Pharmacogenomics Services as an Opportunity for Precision Medicine In Clinical Practice

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SickKids®

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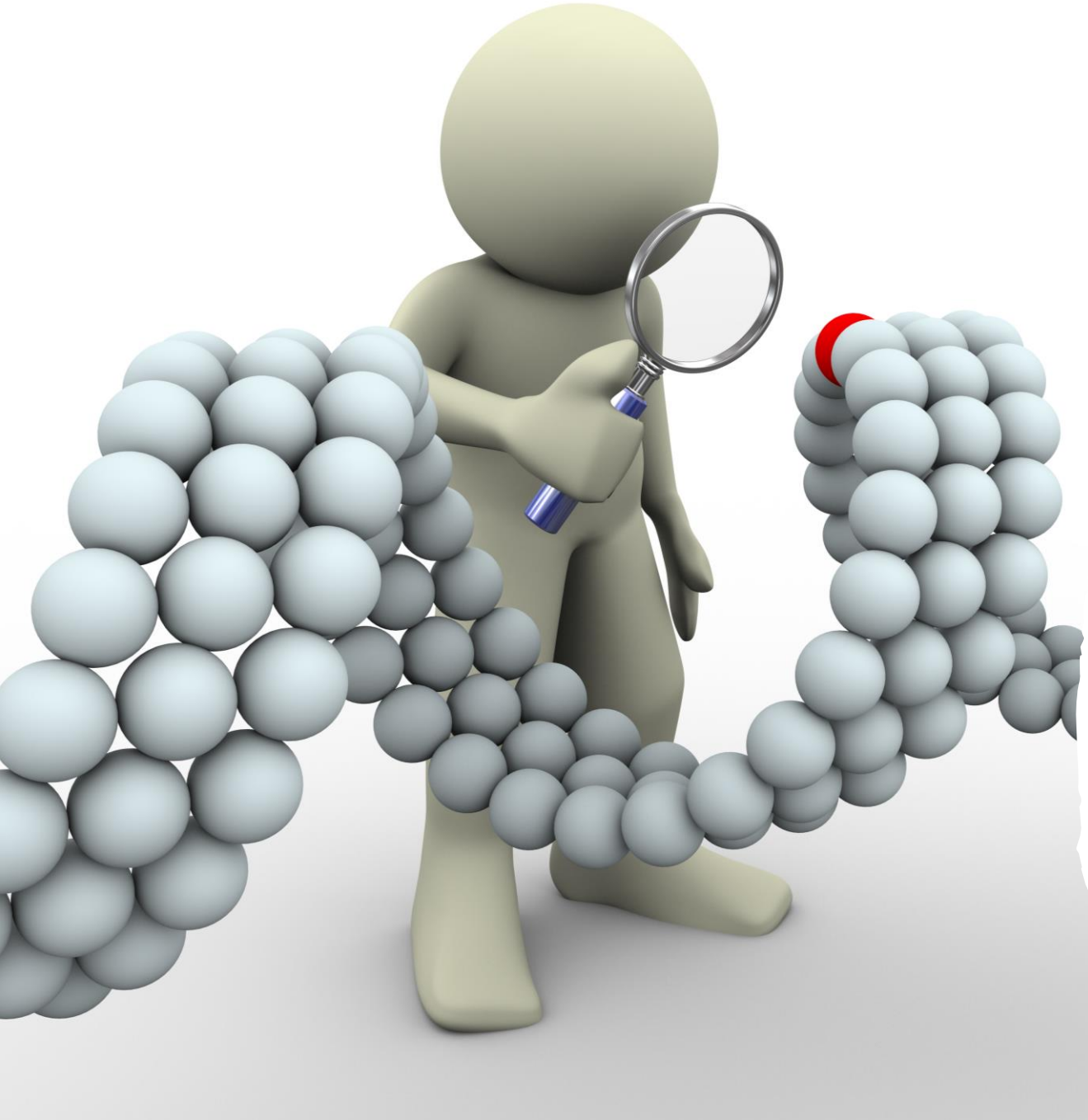
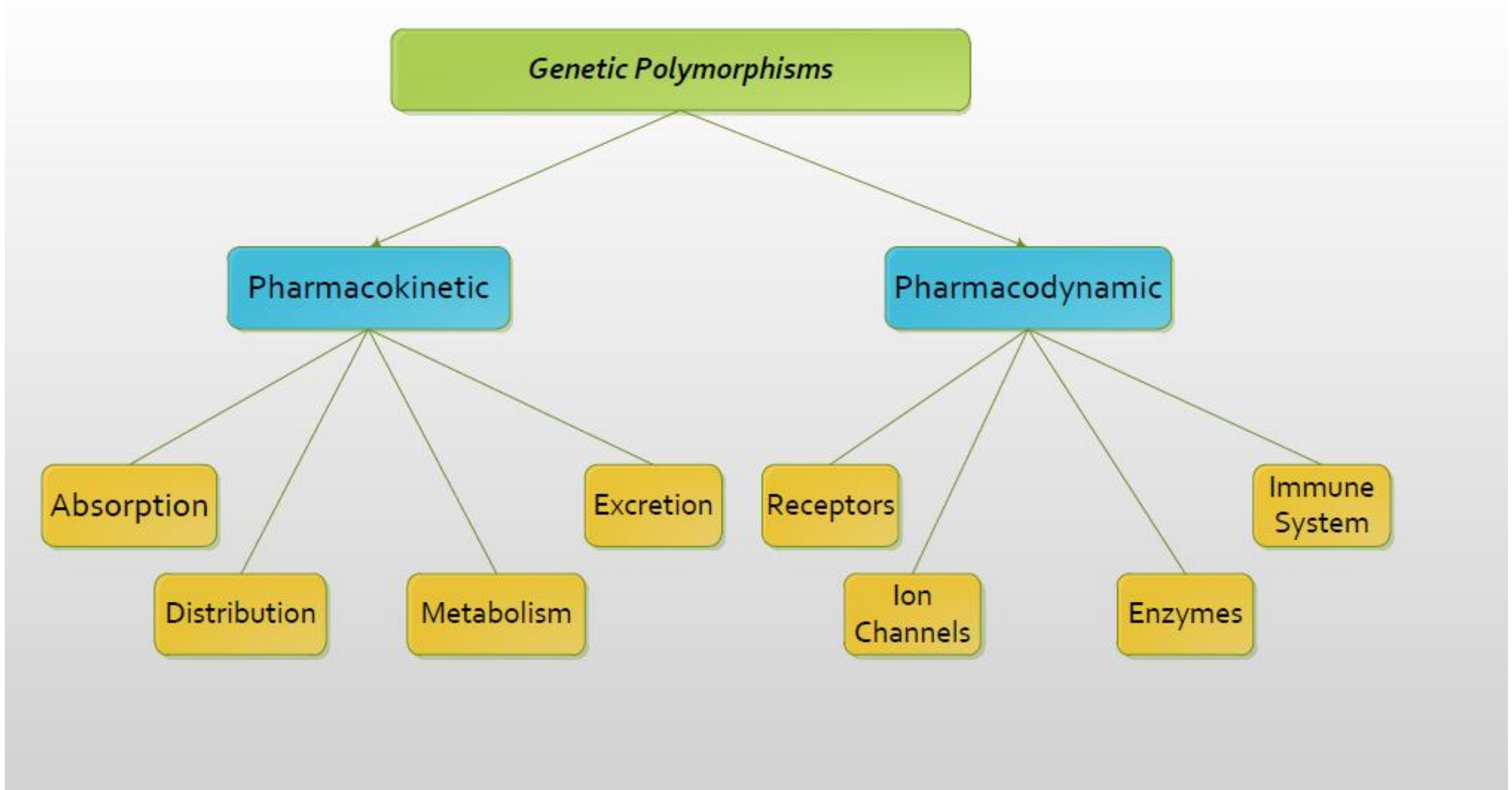


What is pharmacogenomics?

The study of how variations in our genetic make up affect the response to medications


Genetic Polymorphisms
Pharmacokinetic
Pharmacodynamic
Absorption
Distribution
Metabolism
Excretion
Receptors
Ion Channels
Enzymes
Immune System

Major web resources

Name	Link	Main features
PharmGKB	https://www.pharmgkb.org/	Natural language processing and manual curation variants, associations between variants and drugs, drug-centered pathways, genotype-based pharmacogenomic summaries
CPIC	https://cpicpgx.org/	Detailed gene/drug clinical practice guidelines, drug dosing guidelines
PharmVar	https://www.pharmvar.org/genes	CYP450 alleles, CYP450 isoforms, relationship between genotype and phenotype
Cytochrome P450 Drug Interaction Table	http://medicine.iupui.edu/clinpharm/ddis/main-table	Drug and CYP450 isoform interaction
FDA's pharmacogenetic website	https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm	Clinical response and drug exposure variability, dosing recommendation according to genotypes, drug mechanisms, germline or somatic gene variant biomarker
Drug Bank	https://go.drugbank.com/	Detailed information on drugs (i.e. chemical, pharmacological and pharmaceutical and drug targets (i.e. sequence, structure, and pathway)

188 medications with clinical pharmacogenomics guideline annotations

Clopidogrel

Warfarin

Phenytoin

SSRI’s

Tricyclic Antidepressants

Flecainide

Statins

Carbamazepine

SNRI’s

Metoprolol

Propafenone

Atypical Antipsychotics

Tamoxifen

Opioids

Antiemetics

Thioguanines

Tacrolimus

PEG interferon

Abacavir

Cisplatin

Rasbirucase

Ribavarin

Capecitabine

Voriconazole

Inhalation Anesthetics

NSAID’s

Proton Pump Inhibitors

Cytochrome P450 (CYP) drug-metabolizing enzymes

Enzyme activity of CYP2D6, CYP2C9, CYP2C19, CYP3A5 and CYP4F2 can be grouped into different types:

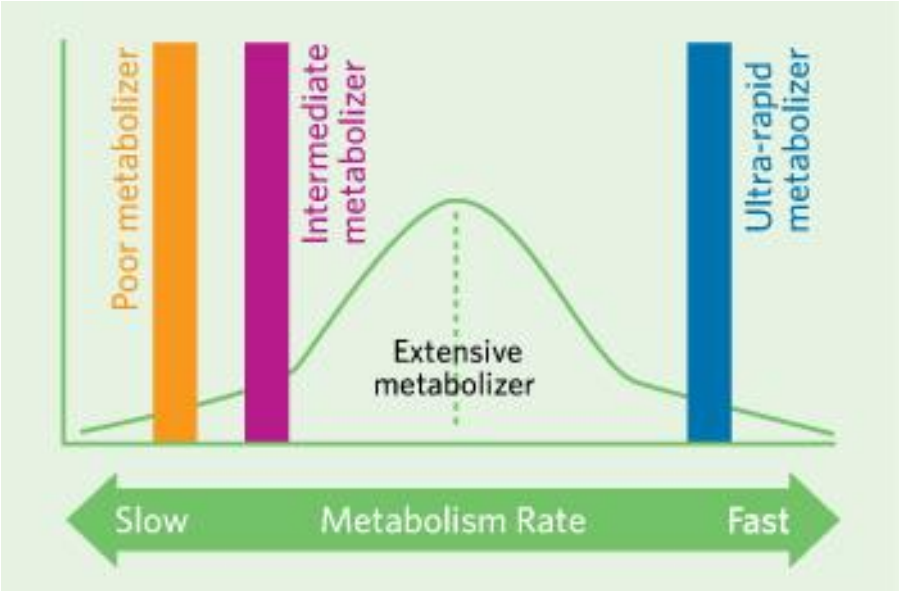
Ultra rapid metabolizer (UM): increased function in enzyme activity

Rapid metabolizer (RM) (currently for CYP2C19 only): increased function in enzyme activity

Normal metabolizer (NM) *or* extensive metabolizer (EM)*:*** normal enzyme activity function

Intermediate metabolizer (IM): impaired function in enzyme activity

Poor metabolizer (PM): non functional enzyme activity



PGx is a precision prevention tool that can reduce unwanted medication side effects, maximize therapeutic response, and reduce health care costs

Increasing access to PGx through collaborations:

- Genome Diagnostics Laboratory
- Cardiac Genome Clinic
- Complex Care team
- Gastroenterology
- Nephrology
- Pain Clinic
- Pharmacy
- Psychiatry
- Oncology

Workflow

PGx test inquiry by wards/clinics through consultation

Eligibility assessment by Division of Clinical Pharmacology & Toxicology

PGx panel testing via DNA labs

PGx findings and report issued by DNA labs PGx consultation report issued by Division of Clinical Pharmacology & Toxicology

PGx consultation clinic service delivered by Pharmacist and supported/ overviewed by Pharmacologist

PGx testing and cardiac transplantation

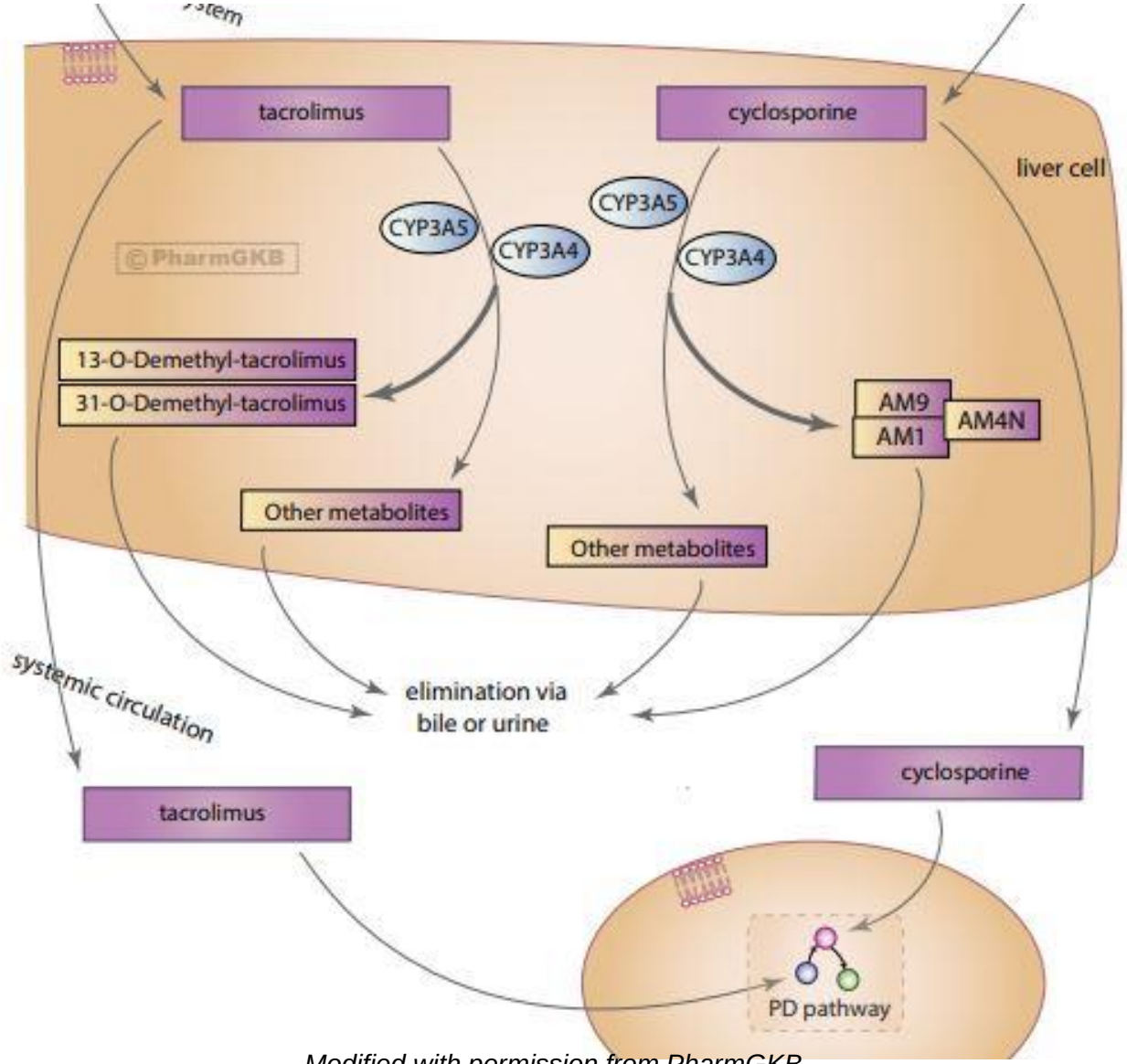
- We followed 17 pre- cardiac transplant patients and 1 post- transplant patient from May 2019 until now
- 75% of patients were recommended to follow modified dosing regimens based on the PGx findings
- Medications which were dose adjusted included clopidogrel, warfarin, ondansetron, tacrolimus, PPI

CYP3A5 and Tacrolimus

Tacrolimus is inactivated by CYP3A5

Average population are CYP3A5 non expressors (poor metabolizers) and show decreased metabolism

CYP3A5 expressors (intermediate metabolizers/ extensive metabolizers) require higher dosing to achieve therapeutic drug concentrations



Modified with permission from PharmGKB

Tacrolimus and CPIC guideline

PHENOTYPE	GENOTYPES	EXAMPLES OF DIPLOTYPES	IMPLICATIONS FOR TACROLIMUS PHARMACOLOGIC MEASURES	THERAPEUTIC RECOMMENDATIONS
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations	Increase starting dose 1.5 to 2 times recommended starting dose. Use therapeutic drug monitoring to guide dose adjustments
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one non-functional allele	*1/*3, *1/*6, *1/*7	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations	Increase starting dose 1.5 to 2 times recommended starting dose. Use therapeutic drug monitoring to guide dose adjustments
Poor metabolizer (CYP3A5 non-expresser)	An individual carrying two non-functional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7	Higher (“normal”) dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments

Tacrolimus dosing and CYP3A5 metabolizer status

Daily Dosing total mg/kg/day	Tacrolimus Level	CYP3A5 metabolizer
0.6 mg/kg/day	level within range	**CYP3A5 expressor**
0.08 mg/kg day	level within range	CYP3A5 non expressor
0.17 mg/kg/day	level within range	CYP3A5 non expressor
0.109 mg/kg/day	level within range	CYP3A5 non expressor
0.045 mg/kg/day	between 4.2-5.2 mcg/L	CYP3A5 non expressor
0.13 mg/kg/day	level within range	CYP3A5 non expressor
0.2 mg/kg/day	level within range	CYP3A5 non expressor
1.65 mg/kg/day	level within range	**CYP3A5 expressor**
0.48 mg/kg/day	Within last 2 weeks: 18.8mcg/l, 16.3mcg/l, 11.2 mcg/l	CYP3A5 non expressor
0.177 mg/kg/day	within last 9 days: 4.8mcg/l, 4mcg/l, 4.3 mcg/l	**CYP3A5 expressor**

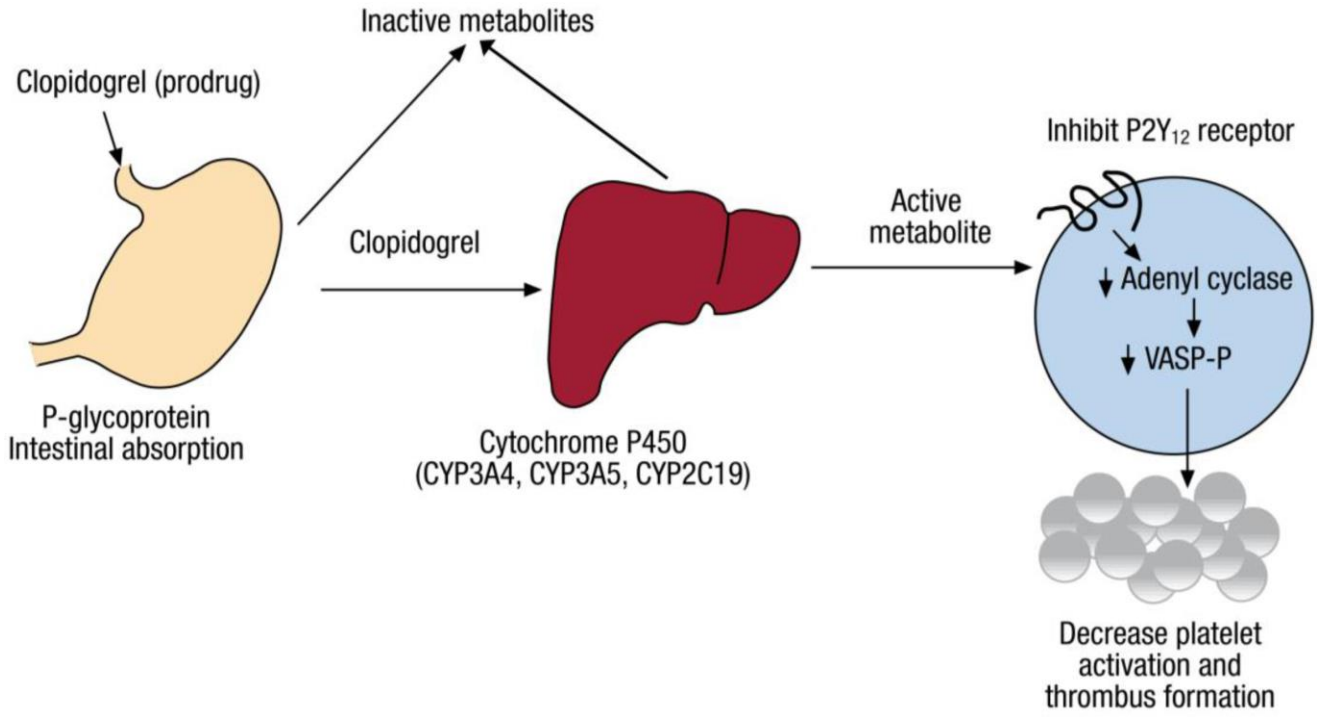
CYP3A5 phenotype frequency

CYP3A5 allele	African Allele	African American	Caucasian	Middle Eastern	East Asians	South/Central Asian	Americas
*1	55.8	60.5	7.8	10.5	25.8	34.2	20.2
*3	29.8	31.6	92.1	88.1	74.2	65.9	76.5
*6	17.2	11.1	0.1	19.0	0.1	0.0	3.7
*7	7.7	12.0	0.0	0.2	0.0	NA	2.5

Modified from PharmGKB CYP3A5 frequencies

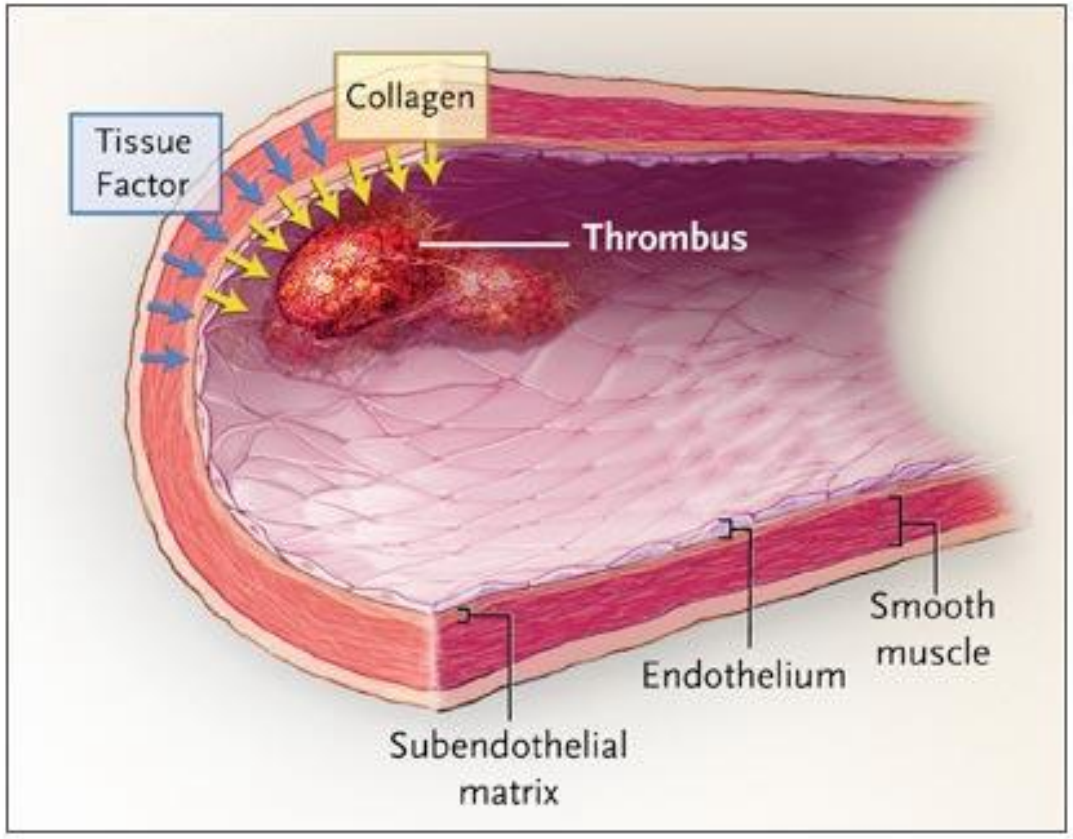
Recent case from the wards

- 2 year old boy with right hypoplastic heart syndrome
- PGx testing revealed that he is a CYP2C19 poor metabolizer, showing minimal to no metabolic CYP2C19 activity
- He is prone to therapeutic failure with clopidogrel
- Aspirin is used instead

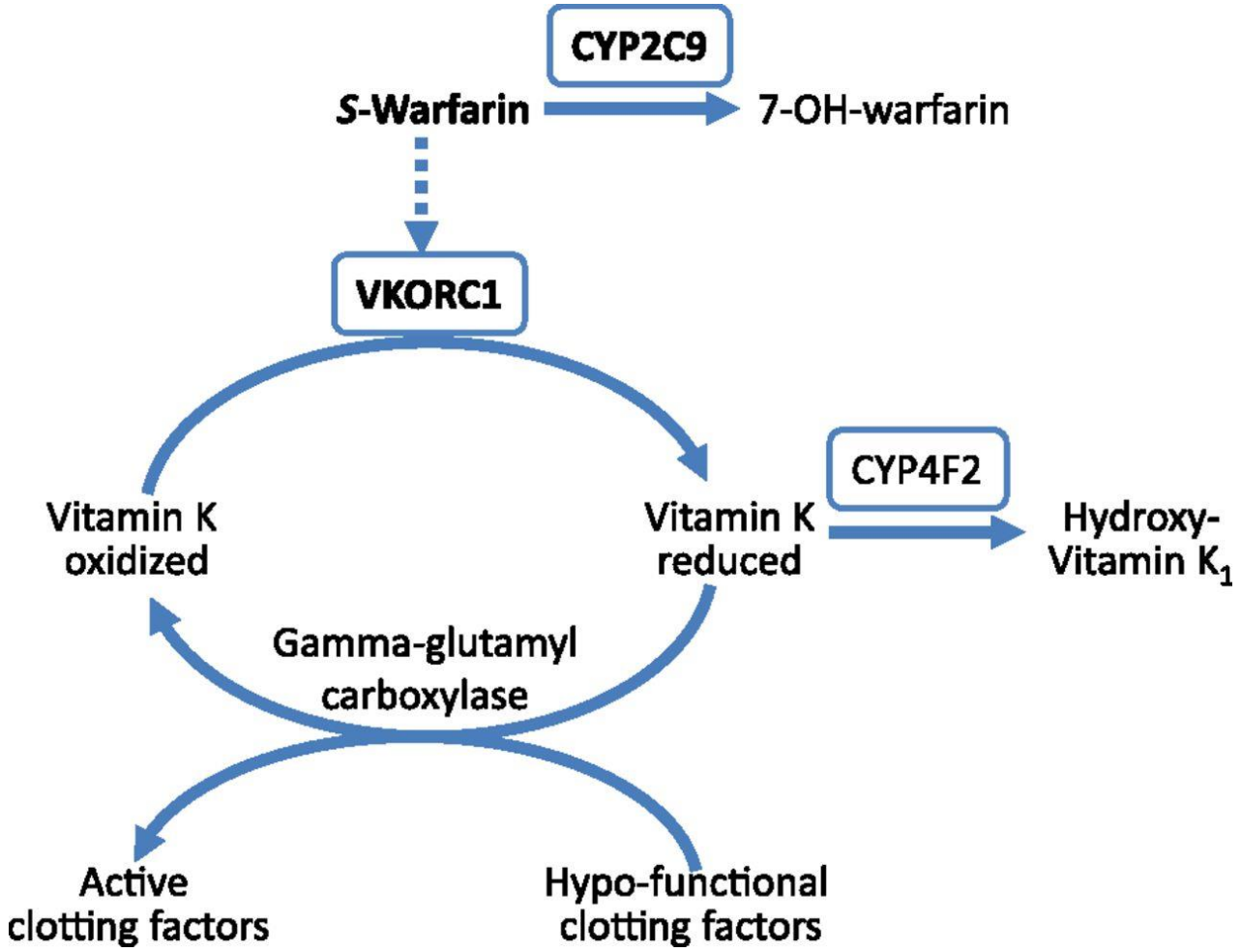


Recent case from PGX clinic

- 21 months young boy with ventricle atrioventricular septal defect and complete pulmonary atresia and history of thrombotic event
- He was put on warfarin with goal INR of 2.5 to 3.5
- Initial standard warfarin dosing was given and INR level rose to 8 after just 1 dose
- PGx data revealed: warfarin sensitivity (lower starting dose would have been sufficient)



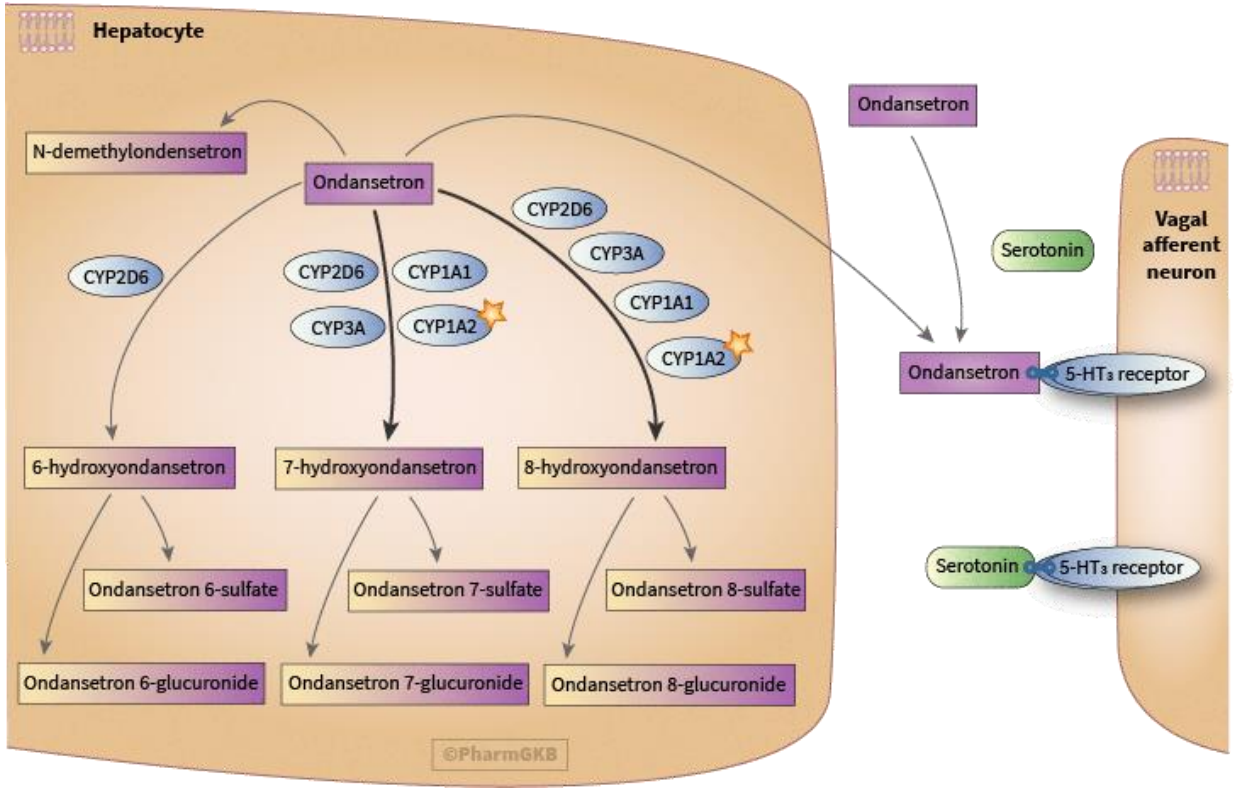
- Warfarin is broken down in the liver by CYP2C9 to its inactive metabolites.
- Warfarin exhibits its anticoagulant effect by inhibiting the VKORC1 enzyme
- Vitamin K epoxide reductase (VKORC1) converts vitamin K into its active form, which is needed to produce clotting factors.
- Certain genetic variants in the VKORC1 gene may decrease the level of active vitamin K, thus causing fewer clotting factors to be available.



Kidney transplant and tacrolimus

- 24 retrospective kidney transplant patients
- 8 of those patients are CYP3A5 expressors with a need of higher tacrolimus dosing (1.5 - 2 fold higher)
- 1 prospective kidney transplant patient – CYP3A5 expressor

Ondansetron and CYP2D6



Phenotype for CYP2D6

Ultrarapid Metabolizer

Activity Score for CYP2D6

4.0

Classification : Moderate

Recommendation

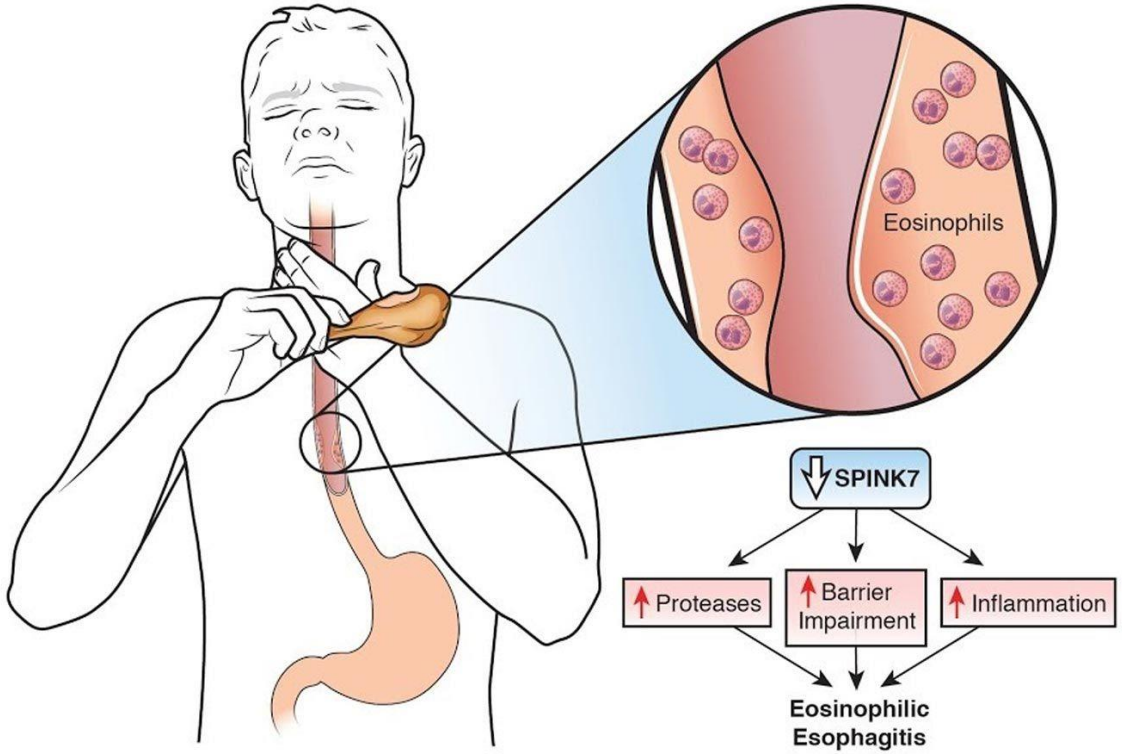
Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron).

Implications for CYP2D6

Increased metabolism to less active compounds when compared to normal metabolizers and is associated with decreased response to ondansetron and tropisetron (i.e. vomiting).

Comments

Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy. Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of CYP2D6 genetic variation to guide use of these drugs.



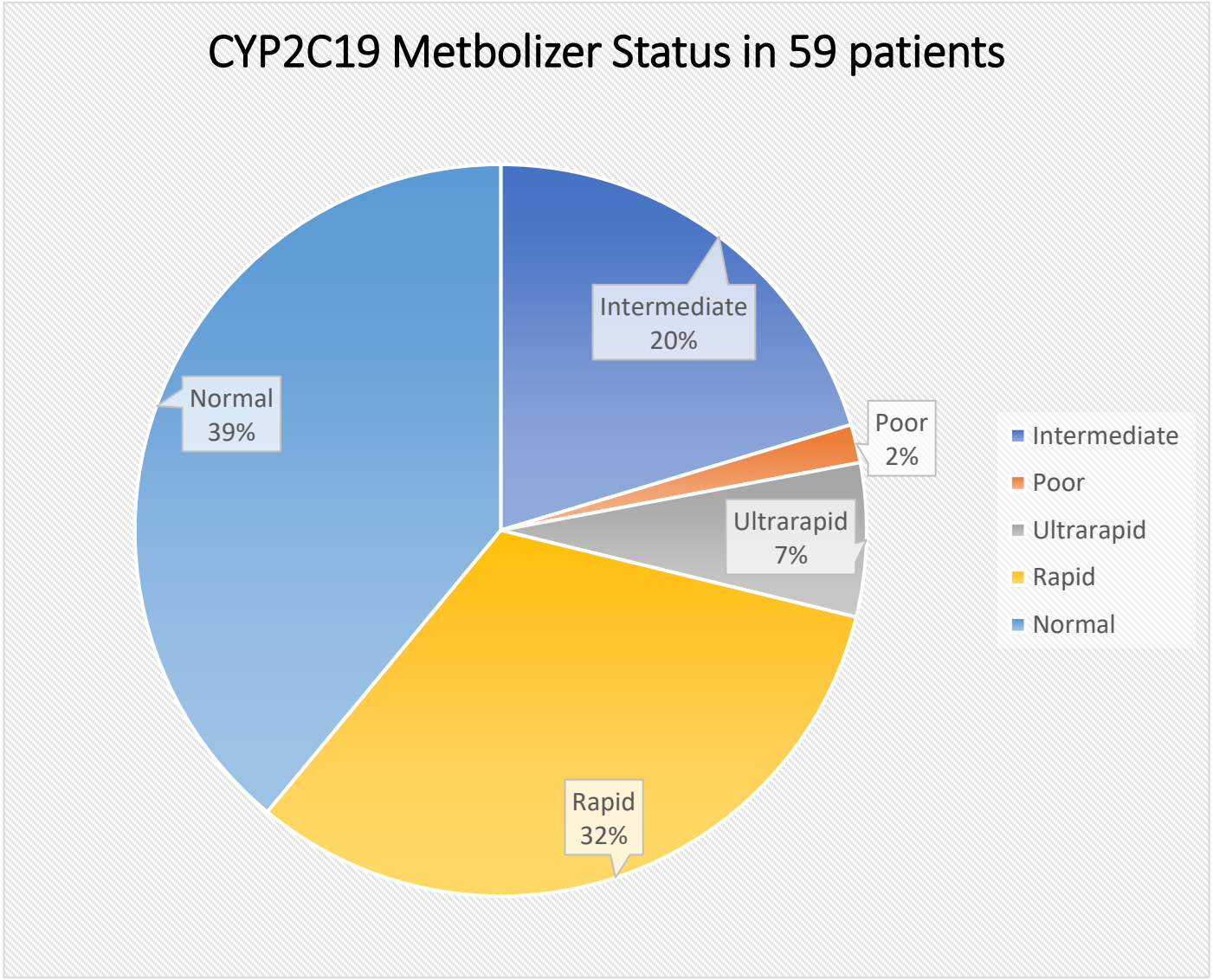
Eosinophilic Esophagitis (EoE)- PGx project

Chronic inflammatory disease

- Common symptoms:
  - Difficulty swallowing
  - Food impaction
  - Poor appetite

Common prescribed medications:

- **Proton pump inhibitors (PPI's)**
- Budesonide
- Fluticasone propionate



Patients	Metabolizer Status	CYP2C19 guided changes to medication therapy
1	Ultra-rapid	not on any medications
3	Ultra-rapid	switched from lansoprazole to rabeprazole
11	Rapid	switched from lansoprazole to rabeprazole
2	Rapid	currently on remission, no change in lansoprazole dosing
1	Rapid	increase in lansoprazole dosing
1	Rapid	awaiting endocscopy, change in lansoprazole dosing will be determined after results
1	Rapid	already switched to esomeprazole prior PGx results
3	Rapid	awaiting clinic/TBD

Patient example

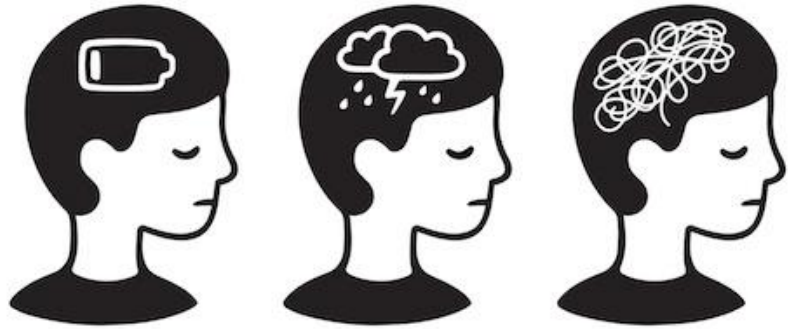
17-year-old male patient diagnosed with depression in February 2021

Patient tried to commit suicide with Tylenol in July 2021

Escitalopram started upon diagnosis and titrated up to 20 mg daily, no side effect

Escitalopram did not change mood or anhedonia (inability to feel pleasure). Discontinued after 3 months

Fluvoxamine started and patient noticed small difference in symptoms; no side effects

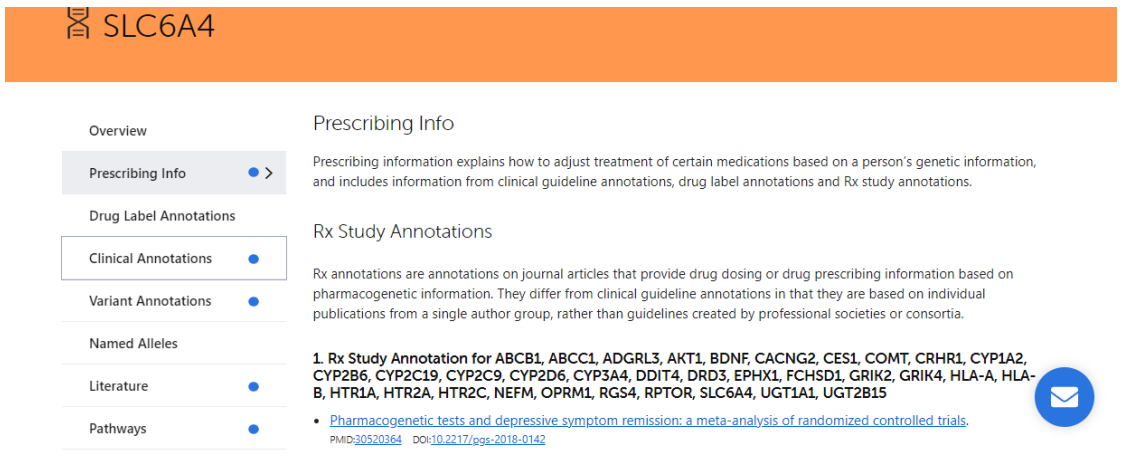


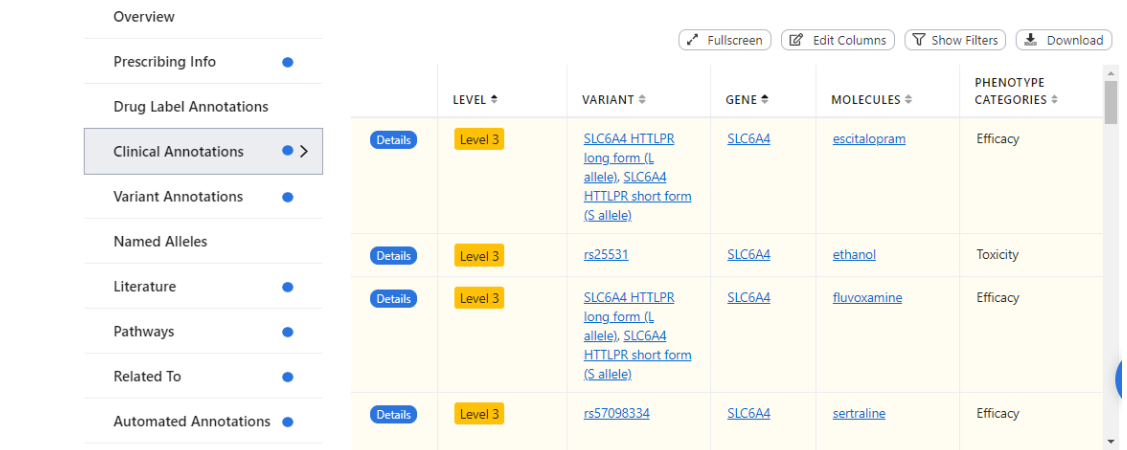
Results

Genetic results:			
Gene	Genotype	Phenotype	Status
CYP2C19	*1/*17	One functional allele and one increased-function allele	Rapid metabolizer
CYP2C9	*1/*1	Two functional alleles	Normal metabolizer
CYP2D6	*1/*1	Two functional alleles	Normal metabolizer
CYP3A5	*3/*3	Two reduced-function alleles	Poor metabolizer
F5	WT/WT	Two normal risk alleles (WT = wild type)	Normal risk
SLCO1B1	*1/*5	One functional allele and one risk allele	Decreased function
TPMT	*1/*1	Two functional alleles	Normal metabolizer
VKORC1	-1639 G>A GG	Two normal function alleles	Normal function

Psychiatry

Amitriptyline	✗	Increased CYP2C19 and normal CYP2D6 enzyme activity may lead to altered levels of active drug and its metabolites. This may affect the clinical response and probability of side effects. Consider an alternative tricyclic antidepressant that is not affected by CYP2C19 metabolism (e.g., desipramine, nortriptyline). If amitriptyline cannot be avoided, utilize therapeutic drug monitoring to guide dose adjustments. This recommendation only applies to higher initial doses, for example used in conditions such as depression.
Citalopram	✗	Increased CYP2C19 enzyme activity may lead to decreased levels of active drug and may affect clinical response. Consider an alternative drug that is not predominantly metabolized by CYP2C19.
Clomipramine	✗	Increased CYP2C19 and normal CYP2D6 enzyme activity may lead to altered levels of active drug and its metabolites. This may affect the clinical response and probability of side effects. Consider an alternative tricyclic antidepressant that is not affected by CYP2C19 metabolism (e.g., desipramine, nortriptyline). If clomipramine cannot be avoided, utilize therapeutic drug monitoring to guide dose adjustments. This recommendation only applies to higher initial doses, for example used in conditions such as depression.
Desipramine	✓	Normal CYP2D6 enzyme activity. Initiate therapy with the standard recommended starting dose.
Doxepin	✓	Increased CYP2C19 and normal CYP2D6 enzyme activity may lead to altered levels of active drug and its metabolites. This may affect the clinical response and probability of side effects. Consider an alternative tricyclic antidepressant that is not affected by CYP2C19 metabolism (e.g., desipramine, nortriptyline). If doxepin cannot be avoided, utilize therapeutic drug monitoring to guide dose adjustments. This recommendation only applies to higher initial doses, for example used in conditions such as depression.
Escitalopram	✗	Increased CYP2C19 enzyme activity may lead to decreased levels of active drug and may affect clinical response. Consider an alternative drug that is not predominantly metabolized by CYP2C19.
Fluvoxamine	✓	Normal CYP2D6 enzyme activity. Initiate therapy with the standard recommended starting dose.


SLC6A4
Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Named Alleles
Literature
Pathways
Prescribing Info
Prescribing information explains how to adjust treatment of certain medications based on a person's genetic information, and includes information from clinical guideline annotations, drug label annotations and Rx study annotations.
Rx Study Annotations
Rx annotations are annotations on journal articles that provide drug dosing or drug prescribing information based on pharmacogenetic information. They differ from clinical guideline annotations in that they are based on individual publications from a single author group, rather than guidelines created by professional societies or consortia.
1. Rx Study Annotation for ABCB1, ABCC1, ADGRL3, AKT1, BDNF, CACNG2, CES1, COMT, CRHR1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HLA-B, HTR1A, HTR2A, HTR2C, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT1A1, UGT2B15
Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials.
PMID:30520364 DOI:10.2217/pgs-2018-0142


Overview
Prescribing Info
Drug Label Annotations
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Literature
Pathways
Related To
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Fullscreen
Edit Columns
Show Filters
Download
LEVEL
VARIANT
GENE
MOLECULES
PHENOTYPE CATEGORIES
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Level 3
SLC6A4 HTTLPR long form (L allele), SLC6A4 HTTLPR short form (S allele)
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Toxicity
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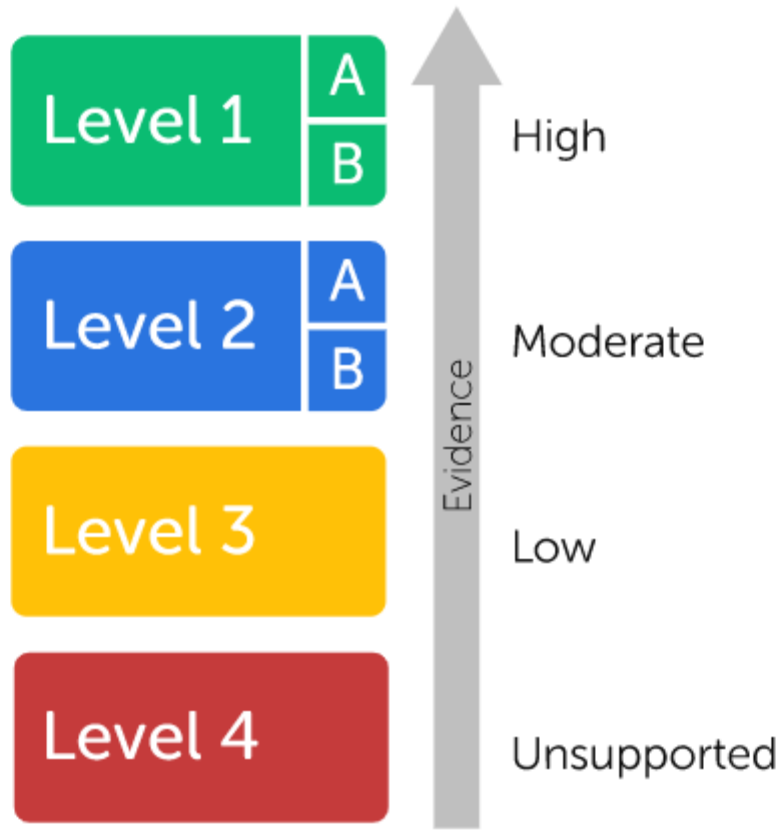
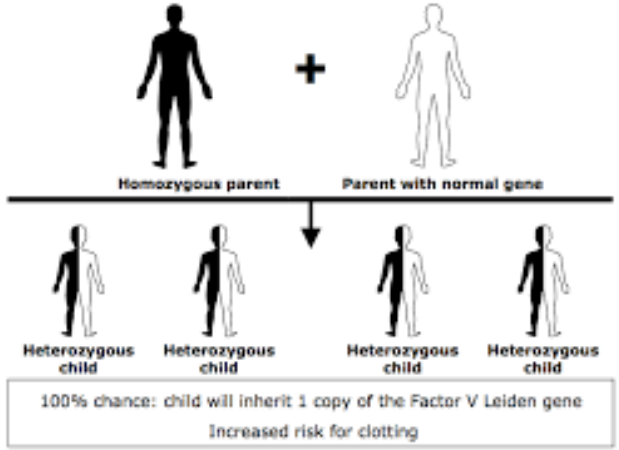
Efficacy

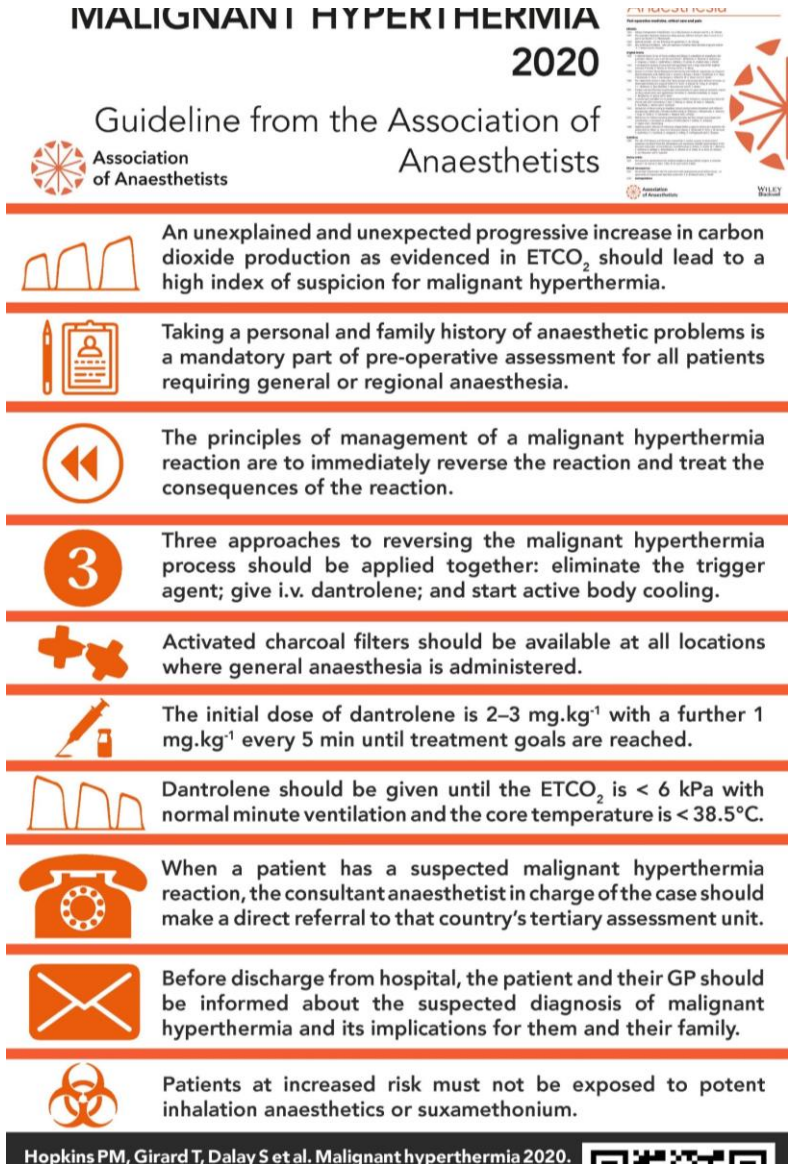
Clinical Annotation Levels of Evidence



Pharmacogenes with disease implication

- Factor V Leiden is a mutation of one of the clotting factors.
- This mutation can increase the chance of developing abnormal blood clots, most commonly in legs or lungs.
- Most people with factor V Leiden never develop abnormal clots, however in some cases this can lead to long-term health problems or become life-threatening.
- Females who carry the factor V Leiden mutation may have an increased tendency to develop blood clots during pregnancy or when taking the hormone estrogen

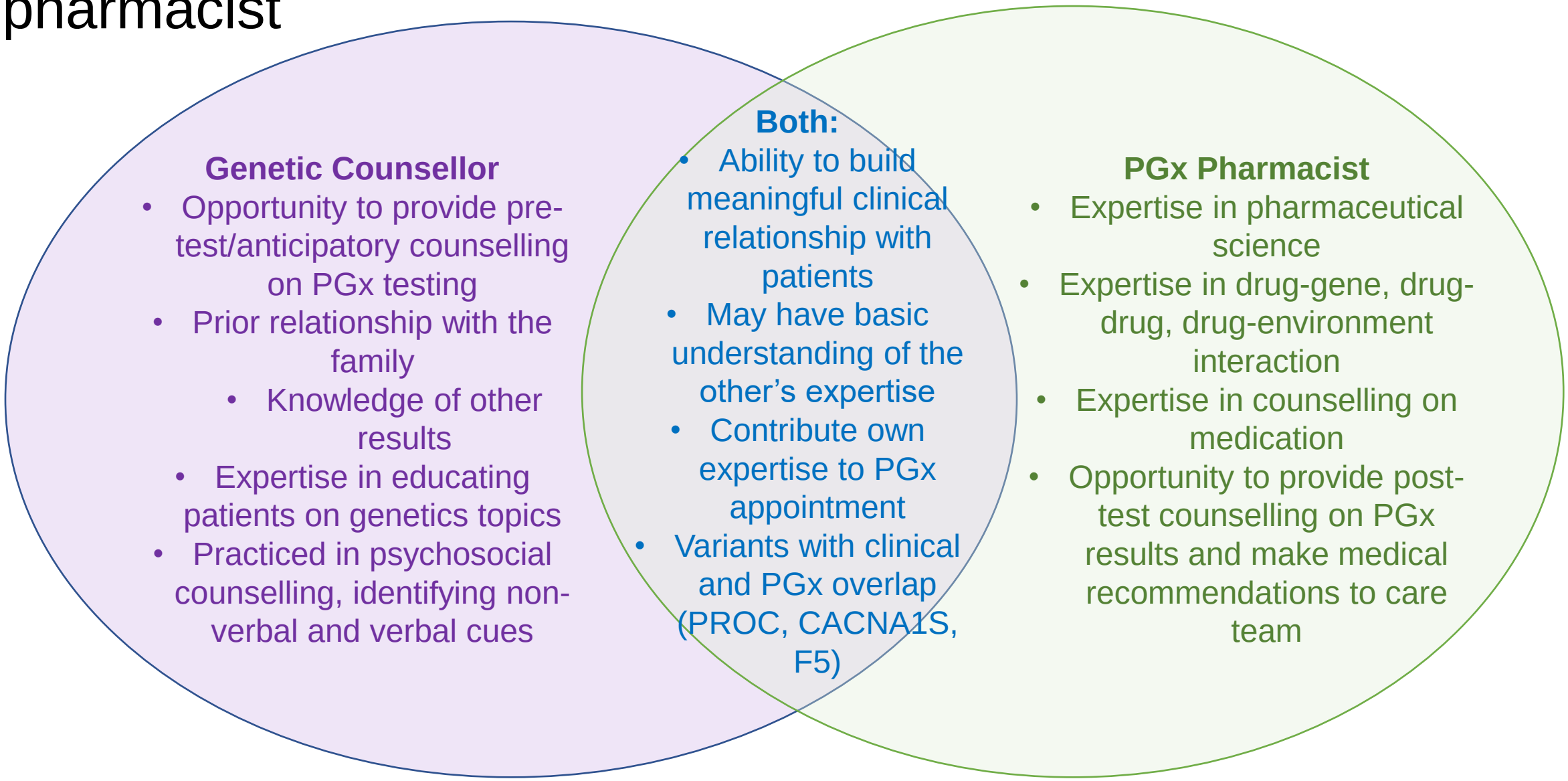




Pharmacogenes with disease implication

- Malignant hypothermia is a rare autosomal dominant condition associated with mutations in RYR1 And CACNA1S genes
- Life threatening adverse response to commonly used inhalational anesthetics (e.g., halothane) and depolarizing muscle relaxants (e.g., succinylcholine) such as fever, sustained muscle contraction, rapid breakdown of muscle (rhabdomyolysis), and other abnormalities.
- Muscle biopsy (gold standard) is used to diagnose malignant hypothermia
- RYR1 and CASNA1S data can be extracted through WGS
- Pharmacogenomics guidelines available

Complimentary knowledge/skillsets of the GC and PGx pharmacist

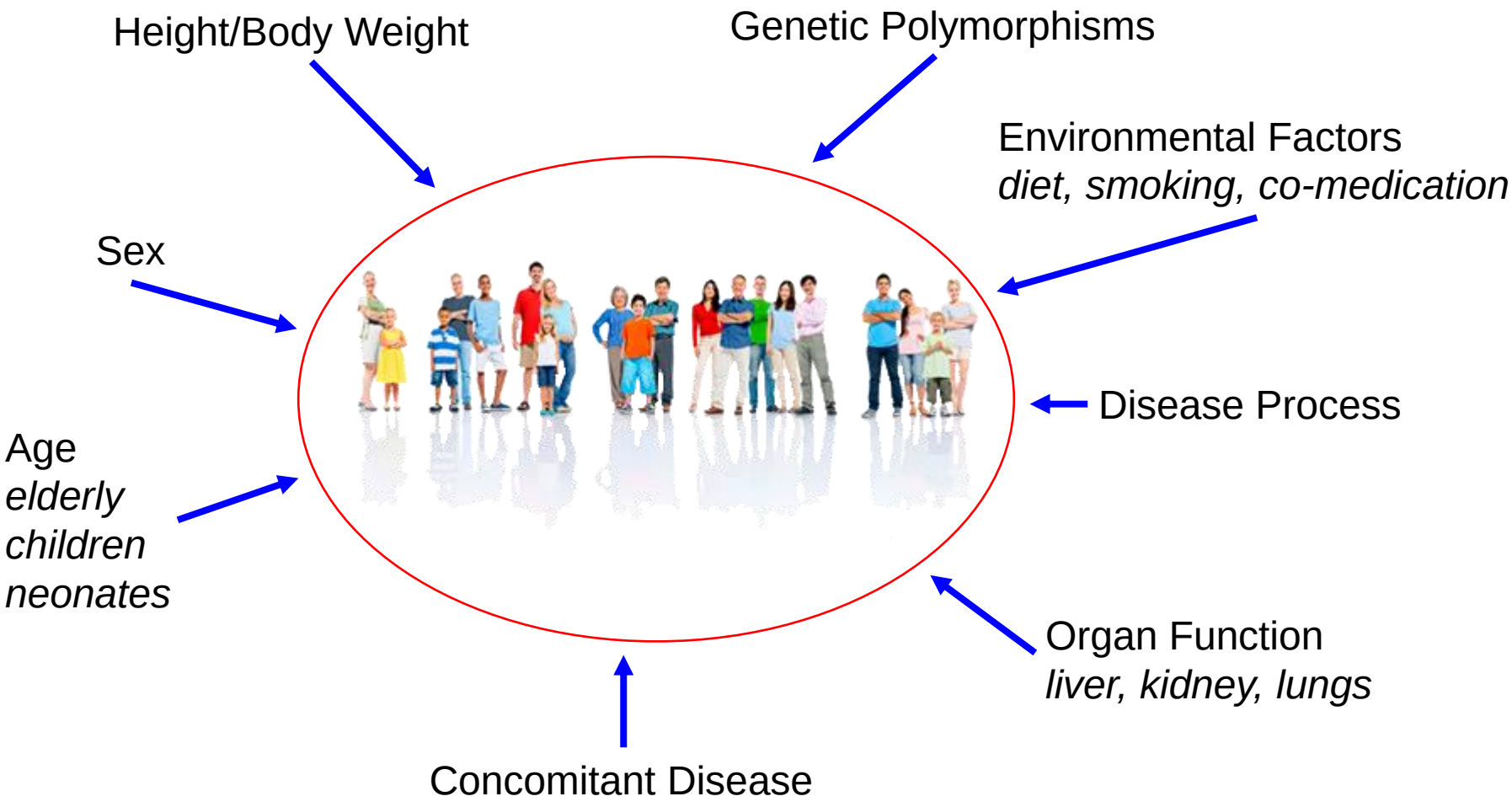


Courtesy of: Kelsey Kalbfleisch, MSc, CGC, CCGC
Genetic Counsellor for the Cardiac Genome Clinic,
Ted Rogers Centre for the Heart Research

Future of PGx in pharmacy practice

- Availability of PGx testing in pharmacies
- Integration of PGx data with clinical decision tools in electronic health records
- Influence of PGx in precision medicine in research
- Drug development

Factors determining inter-individual variations in drug response




THANK YOU