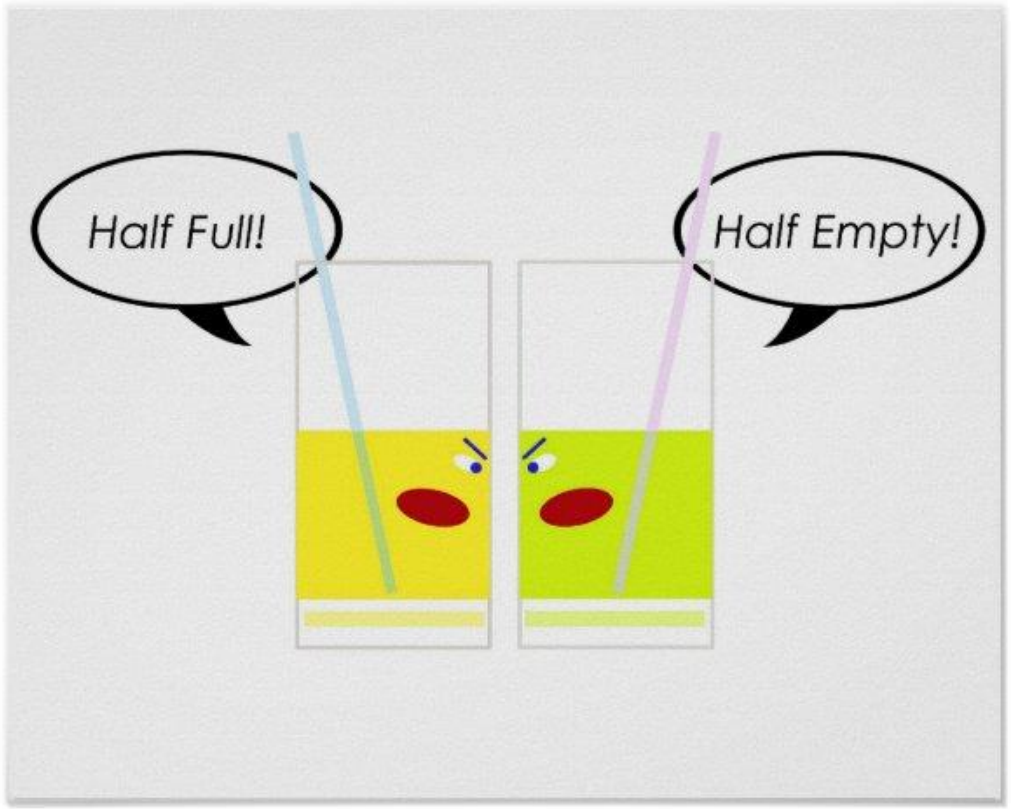
PGX AND TDM IN PSYCHOPHARMACOLOGY

GWEN MCMILLIN, PHD, DABCC(CC,TC)

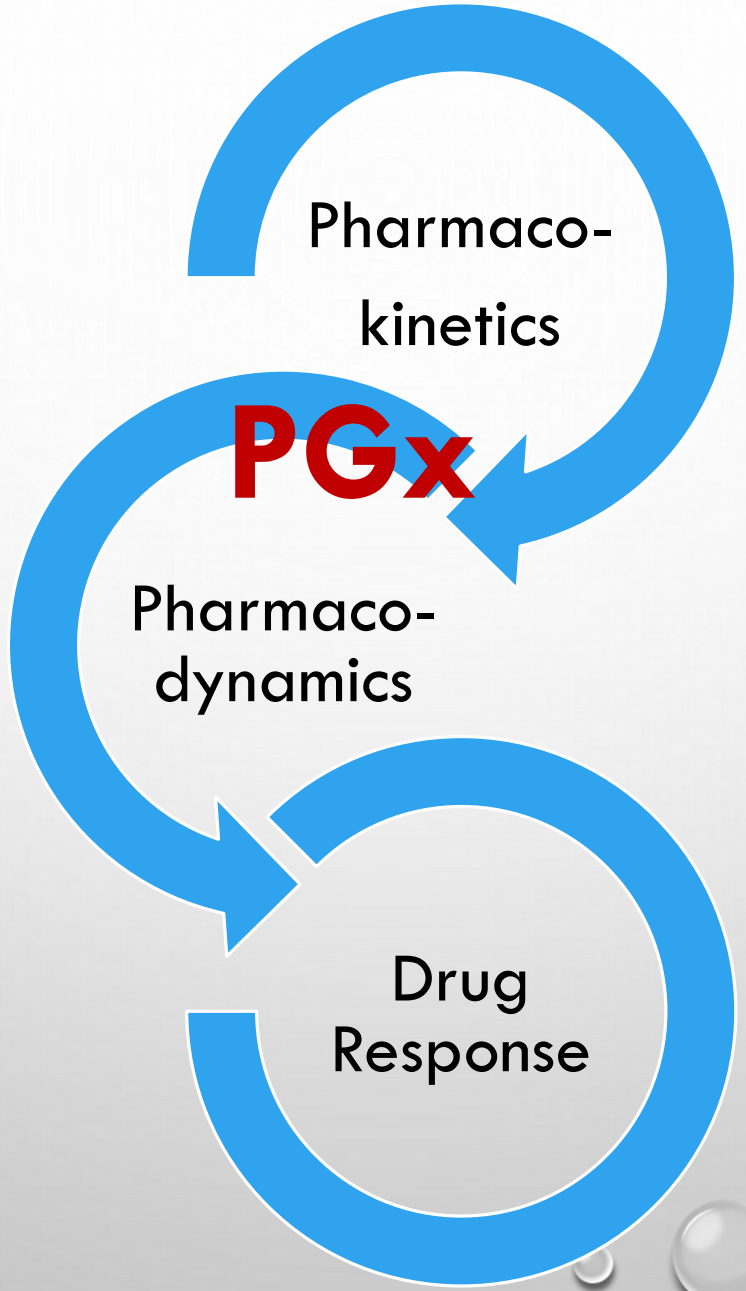
UNIVERSITY OF UTAH, DEPT OF PATHOLOGY

ARUP LABORATORIES


Half Full!
Half Empty!

OUTLINE

- NUTS AND BOLTS OF PHARMACOGENOMICS (PGX) TESTING
- EXAMPLES RELEVANT TO BEHAVIORAL HEALTH CARE
  - SINGLE GENE-DRUG ASSOCIATIONS
  - MULTIPLE GENE-DRUG ASSOCIATIONS
  - TDM
- IMPLEMENTATION
  - VARIABLES TO CONSIDER WHEN SELECTING A TEST
  - FACTORS FOR SUCCESS



The right concentration, at the right time

TDM

Physiology to support mechanism(s) of action

CLINICAL MONITORING

Adherence
Co-medications
Nutritional status
Demographics
Clinical status
Genetics
Psychology

PGX

POSSIBLE INDICATIONS FOR PGX

- MANDATED FOR SAFETY
- CLINICALLY ACTIONABLE PGX ASSOCIATIONS FOR MEDICATIONS UNDER CONSIDERATION
- PATIENT HAS FAILED MULTIPLE MEDICATIONS
- PERSONAL OR FAMILY HISTORY OF AT LEAST ONE SERIOUS ADVERSE DRUG REACTIONS
- RELEVANT TESTING IS AVAILABLE WITH REASONABLE LOGISTICS

U-PGx | Ubiquitous Pharmacogenomics

upgx.eu

Home U-PGx PREPARE Education News Login Members Contact

EXAMPLES OF US FACILITIES THAT ARE EARLY ADOPTERS

- PG4KDs at St. Jude Children's Research Hospital
- University of Florida Health Personalized Medicine Program
- My Drug Genome program at Vanderbilt University
- Center for Personalized Therapeutics at University of Chicago
- Center for Pharmacogenomics at the Ohio State University
- Mayo Clinic Center for Individualized Medicine

PharmGKB.org

FDA DRUG LABELS THAT CONTAIN PGX

(N=404 ENTRIES AS OF APRIL, 2020)

18 therapeutic areas,

of which top 10 are :

- Oncology (n=164)
- **Psychiatry (n=37)**
- Infectious Disease (n=35)
- Neurology (n=28)
- Hematology (n=26)
- Anesthesiology (n=24)
- Cardiology (n=18)
- Gastroenterology (n=16)
- Rheumatology (n=10)
- Pulmonology (n=9)

88 genetic biomarkers,

of which top 10 are :

- ***CYP2D6* (n=68)**
- *G6PD* (n=39)
- ***CYP2C19* (n=22)**
- *ESR*, *PGR* (n=21)
- *ERBB2* (n=17)
- ***CYP2C9* (n=14)**
- *IFNL3* (n=12)
- *BCR-ABL1* (n=10)
- *EGFR* (n=10)
- *UGT1A1* (n=9)
- *ALK* (n=9)

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

NEW FDA RESOURCE TABLE, 2020

- GERMLINE ASSOCIATIONS ONLY, WITH A CLINICAL FOCUS
- CATEGORIZES ASSOCIATIONS IN 3 LISTS, BASED ON EVIDENCE :
  - **SUPPORT THERAPEUTIC MANAGEMENT RECOMMENDATIONS** : 51 DRUGS, 13 GENES
  - **POTENTIAL** IMPACT ON SAFETY OR RESPONSE : 19 DRUGS, 7 GENES
  - **POTENTIAL** IMPACT ON PHARMACOKINETIC PROPERTIES ONLY : 37 DRUGS, 5 GENES
- BASED ON FDA CLEARED LABELING AND AN INTERNAL (FDA) WORKGROUP REVIEW
- INTENDED TO BE DYNAMIC AND OPEN TO PUBLIC COMMENT

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

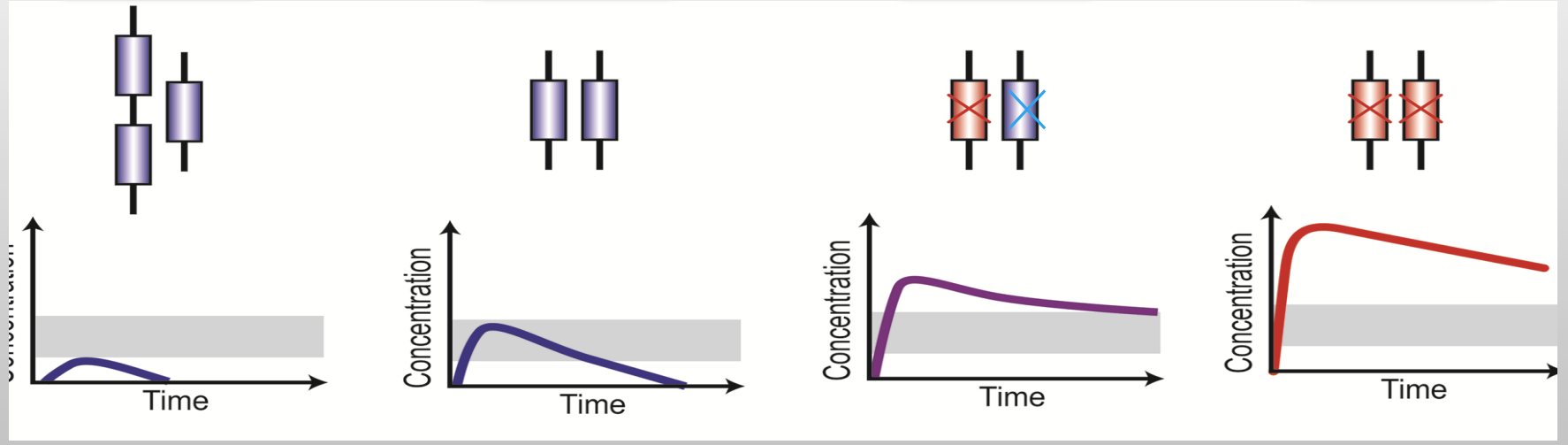
FDA RESOURCE TABLE EXAMPLES

- FIRST TIER :
  - *CYP2D6* AND AMPHETAMINE, ARIPIPRAZOLE, ATOMOXETINE, BREXPIPRAZOLE, CITALOPRAM, CLOBAZAM, CLOZAPINE, ILOPERIDONE, THIORIDAZINE AND VENLAFAXINE
  - *CYP2C9* AND DRONABINOL
  - *HLA-B*15:02* AND CARBAMAZEPINE
- SECOND TIER :
  - *CYP2D6* AND PERPHENAZINE
  - *HLA-A*31:01* AND CARBAMAZEPINE
- THIRD TIER :
  - *CYP2D6* AND AMITRIPTYLINE, AMOXAPINE, CLOMIPRAMINE, DESIPRAMINE, DIAZEPAM, DOXEPIN, FLUVOXAMINE, IMIPRAMINE, NORTRIPTYLINE, PAROXETINE, PROTRIPTYLINE, RISPERIDONE, TRIMIPRAMINE
  - *CYP2C19* AND ESCITALOPRAM

Pharmacogenetic associations for which the data support therapeutic management recommendations

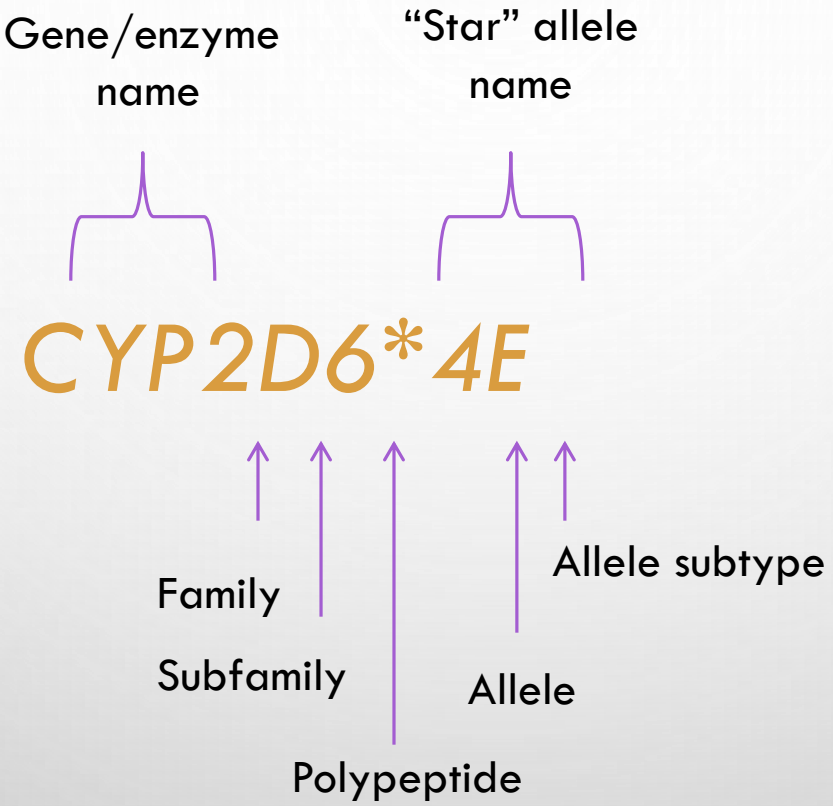
Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Aripiprazole Lauroxil	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. Refer to FDA labeling for specific dosing recommendations.
Azathioprine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolizers. Dosage reduction is recommended in intermediate metabolizers for NUDT15 or TPMT. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for

Ultra-rapid metabolizer : multiple copies of normal alleles	**Normal/ Extensive metabolizer:** 2 normal alleles	**Intermediate metabolizer:** Mix of normal, decreased and/or no function alleles	**Poor metabolizer:** 2 no function alleles



Effect on drug response is drug-dependent…

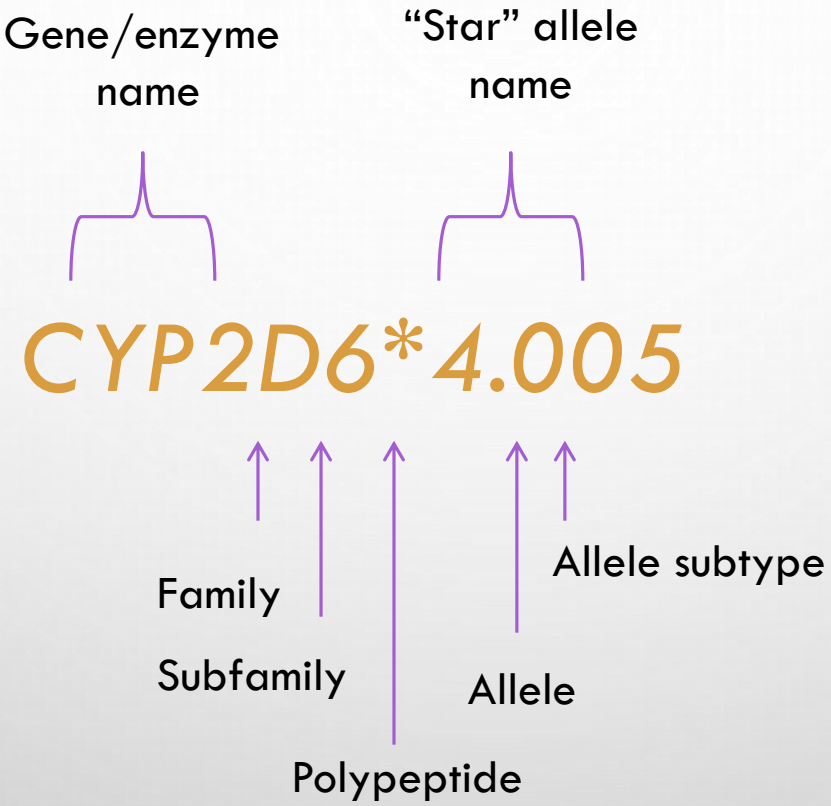
CYTOCHROME P450 (CYP) NOMENCLATURE



100C>T
1661G>C
1846G>A
4180G>C

cypalleles.ki.se

CYTOCHROME P450 (CYP) NOMENCLATURE



100C>T
1661G>C
1846G>A
4180G>C

**1 suggests that no variants were detected*

PharmVar.org

ASSIGNMENT OF FUNCTIONAL STATUS

PharmVar
Pharmacogene Variation Consortium

HOME ABOUT GENES SUBMISSIONS MEMBERS RESOURCES CONTACT

PV ID Looku

CYP2D6*4		PV00429	1847G>A (splicing defect/169frameshift)		no function ✕
CYP2D6*4.001	CYP2D6*4A	PV00235	-1426C>T, -1235A>G, -1000G>A, 100C>T (P34S), 310G>T, 745C>G, 842T>G, 973C>A (L91M), 983A>G (H94R), 996C>G, 1662G>C, 1847G>A (splicing defect/169frameshift), 2098A>G, 3385A>C, 3583A>G, 4181G>C (S486T), 4402C>T	Def	deposited by Gaedigk et al. and by Nofziger Gough et al. 1990 Hanioka et al. 1990 Kagimoto el al 1990
CYP2D6*4.002	CYP2D6*4B	PV00237	100C>T (P34S), 973C>A (L91M), 983A>G (H94R), 996C>G, 1847G>A (splicing defect/169frameshift), 4181G>C (S486T)	Lim	Kagimoto el al 1990
CYP2D6*4.003	CYP2D6*4C	PV00236	100C>T (P34S), 1662G>C, 1847G>A (splicing defect/169frameshift), 3888T>C, 4181G>C (S486T)	Lim	Yokota et al. 1993
CYP2D6*4.004	CYP2D6*4D	PV00847	-1426C>T, -1000G>A, 100C>T (P34S), 310G>T, 842T>G, 1038C>T, 1662G>C, 1847G>A (splicing defect/169frameshift), 2098A>G, 3385A>C, 3583A>G, 4181G>C (S486T), 4402C>T	Def	Liau et al. deposited by Gaedigk et al.
CYP2D6*4.005	CYP2D6*4E	PV00254	100C>T (P34S), 1662G>C, 1847G>A (splicing defect/169frameshift), 4181G>C (S486T)	Lim	Marez et al. 1997
CYP2D6*4.006	CYP2D6*4F	PV00257	100C>T (P34S), 973C>A (L91M), 983A>G (H94R), 996C>G, 1662G>C, 1847G>A (splicing defect/169frameshift), 1859C>T, 4181G>C (S486T)	Lim	Marez et al. 1997

ALLELE FREQUENCIES VARY BY ETHNICITY: *CYP2D6* AND *CYP2C19* EXAMPLES

Allele	Europeans	African	East Asian	South Asian	American
*CYP2C19*2*	18.3	18.1	31.0	**34.0**	10.1
*CYP2C19*3*	rare	rare	**6.7**	rare	rare
*CYP2C19*17*	22.4	**23.5**	1.5	13.6	12.0
*CYP2D6*3*	**4.1**	rare	rare	rare	rare
*CYP2D6*4*	15.5	11.9	rare	11.6	**15.7**
*CYP2D6*5*	3.0	4.0	**6.5**	2.0	3.0
*CYP2D6*10*	rare	3.2	**58.7**	6.5	rare
*CYP2D6*17*	rare	**19.7**	rare	rare	1.0
*CYP2D6*29*	rare	**9.2**	rare	rare	rare
*CYP2D6*41*	3.0	3.0	3.0	**13.5**	3.5
CYP2D6xN	2.3	**9.3**	2.0	1.5	1.0

Van Westrhenen R, et al *Frotiers in Psych*, 11:94, 2020

EFFORTS TO STANDARDIZE THE "MUST TEST" PGX VARIANTS UNDERWAY

- CURRENTLY PUBLISHED FOR CYP2C9 AND CYP2C19
- CYP2D6 IS IN PROGRESS, OTHER GENES PLANNED
- ORGANIZED INTO TIERS OF VARIANTS
- GUIDELINES AND RELATED WEBINARS ARE AVAILABLE THROUGH AMP.ORG
- RECOGNIZED BY THE COLLEGE OF AMERICAN PATHOLOGISTS

AMP ASSOCIATION FOR MOLECULAR PATHOLOGY

COLLEGE of AMERICAN PATHOLOGISTS

PREDICTING PHENOTYPE

Term/Gene Category	Final Term[a]	Functional Definition	Genetic Definition	Example diplotypes/alleles
Allele Functional Status-all genes	Increased Function	Function greater than normal function	N/A	*CYP2C19*17*
	Normal Function	Fully functional/wild-type	N/A	*CYP2C19*1*
	Decreased Function	Function less than normal function	N/A	*CYP2C19*9*
	No Function	Non-functional	N/A	*CYP2C19*2*
	Unknown Function	No literature describing function or the allele is novel	N/A	*CYP2C19*29*
	Uncertain Function	Literature supporting function is conflicting or weak	N/A	*CYP2C19*12*
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 and non-drug metabolizing enzymes[b] (*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-Carrier status (*HLA-B*)	Positive	Detection of high-risk allele	Carrier of high-risk allele	*HLA-B*15:02*
	Negative	High risk-allele not detected	Not a carrier of high-risk allele	

[a]All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 Decreased Function)
[b]This set of terms will be used at the discretion of the CPIC guideline authors if applicable for genes that do not fit into other term/gene categories.

PHENOTYPE PREDICTIONS MAY CHANGE

Citation: Clin Transl Sci (2019) XX, 1–9; doi:10.1111/cts.12692

ARTICLE

Standardizing *CYP2D6* Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group

Kelly E. Caudle[1,*], Katrin Sangkuhl[2], Michelle Whirl-Carrillo[2], Jesse J. Swen[3], Cyrine E. Haidar[1], Teri E. Klein[2], Roseann S. Gammal[1,4], Mary V. Relling[1], Stuart A. Scott[5,6], Daniel L. Hertz[7], Henk-Jan Guchelaar[3] and Andrea Gaedigk[8,9]

- CHANGED PHENOTYPE PREDICTIONS TO NARROW THE RANGE FOR "NORMAL" WHICH INCREASED THE EXPECTED PROPORTION OF INTERMEDIATE METABOLIZERS
- EMPHASIS ON ACTIVITY SCORES; CHANGED ACTIVITY SCORE OF *CYP2D6*10* TO 0.25

GENETIC VARIATION IN DRUG METABOLIZING ENZYMES IS ALSO USED TO PREDICT THE *CYP2D6* ACTIVITY SCORE

Allele functional status	Allele activity score
Normal function	1
Decreased function	0.5
*10	0.25
No function	0

The CYP2D6 activity score is a quantitative value based on the sum of the allele activity scores

(Allele 1 Score) + (Allele 2 Score) = Total Score

May be modified based on known co-administration of inhibitors or inducers

Table 3 Final consensus *CYP2D6* genotype to phenotype translation compared to previously reported CPIC and DPWG methods

Inferred CYP2D6 phenotype	Previous CPIC definition (AS)	Previous DPWG definition (AS)	Consensus definition (AS)	Consensus contiguous definition (AS)	Examples of *CYP2D6* diplotypes for consensus translation method
UM	> 2	> 2.5	> 2.25	> 2.25	**1/*1xN, *1/*2xN*[b], **2*[a]*/*2xN*[b], **1x2/*9*
NM	1–2	1.5–2.5	1.25	$1.25 \leq x \leq 2.25$	**1/*10*
			1.5		**1/*41, *1/*9*
			2.0		**1/*1, *1/*2*
			2.25		**2x2/*10*
IM	0.5	0.5–1	0.25	$0 < x < 1.25$	**4/*10*
			0.5		**4/*41, *10/*10*
			0.75		**10/*41*
			1		**41/*41, *1/*5*
PM	0	0	0	0	**3/*4, *4/*4, *5/*5, *5/*6*

AS, activity score; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.
[a]*CYP2D6*2* is currently considered to be a normal function allele by CPIC and DPWG; however, this function assignment has been challenged[32] and some laboratories report *CYP2D6*2* function differently. Function of this allele will be reassessed as additional data become available. [b]N is categorical and indicates the number of copy variants (e.g., **1x2*, **1x3*, etc).

GENE-BASED DOSING GUIDELINES AS OF 4/16/2020

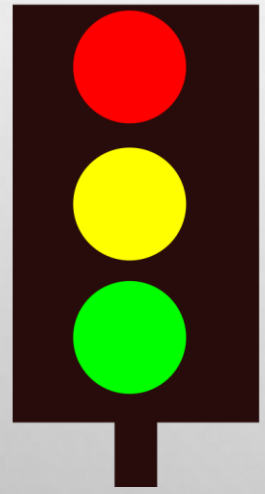
- ROYAL DUTCH ASSOCIATION FOR THE ADVANCEMENT OF PHARMACY PHARMACOGENOMICS WORKING GROUP (DPWG), N=93
- CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC), N=54
  - YOUTUBE VIDEO GUIDELINES AVAILABLE FOR SOME
- CANADIAN PHARMACOGENOMICS NETWORK FOR DRUG SAFETY (CPNDS), N=8
- PROFESSIONAL ORGANIZATIONS (E.G. ONCOLOGY, INFECTIOUS DISEASE)

COMMERCIAL SOFTWARE PRODUCTS

- PROPRIETARY COMMERCIAL PRODUCTS ARE AVAILABLE
  - INDEPENDENT OF LAB (E.G., GENEDOSE™, YOUSCRIPT®)
  - EXCLUSIVE TO A LAB (E.G., PGXONE™ VIA ADMERA HEALTH, GENESIGHT® VIA ASSUREX HEALTH, DNA INSIGHT® VIA PATHWAY GENOMICS)
- SOME INTEGRATE GENETICS WITH CLINICAL AND DEMOGRAPHIC DATA AND/OR OFFER INTERACTIVE RISK MITIGATION TOOLS FOR POLYPHARMACY
- ALL TOOLS PROVIDE DECISION SUPPORT TOOLS BUT FEW ARE SUPPORTED BY RANDOMIZED CLINICAL TRIALS, AND NO STUDIES DIRECTLY COMPARE EFFECTIVENESS OF THE CLINICAL DECISION SUPPORT

Bousman C, *Lancet Psychiatry*, 2016

GUIDANCE STRATEGIES



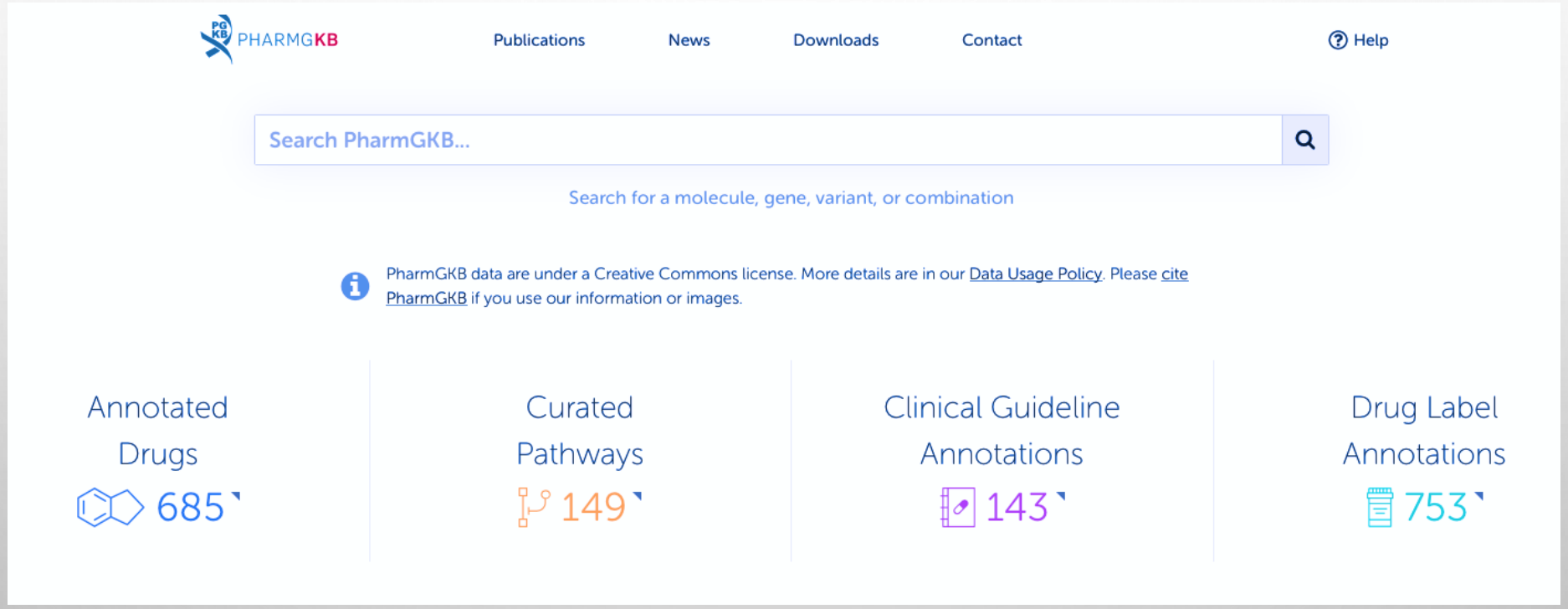
DRUG SELECTION/AVOIDANCE

- RISK OF A SERIOUS ADVERSE DRUG REACTION
- LIKELIHOOD OF RESPONSE

OPTIMIZE DOSING

- ESTIMATE OPTIMAL DOSE AND DOSING FREQUENCY
  - STANDARD
  - LOWER THAN USUAL (SENSITIVE)
  - HIGHER THAN USUAL (RESISTANT)
- OFTEN RECOMMEND TDM

PHARMACOGENOMICS KNOWLEDGE BASE



PharmGKB.org, accessed 4/16/2020

LEVELS OF EVIDENCE: BENZODIAZEPINES

	CYP2C9	*CYP2C19*	*CYP3A4*	*CYP3A5*	*UGT2B15*	*SCN1A*
Clobazam		2A				3
Diazepam	NR	3				
Oxazepam					3	
Midazolam			3	3		
Lorazepam					3	

Disclaimers apply to this and the next several slides:

- Levels of evidence represent those curated by the PharmGKB.org wherein 1A is the highest possible level
- The genes and drugs provided are examples and do not represent all relevant drug/gene associations

LEVELS OF EVIDENCE: STIMULANTS (E.G. ADHD)

	ABCB1	CYP2D6	ADRA2A	COMT	DRD2/ANNK1	HTR1A	SLCA2
Amphetamine					3		
Methamphetamine						3	
Atomoxetine		1A					3
Methylphenidate	3		3	3			3
Modafinil	3			3			

LEVELS OF EVIDENCE: ANTIPSYCHOTICS

	ABCB1	*CYP2C9*	*CYP2D6*	*COMT*	*DRD2/ANNK1*	*HTR1A*	*HTR2A*	*MTHFR*
Aripiprazole			3		3			
Clozapine	3			3	3	3		3
Haloperidol			3	3				
Lithium	3							
Olanzepine	3	3			3	3	3	3
Quetiapine				3		3		
Risperidone	3		2A	3	2A	3	3	

LEVELS OF EVIDENCE: ANTIDEPRESSANTS

	ABCB1	CYP2B6	CYP2C19	CYP2D6	COMT	GRIK4	HTR1A	HTR2A	SLC6A1
Amitriptyline	3		1A	1A					
Nortriptyline	3			1A					
Bupropion		2A	3		3			3	
Citalopram	3		1A	3		2B		2B	
Fluoxetine				1A	3		3	3	
Paroxetine	3			1A		2B	2B	3	
Sertraline			1A			2B	3		
Venlafaxine	3			2A	3				3

EXAMPLES OF POSITIVE OUTCOMES FROM MULTI-GENE PGX TESTING

- IMPROVED ANTIDEPRESSANT EFFICACY AND ADHERENCE
  - 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)
- REDUCED LENGTH OF STAY IN A PSYCHIATRIC HOSPITAL
  - 36.3 DAYS VS 46.6 DAYS (BATTIG VAD ET AL, *PHARMACOPSYCHIATRY*, 2020)

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, STIMULANTS, BENZODIAZEPINES, MOOD STABILIZERS, ETC.

- 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

cpicpgx.org

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

SOURCES OF INACCURATE PGX RESULTS

- PRE-ANALYTIC :
  - ORDERING THE WRONG TEST
  - INTERFERING SUBSTANCES (E.G. PRESERVATIVE)
  - SPECIMEN QUALITY
  - NON-STANDARD SPECIMEN
  - SPECIMEN MIX-UP
- ANALYTIC :
  - INSTRUMENT
  - ASSAY DESIGN
  - REAGENTS
  - CONTAMINATION
  - UNDETECTED ALLELE DROPOUT
- POST-ANALYTIC :
  - INSUFFICIENT CONTENT LEADING TO INACCURATE DIPLOTYPE CALLS, MISSED ALLELES
  - MISINTERPRETATION OF *1
  - INACCURATE INTERPRETATION
    - PHENOTYPE PREDICTION INACCURATE OR INCONSISTENT WITH FUNCTIONAL/BIOCHEMICAL/CLINICAL PHENOTYPE
    - INAPPROPRIATE DRUG-GENE GUIDANCE
    - UNRECOGNIZED SUBSTRATE SPECIFICITY OF DRUG-GENE INTERACTIONS
    - MULTI-GENE IMPACT(S)
    - NON-GENETIC IMPACT(S)

TDM

POSSIBLE INDICATIONS FOR TDM

- MANDATORY, FOR SAFETY
- THERAPEUTIC RANGE ESTABLISHED FOR MEDICATIONS OF INTEREST
- NARROW THERAPEUTIC RANGE
- CONCERNS ABOUT PATIENT ADHERENCE
- CONCERNS ABOUT PHARMACOKINETICS (E.G., CLINICAL STATUS, EXTREME AGES, PGX RESULTS)
- POLYPHARMACY AND/OR CHANGES IN MEDICATIONS
- PATIENT HAS FAILED TO RESPOND OR RESPONSE HAS DETERIORATED
- PATIENT HAS EXPERIENCED A SERIOUS ADVERSE DRUG REACTION
- RELEVANT TESTING IS AVAILABLE WITH REASONABLE LOGISTICS

TDM EXAMPLE: ATYPICAL ANTIPSYCHOTICS

	Dose range (mg/d)	Therapeutic range in plasma (ng/mL), C_{min}	Level of recommendation for TDM (scale of 1-5)
Amisulpride	300-800	200-320	1
Aripiprazole	15-30	150-210	2
Clozapine	200-600	350-500	1
Olanzepine	10-20	20-40	1
Quetiapine	200-600	50-500	2
Paliperidone	3-12	20-60	2
Risperidone	2-4	20-60	2
Ziprasidone	120-160	50-130	2

Urban AE & Cubala WJ, *Psychiatr Pol* 51(6):1059-77, 2017

INTEGRATING PGX AND TDM FOR RISPERIDONE

- CALCULATED RISPERIDONE/9-OH RATIO AND COMPARED GENETICALLY DERIVED PHENOTYPE TO PUBLISHED MEDIAN :
  - UM ~ 0.03
  - NM ~ 0.08
  - IM ~ 0.56
  - PM ~ 2.5
- STRONG CYP2D6 INHIBITOR >1
- CYP3A4 INHIBITORS AND RENAL INSUFFICIENCY MAY ALSO CHANGE PHENOTYPE

- PROPOSED MODEL TO PREDICT REAL-WORLD PHENOTYPE WITH A CONCENTRATION-TO-DOSE (C/D) RATIO UNDER C_{MIN} CONDITIONS
  - DETERMINE NORMAL C/D
  - (TOTAL RISPERIDONE + 9-OH IN NG/ML) / (RISPERIDONE DOSE IN MG/D)
  - C/D < 1/2 OF NORMAL ~ DOSE TOO LOW
  - C/D > 2X NORMAL ~ DOSE TOO HIGH

De Leon J, *Neuropharmacology*, 2019

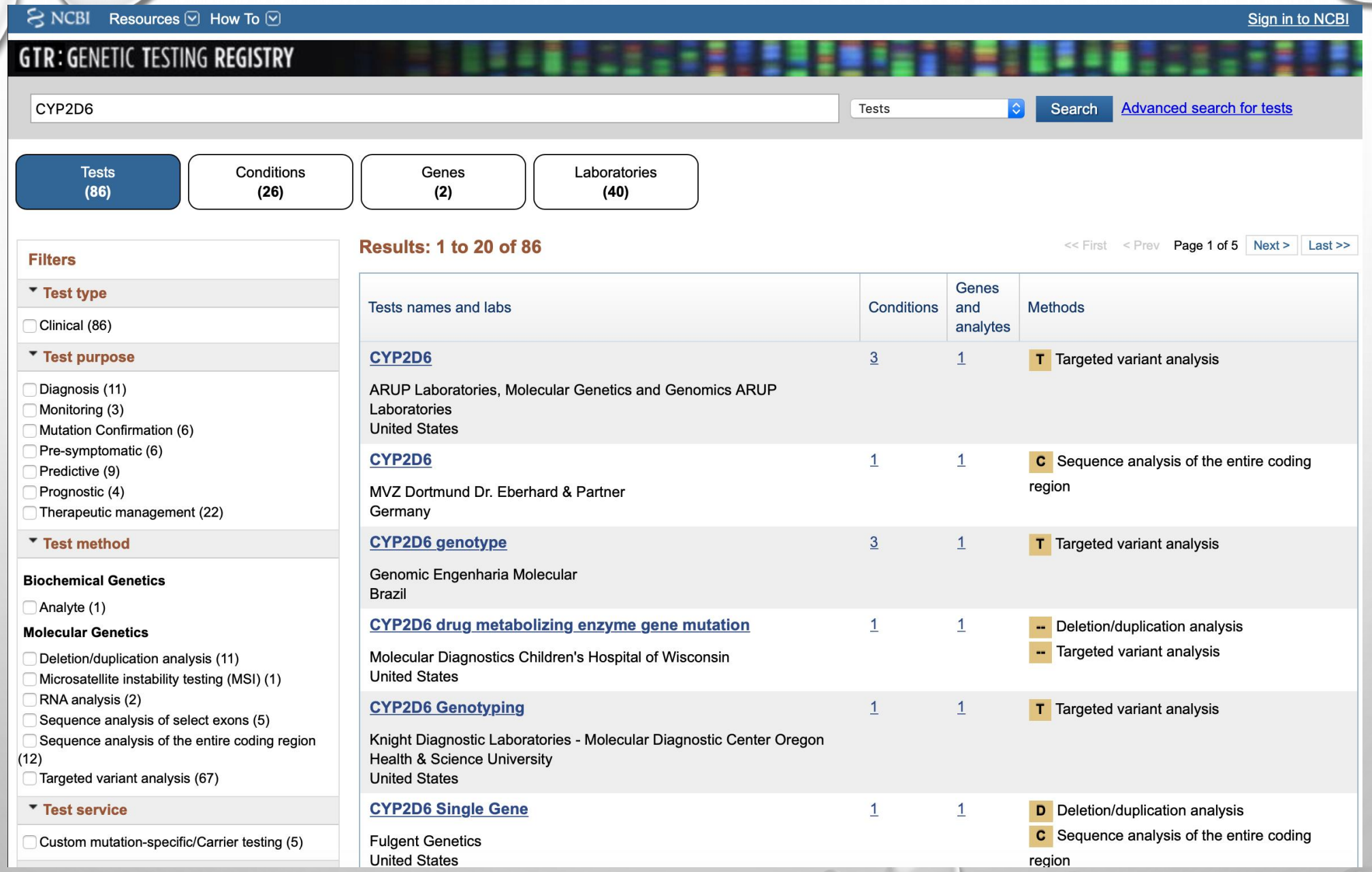
SOURCES OF INACCURATE TDM RESULTS

- PRE-ANALYTIC :
  - TIMING OF SPECIMEN COLLECTION RELATIVE TO LAST DOSE
  - ORDERING THE WRONG TEST
  - INTERFERING SUBSTANCES (E.G. PRESERVATIVE)
  - SPECIMEN QUALITY
  - NON-STANDARD SPECIMEN
  - SPECIMEN MIX-UP
- ANALYTIC :
  - INSTRUMENT
  - ASSAY DESIGN
  - INTERFERENCE
  - CONTAMINATION
- POST-ANALYTIC :
  - INACCURATE INTERPRETATION
    - ADHERENCE
    - UNRECOGNIZED CO-MEDICATIONS OR OTHER CHANGES THAT COULD AFFECT PHARMACOKINETICS
    - INAPPROPRIATE THERAPEUTIC RANGE
    - ASSUMED EQUALITY TO PREVIOUS/ALTERNATE LABORATORY METHODS

SUCCESSFUL IMPLEMENTATION

PICKING THE RIGHT TEST

- TEST CONTENT SHOULD ALIGN WITH PATIENT POPULATION, CLINICAL INDICATION(S) AND AVAILABLE INTERPRETATION TOOLS
  - PGX
    - GENES INCLUDED ?
    - VARIANTS DETECTED, WHICH MAY DEPEND ON TECHNOLOGY USED FOR TESTING
  - TDM
    - DRUGS AND METABOLITES INCLUDED ?
    - ANALYTICAL MEASUREMENT RANGE IS APPROPRIATE
- LOGISTICS
  - SPECIMEN AND APPROPRIATE HANDLING
  - TIME TO RESULT
  - COST/REIMBURSEMENT



ncbi.nlm.nih.gov/gtr/

FACTORS THAT CONTRIBUTE TO SUCCESSFUL IMPLEMENTATION OF PGX AND TDM

- MULTI-DISCIPLINARY APPROACH :
  - LABORATORY
  - PHARMACY
  - PROVIDERS
  - ADMINISTRATORS/PAYERS
  - REGULATORS
- TRANSPARENCY ABOUT WHEN TO ORDER WHICH TESTS
- CONSENSUS ON HOW RESULTS WILL BE UTILIZED; ALGORITHMS ARE OFTEN HELPFUL
- 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
- TDM MAY REPRESENT THE BEST OPPORTUNITY FOR DOSE OPTIMIZATION
- SUCCESSFUL IMPLEMENTATION REQUIRES AN MULTI-DISCIPLINARY APPROACH

THANK YOU FOR YOUR ATTENTION!

GWEN.MCMILLIN@ARUPLAB.COM