Pharmacogenetics in Mental Health: Practical Considerations

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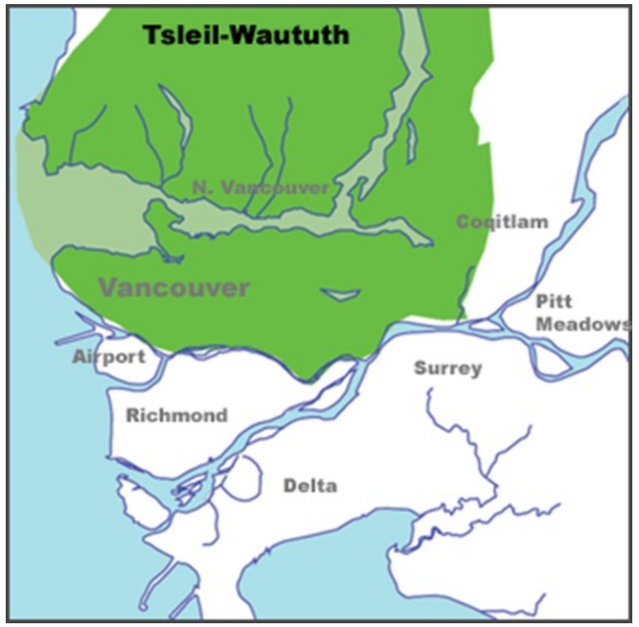
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



DISCLOSURE

Honoraria: Alberta Pharmacists' Association, Ontario Pharmacy Association, DrugBank

Grants: Canadian Institutes of Health Research, Genome Canada, Alberta Innovates, Alberta Children's Hospital Foundation, Libin Cardiovascular Institute, Australian National Health & Medical Research Council

Other: Founder, Sequence2Script Inc

Learning Objectives

At the end of this session, you will be able to:

01

Explain the rationale and evidence for using PGx-guided prescribing

02

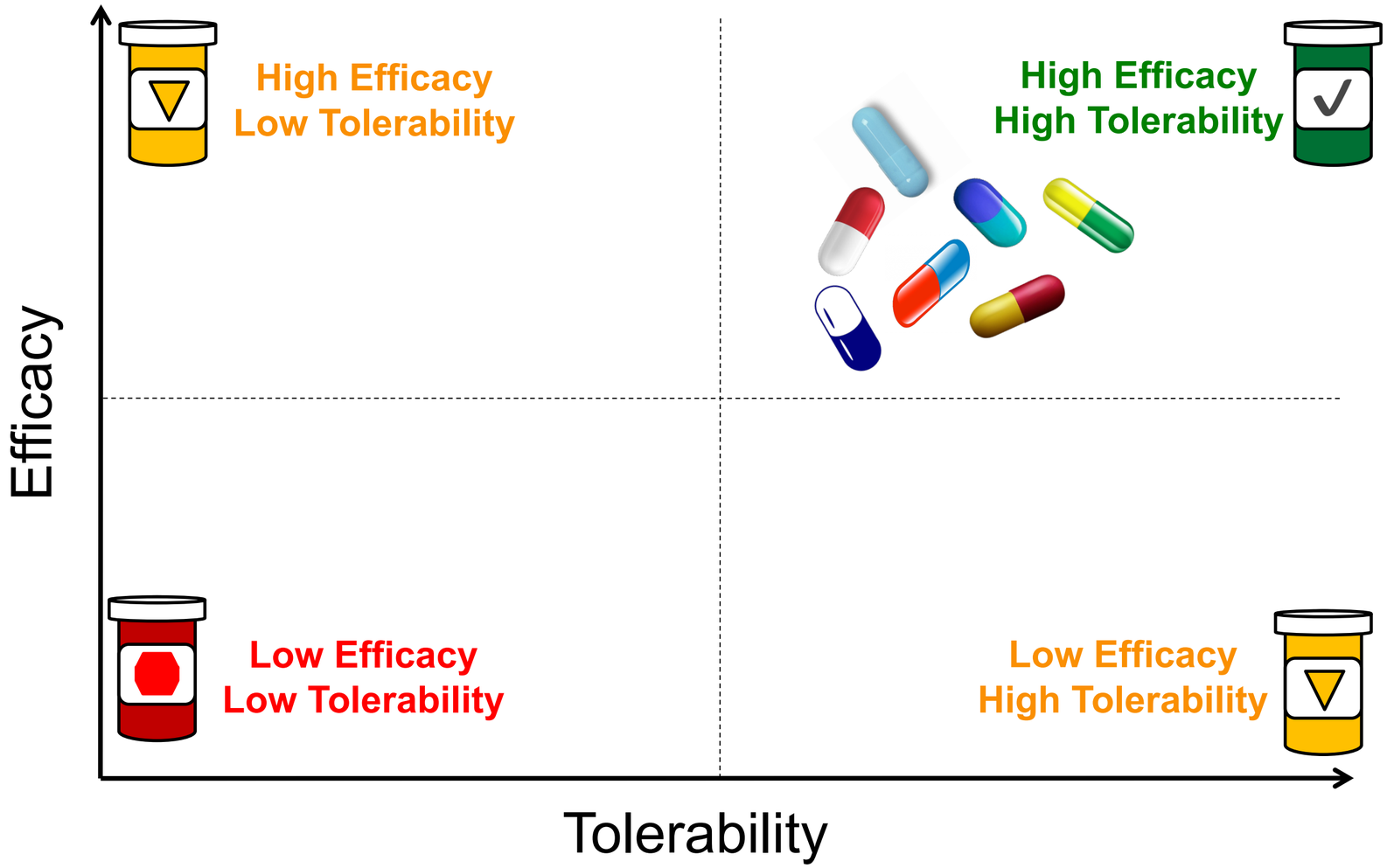
Identify care situations where PGx testing could be useful

03

Describe key considerations for using PGx-guided prescribing in practice

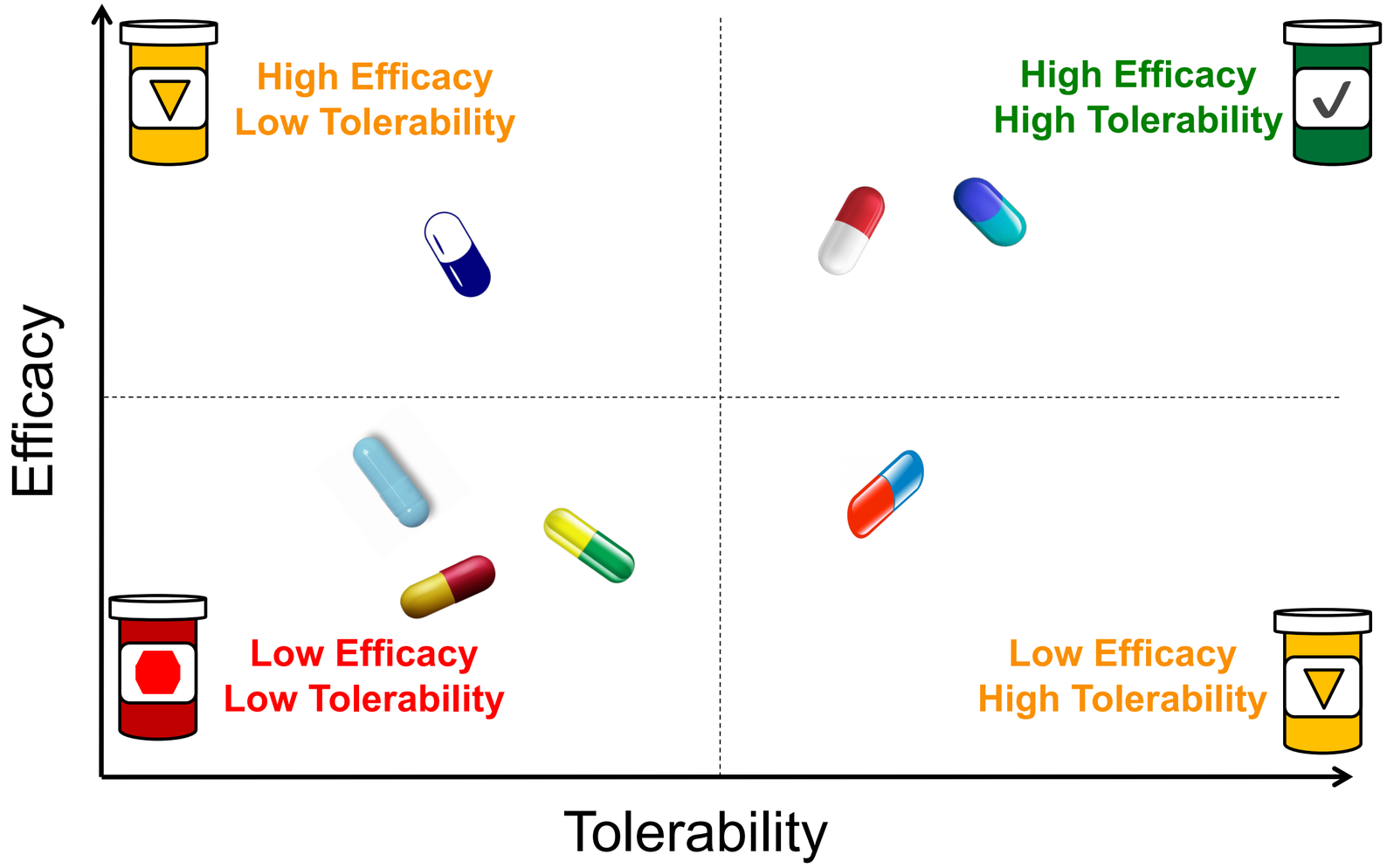
The Rationale

At the population level
medications are efficacious and tolerable

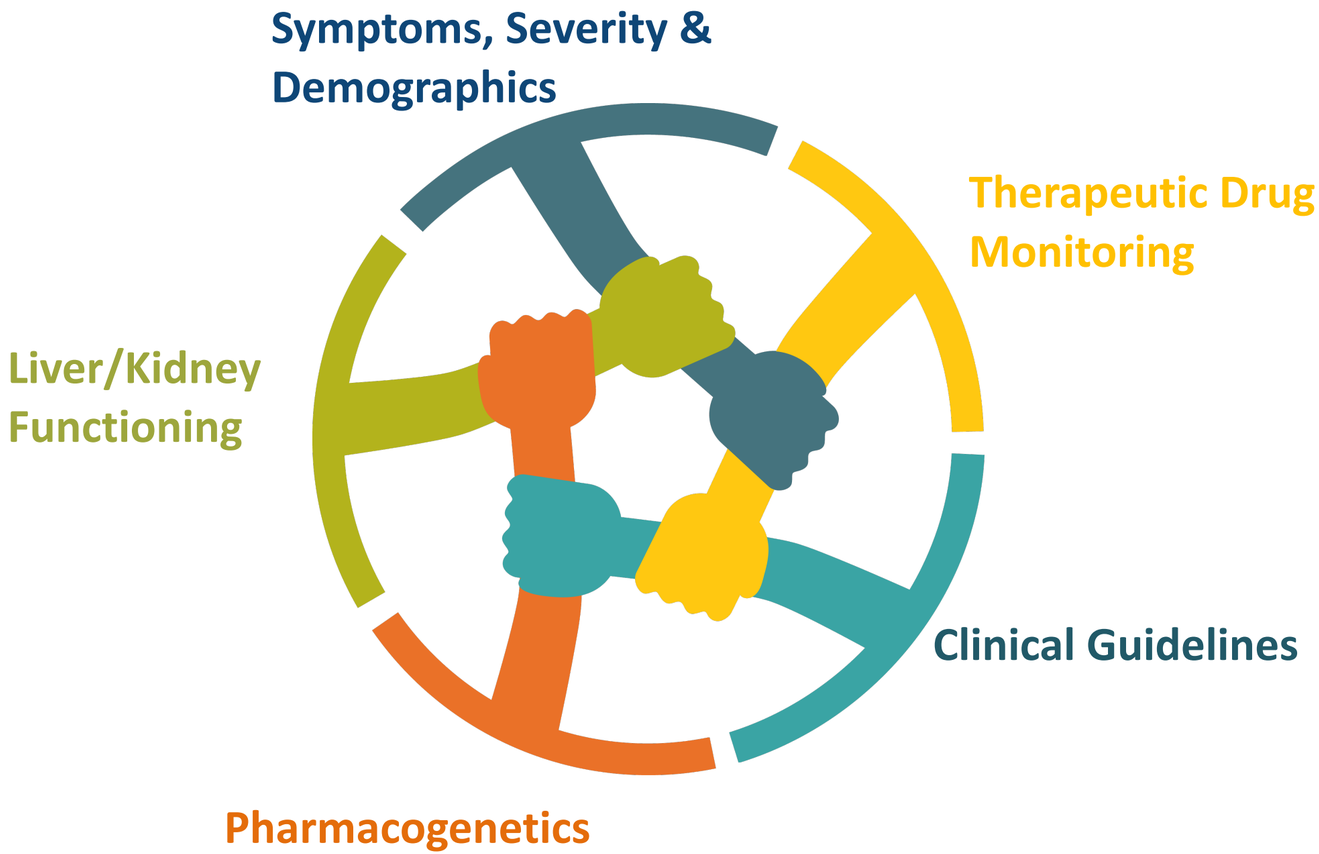


The Rationale

At the individual level
efficacy and tolerability can vary

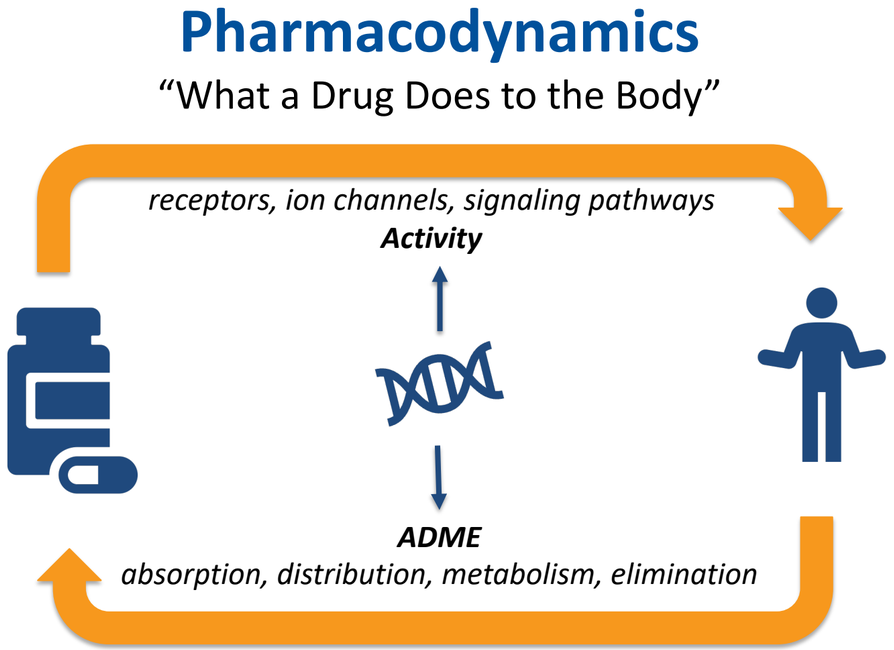


Personalized Prescribing Strategies

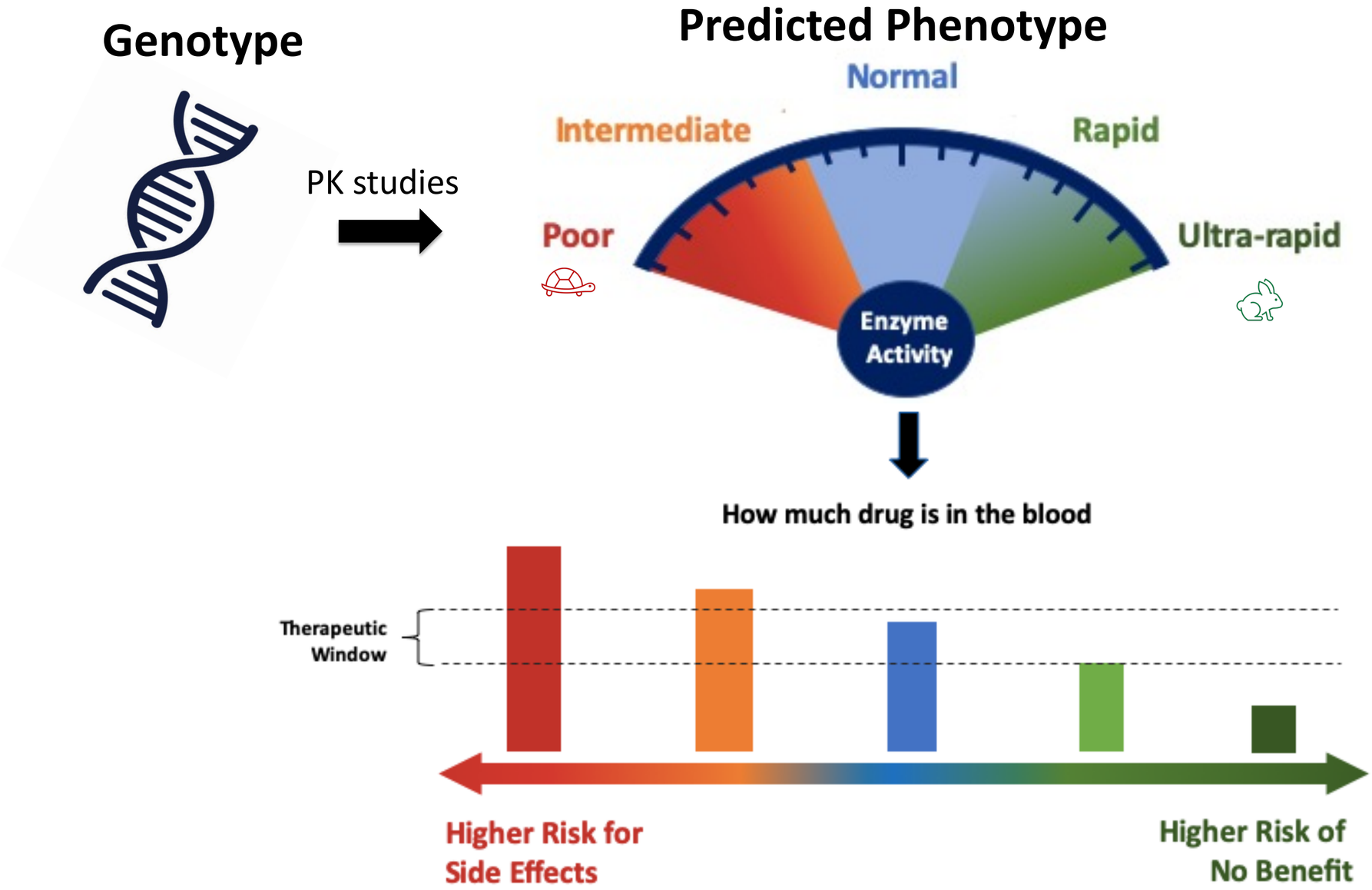


Pharmacogenetics

Uses genetic information to predict
a person's ability to process & react to medications



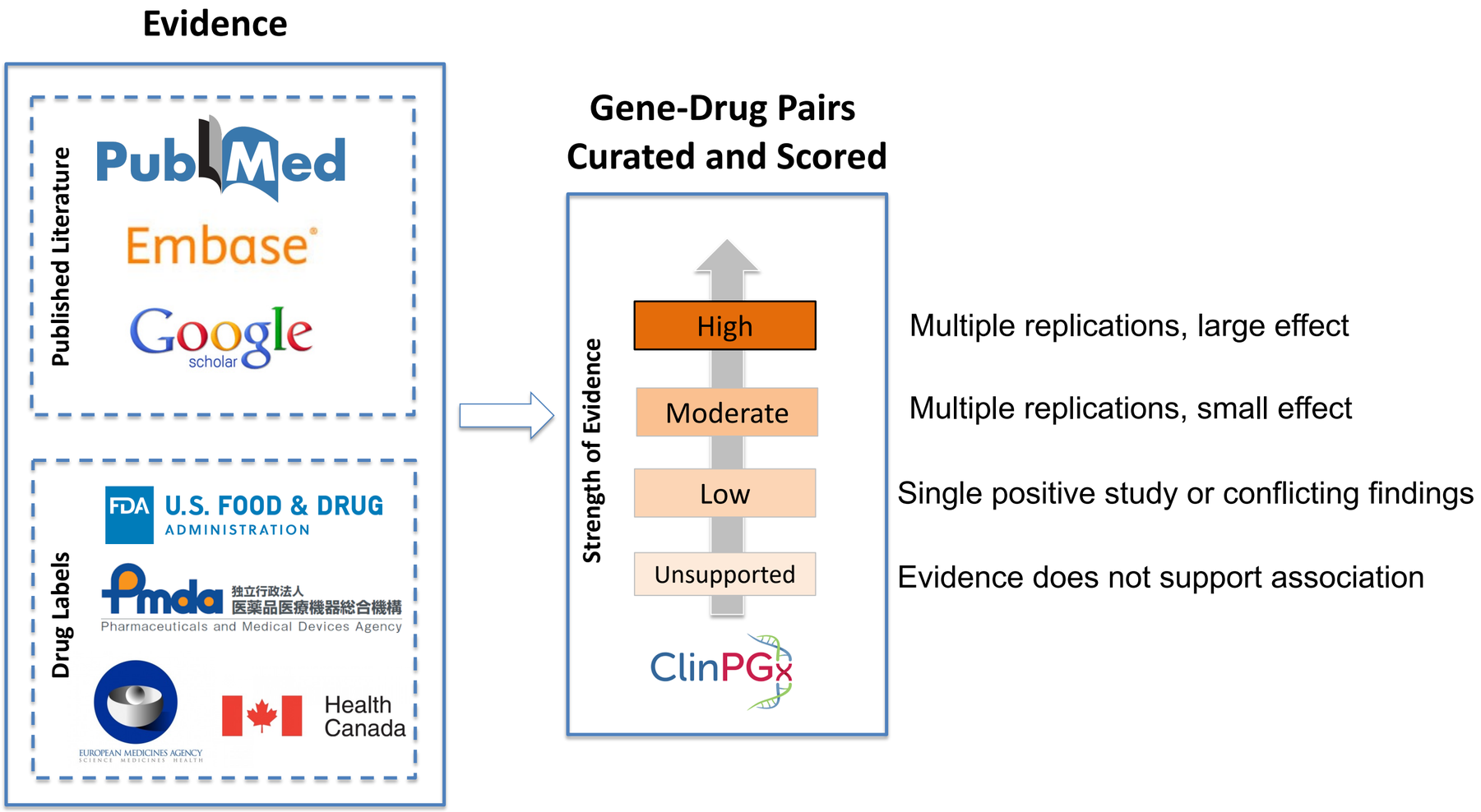
Pharmacogenetics in a Nutshell



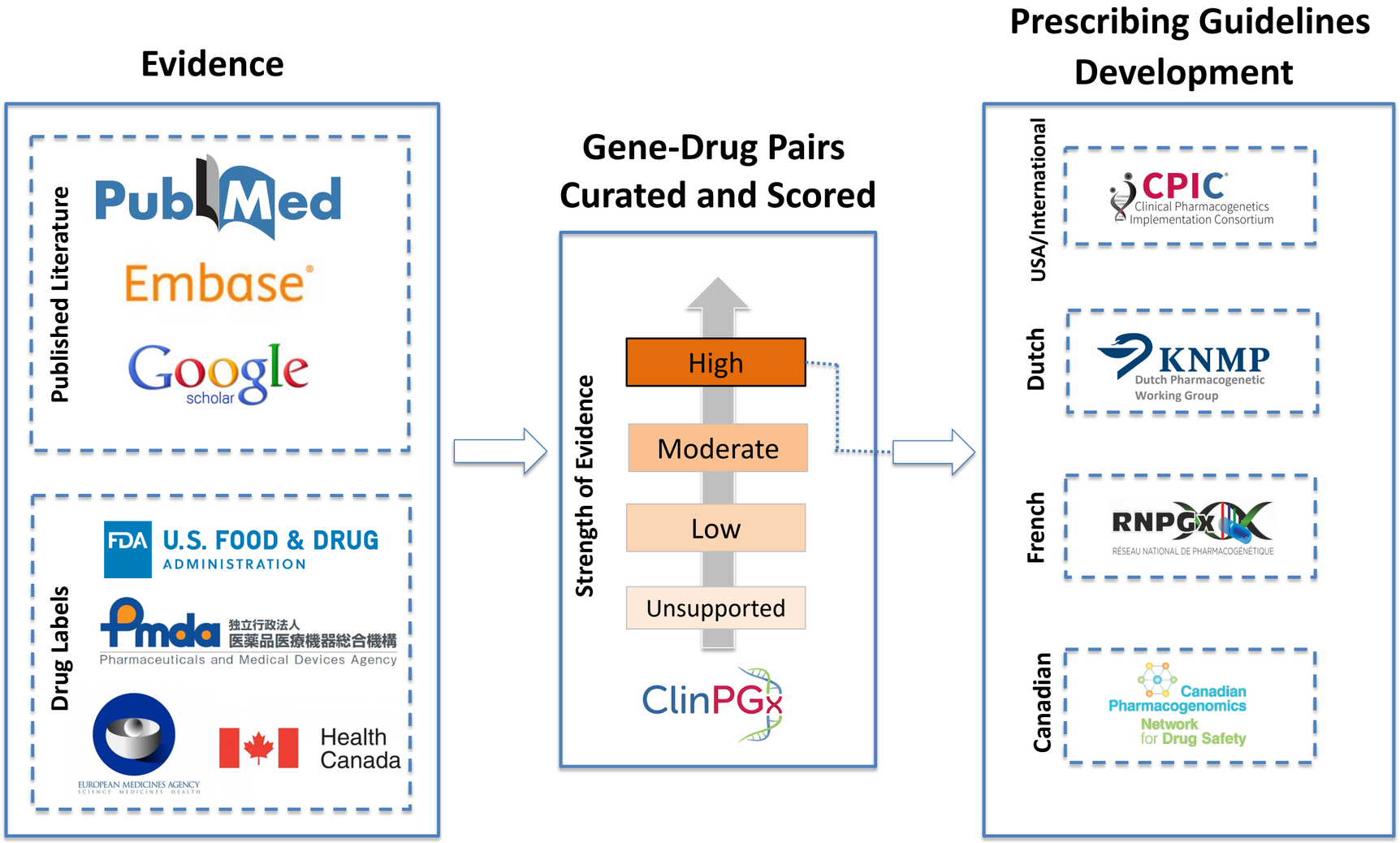
Note: Pro-drugs will have the inverse relationship

The Evidence

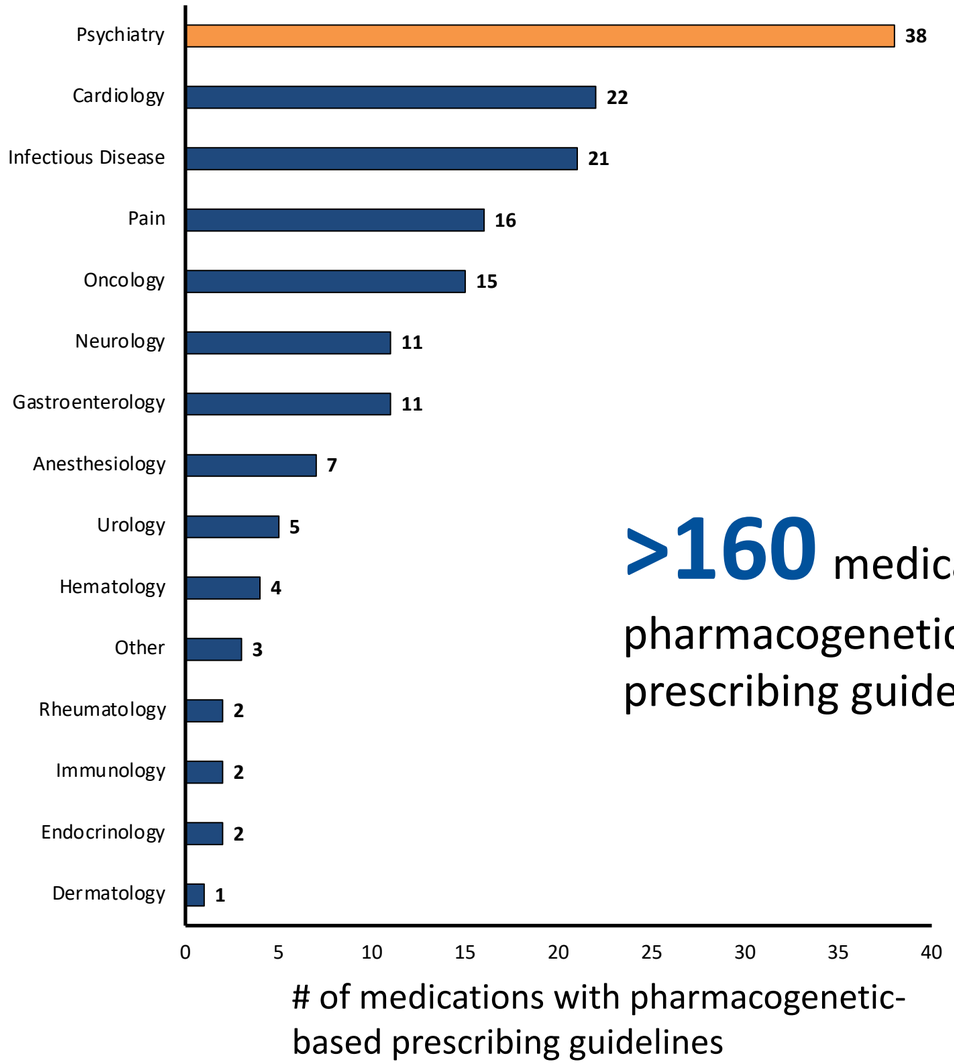
The Evidence



The Evidence



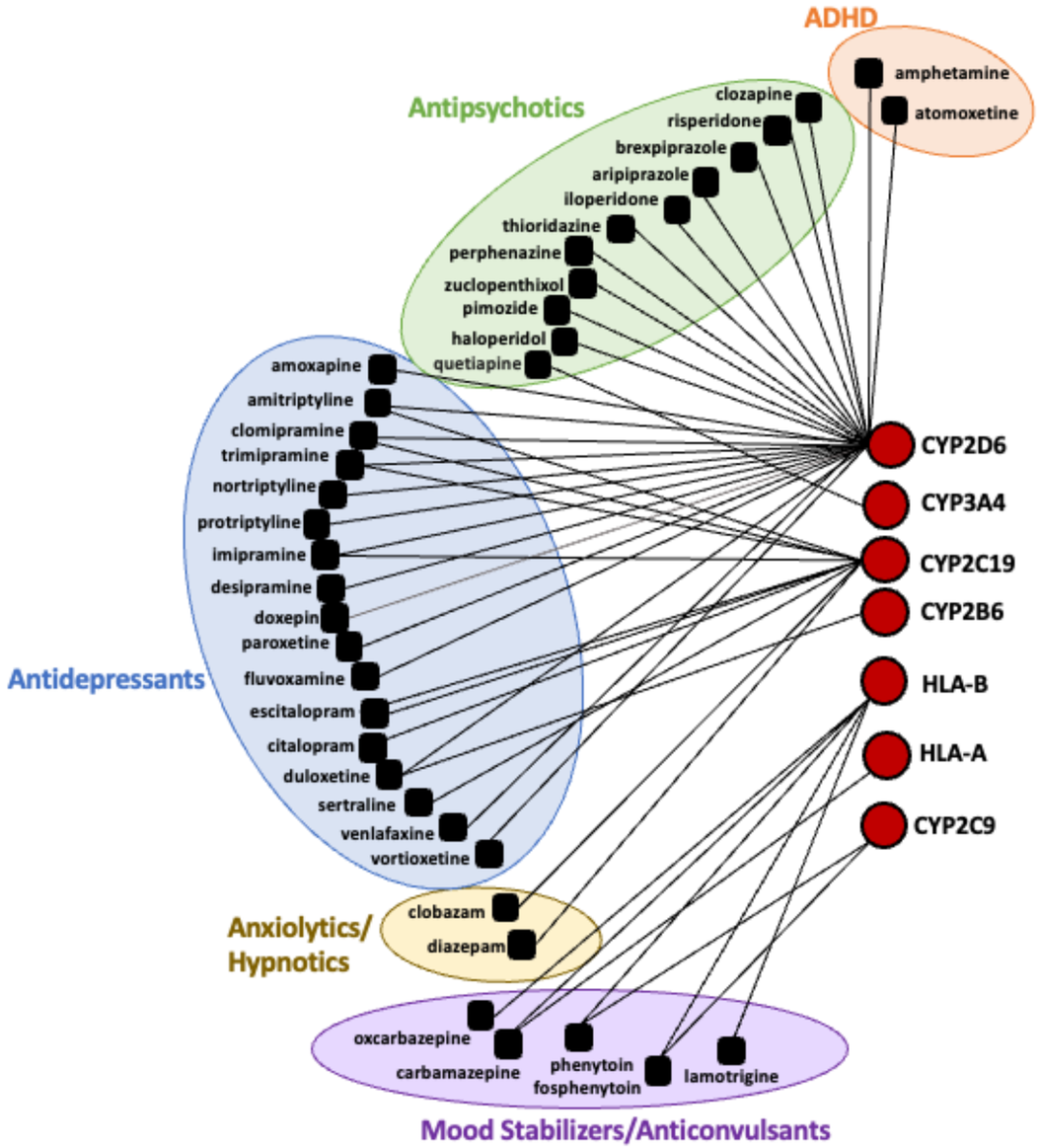
Prescribing Guidelines



>160 medications have pharmacogenetic-based prescribing guidelines

Data Source: https://www.pharmgkb.org/

Pharmacogenetic Guidelines - Psychiatry



7 genes & 38 medications

Consensus Recommendations

Review and Consensus on Pharmacogenomic Testing in Psychiatry

Authors
Chad A. Bousman[1, 2, 3, 4], Susanne A. Bengesser[5], Katherine J. Aitchison[6], Azmeraw T. Amare[7, 8], Harald Aschauer[9], Bernhard T. Baune[10, 4, 11], Bahareh Behroozi Asl[3], Jeffrey R. Bishop[12], Margit Burmeister[13], Boris Chaumette[14, 15], Li-Shiun Chen[16], Zachary A. Cordner[17], Jürgen Deckert[18], Franziska Degenhardt[19], Lynn E. DeLisi[20], Lasse Folkersen[21], James L. Kennedy[22, 23], Teri E. Klein[24], Joseph L. McClay[25], Francis J. McMahon[26], Richard Musil[27], Nancy L. Saccone[16], Katrin Sangkuhl[24], Robert M. Stowe[28], Ene-Choo Tan[29], Arun K. Tiwari[22, 23], Clement C. Zai[22, 23], Gwyneth Zai[22, 23], Jianping Zhang[30], Andrea Gaedigk[31], Daniel J Müller[22, 23]

Pharmacopsychiatry (2021)

ISPG INTERNATIONAL SOCIETY OF PSYCHIATRIC GENETICS

The current evidence <u>supports</u> PGx testing for specific:

- Antidepressants (CYP2C19 & CYP2D6)
- Antipsychotics (CYP2D6)
- Mood stabilizers (CYP2C9, HLA-A, HLA-B)
- ADHD medications (CYP2D6)

The current evidence <u>does not support</u> PGx testing for:

- Anxiolytics/Hypnotics
- Addiction medications
- Genetic variants in pharmacodynamic genes (e.g., *SLC6A4, COMT, MTHFR, DRD2*)

Case Example #1

Clinical Presentation: Patient was admitted to hospital with suicidal ideation and catatonic symptoms. Prior to admission the patient was given trials of citalopram and escitalopram at maximum doses but showed minimal response. Decision was made to start ECT. Patient's mental state improved, and they were prescribed sertraline prior to discharge from hospital. Shortly after discharge, depressive symptoms recurred, and the patient was re-admitted. PGx testing was ordered.

Gene	Genotype	Predicted Phenotype
CYP2B6	*4/*4	Ultrarapid Metabolizer
CYP2C19	*17/*17	Ultrarapid Metabolizer
CYP2D6	*2/*17	Normal Metabolizer

*Based on a case published by: Bousman et al, Chapter 7, *Precision Psychiatry*, APA Publishing, 2021

Case Example #1

Evidence & Guidelines

Gene	Genotype	Predicted Phenotype
CYP2B6	*4/*4	Ultrarapid Metabolizer
CYP2C19	*17/*17	Ultrarapid Metabolizer
CYP2D6	*2/*17	Normal Metabolizer

CYP2C19 Substrates

citalopram
escitalopram
sertraline
(CYP2C19 & CYP2B6)

Drug Labels mention CYP2C19 (citalopram & escitalopram)

U.S. FOOD & DRUG ADMINISTRATION

Health Canada

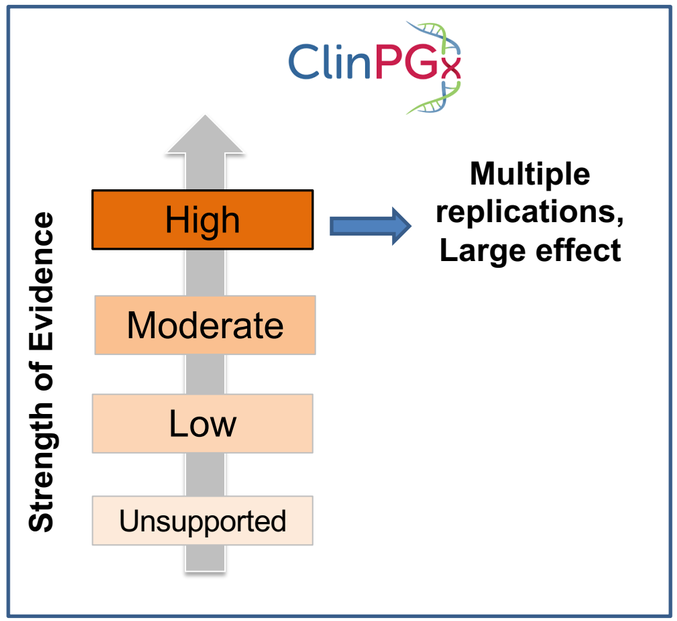
Pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

swissmedic

Dosing Guidelines (es/citalopram and sertraline)

CPIC® Clinical Pharmacogenetics Implementation Consortium

"Consider an alternative drug not predominantly metabolized by CYP2C19."



Case Example #1

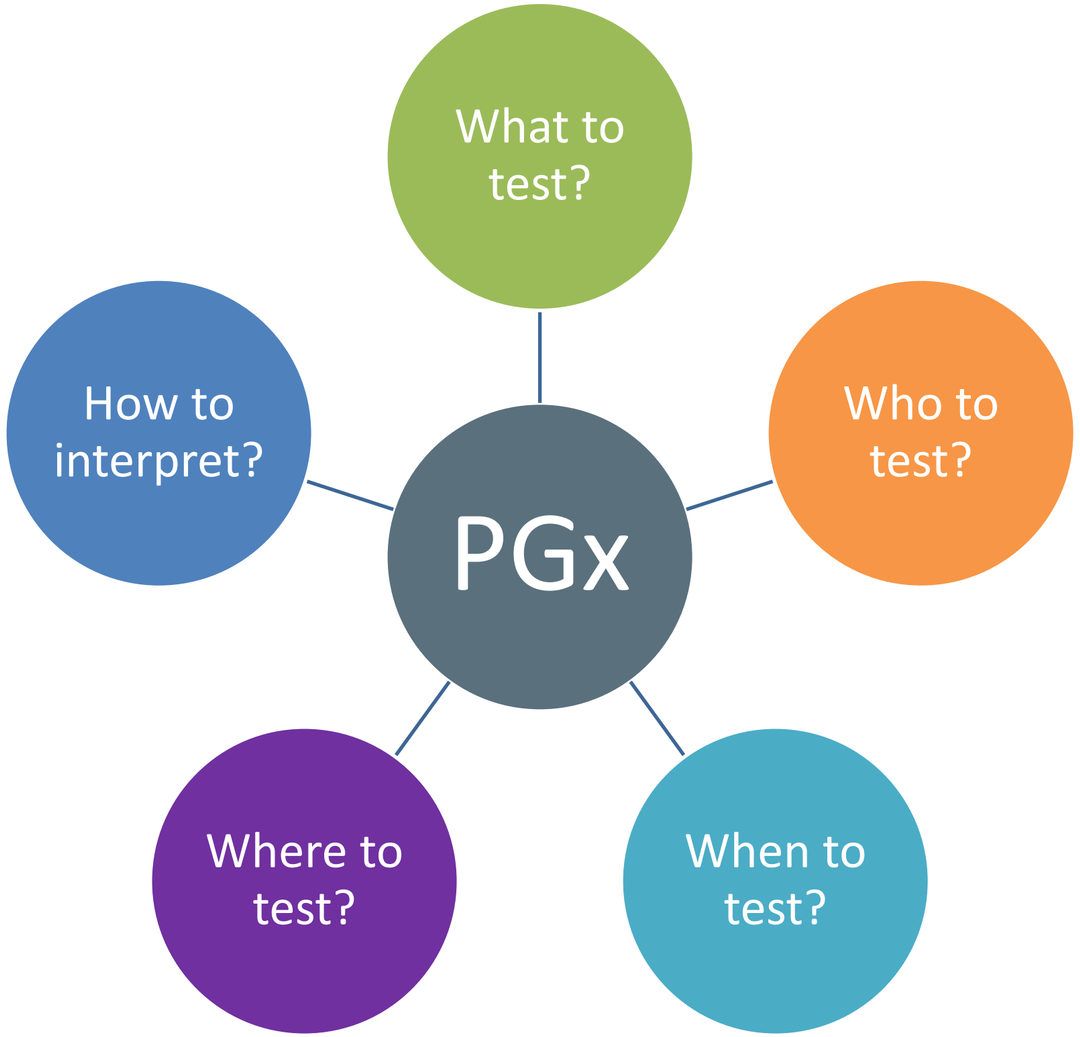
Case Conclusion:

- Sertraline was discontinued
- Paroxetine was prescribed (*CYP2D6* substrate)
- Patient was discharged three weeks later and remains well in the community with no further relapses

Take Home Message:

- PGx testing could significantly reduce these types of experiences, expedite time to response, & avoid unnecessary treatments

Clinical Implementation of PGx FAQs



What to Test?

Test providers are not using the same playbook

< 60% agreement in prescribing advice across tests

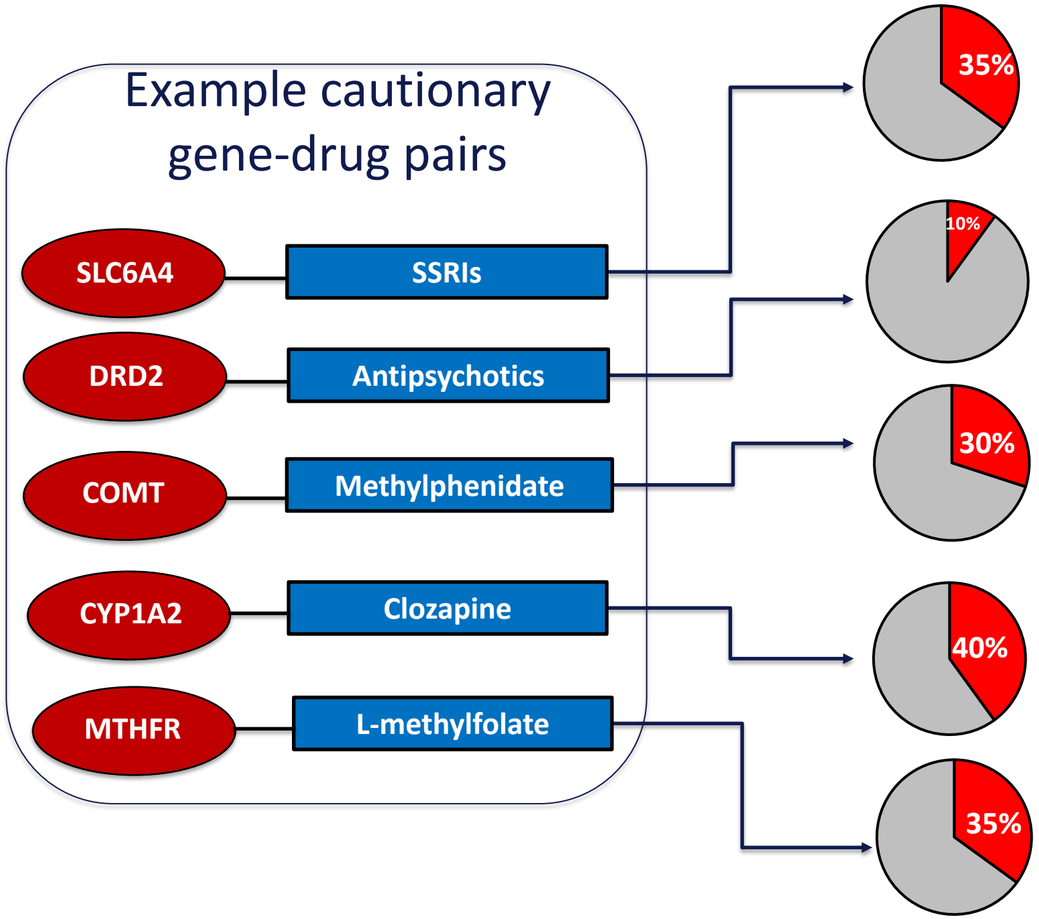
Bousman & Dunlop, *The Pharmacogenomics J,* 2018

⚠ Cautionary Content ⚠

Good face validity

Good biological plausibility

Inconclusive clinical validity



Bousman & Hopwood, *The Lancet Psychiatry,* 2016

Case Example #2

Clinical Presentation: Patient was admitted to the hospital on an involuntary basis due to bizarre behavior & command hallucinations. History of multiple medication failures (haloperidol, paliperidone, olanzapine, ziprasidone, citalopram, lithium, valproic acid). Treatment team decided clozapine was the next best step. Patient's family and family doctor opposed this decision based on pharmacogenetic testing results ordered by the patient's family doctor.

Gene	Predicted Phenotype
HLA-B	Negative
CYP2C19	Normal Metabolizer
CYP2D6	Normal Metabolizer
UGT2B15	Normal Metabolizer
★ **DRD2 rs1799732**	**Poor responder (clozapine, olanzapine, risperidone)**

*Based on case published by: Rahman et al, *Am J Psych*, 2017

Case Example #2

Evidence for DRD2 and Clozapine

Gene	Predicted Phenotype
HLA-B	Negative
CYP2C19	Normal Metabolizer
CYP2D6	Normal Metabolizer
UGT2B15	Normal Metabolizer
DRD2 rs1799732	**Poor responder (clozapine, olanzapine, risperidone)**

No Mention on Drug Labels

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada

Pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

EUROPEAN MEDICINES AGENCY SCIENCE · MEDICINES · HEALTH

No Dosing Guidelines

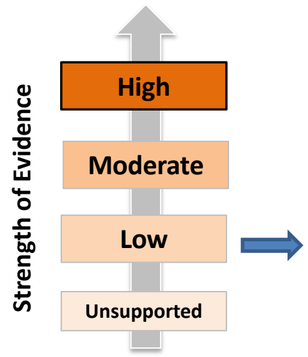
CPIC® Clinical Pharmacogenetics Implementation Consortium

KNMP

RNPGx RÉSEAU NATIONAL DE PHARMACOGÉNÉTIQUE

Canadian Pharmacogenomics Network for Drug Safety

ClinPGx



Not yet replicated or conflicting findings

Case Example #2

Case Conclusion:

- Clozapine was commenced after approval from the medical director and the patient consented

- The patient responded rapidly and was discharged – gradually returned to their previous level of functioning.

Take Home Message:

- Only implement gene-drug pairs that have prescribing guidelines

Who should be offered testing?

No consensus but there are evidence-based indications

Starting a drug with a PGx guideline

No response despite high adherence

Side effects at low doses

Reluctance or low adherence to pharmacotherapy

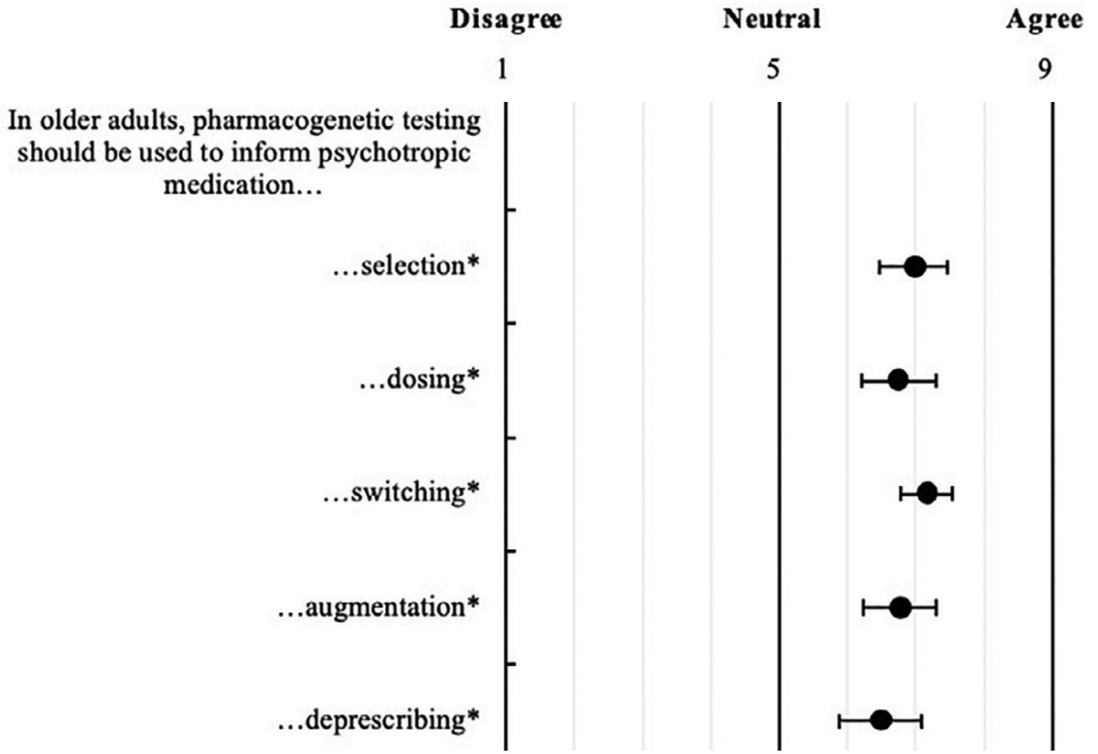
Deprescribing

Who should be offered testing?

Psychiatrists' Perceptions

Modest agreement that PGx testing should be used to inform:

- Selection
- Dosing
- Switching
- Augmentation
- Deprescribing



N = 40

Bousman et al., AJGP, 2022

Case Example #3

Clinical Presentation: Patient was brought to an emergency psychiatric clinic for hallucinations, delusions of persecution, and disorganized speech. Patient was prescribed aripiprazole but experienced intolerable side effects within 4 days. Switched to risperidone but after 1 week presented with intolerable side effects. Patient refused clozapine, olanzapine, & quetiapine owing to weight gain concerns but accepted haloperidol, which resulted in tremors, stiffness, and notable anhedonia. Treatment team decided to order PGx testing.

Gene	Predicted Phenotype
CYP2C19	Normal Metabolizer
CYP2D6	Poor Metabolizer

*Based on case published by: Korchia et al, *J Psychiatry Neurosci 2023;48(1)*

Case Example #3

Evidence & Guidelines

Gene	Predicted Phenotype
CYP2C19	Normal Metabolizer
CYP2D6	Poor Metabolizer

CYP2D6 Substrates

aripiprazole
risperidone
haloperidol

Drug Labels mention CYP2D6 (aripiprazole & risperidone)

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Health Canada

独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

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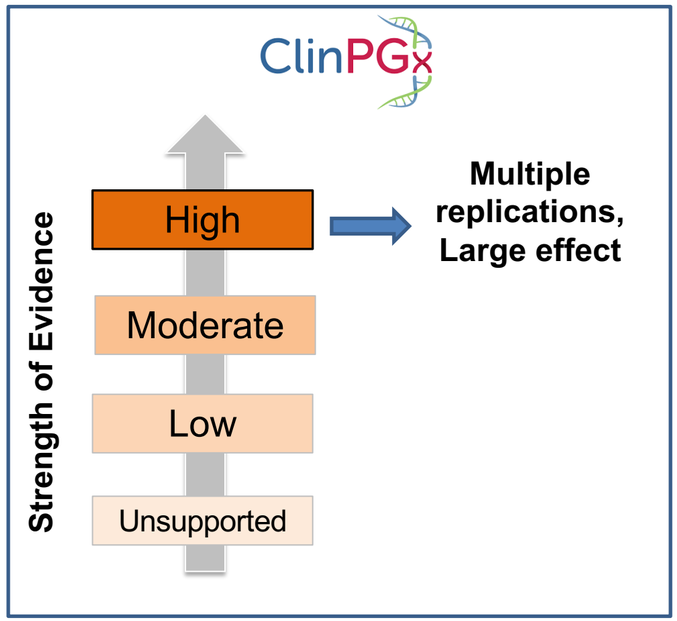
Dosing Guidelines (aripiprazole, risperidone, haloperidol)

KNMP

Aripiprazole: "Use 68-75% of the standard maximum dose

Risperidone: "Use 67% of the standard dose"

Haloperidol: "Use 60% of the standard dose"



Case Example #3

Case Conclusion:

- Paliperidone was commenced (limited metabolism by CYP2D6)
- The patient responded rapidly and was discharged.

Take Home Message:

- In patients presenting with higher sensitivity to drug associated adverse events, PGx testing should be considered.

Who should be offered testing?

Managing Expectations!

PGx testing CAN:

- Enhance other prescribing strategies (e.g., TDM)
- Reduce uncertainty related to prescribing
- Reduce the probability of inefficacy or toxicity to certain medications

PGx testing CANNOT:

- Identify the ‘best’ medication for an individual
- Determine if a medication will work
- Eliminate the risk of side effects/adverse drug reactions

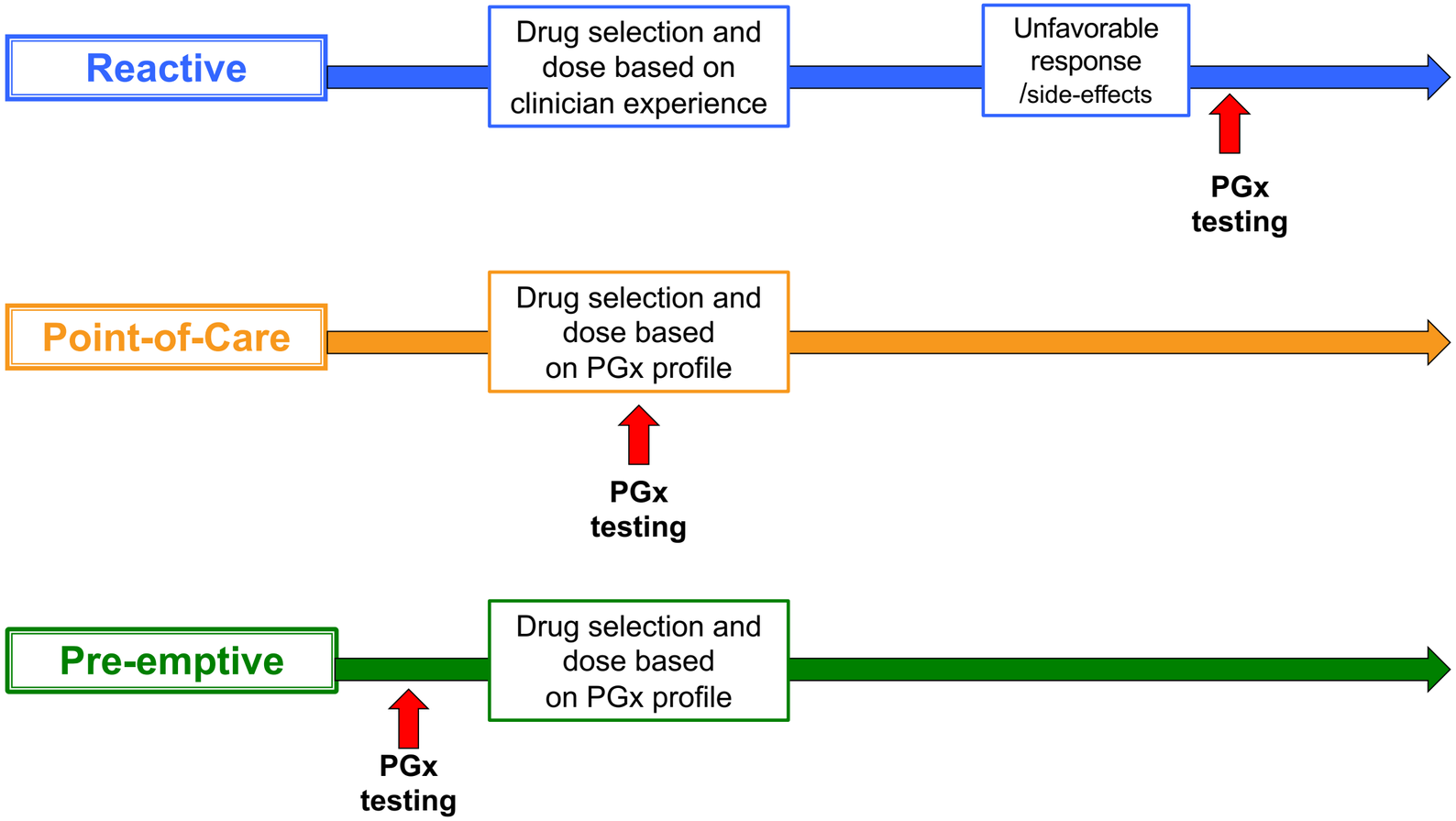
When is the best time to order a test?

Three main approaches

Some Canadians are covered for PGx testing (indication specific)

63% of CAPs asked to order PGx by family

Soda et al, *Psych Res*, 2023



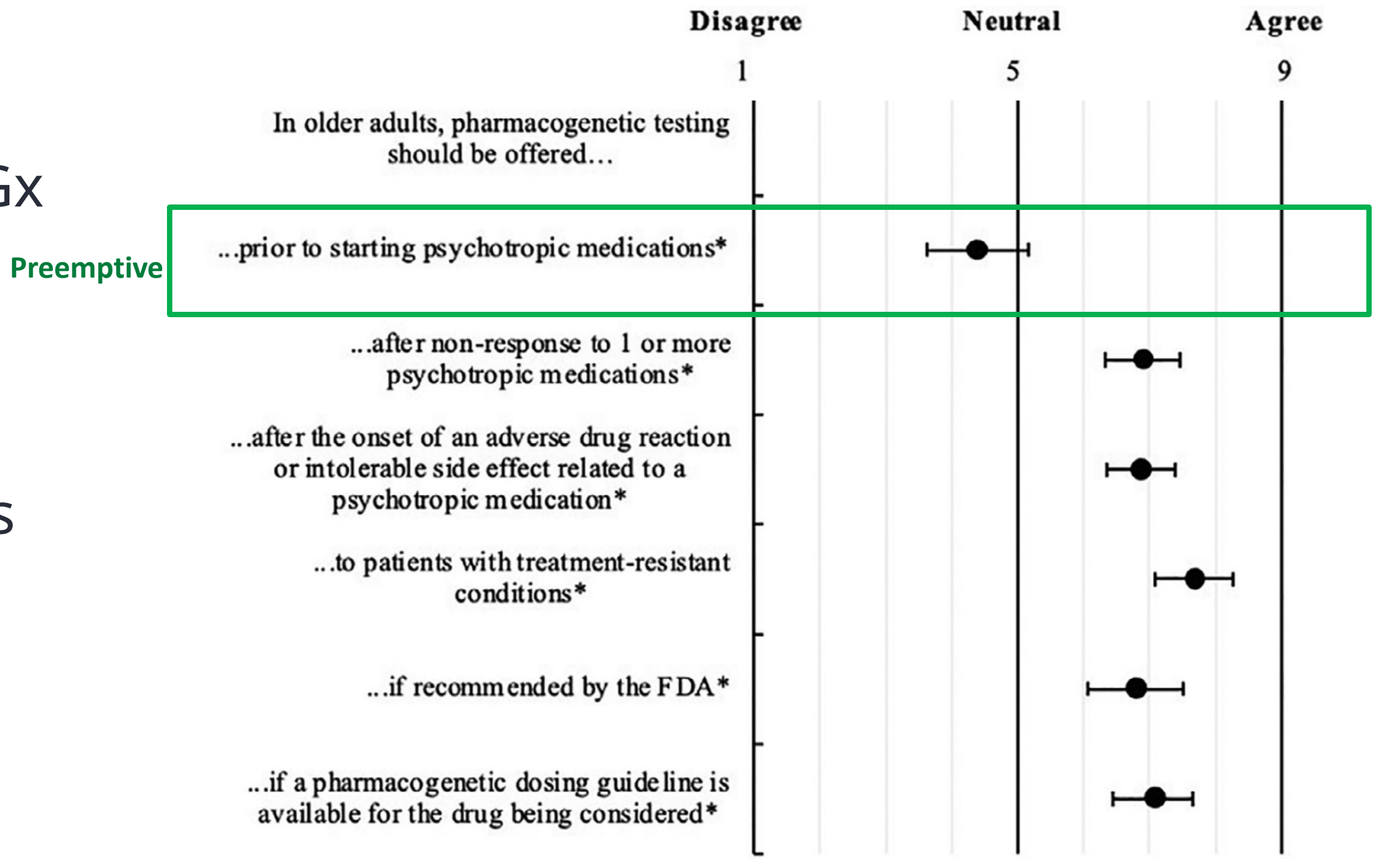
When is the best time to order a test?

Psychiatrists' Perceptions

Modest-strong agreement that PGx testing should be offered:

Reactive
- After non-response >1 drug
- Onset of an ADR
- Treatment-resistant conditions

Point of Care
- FDA recommended
- PGx guideline available

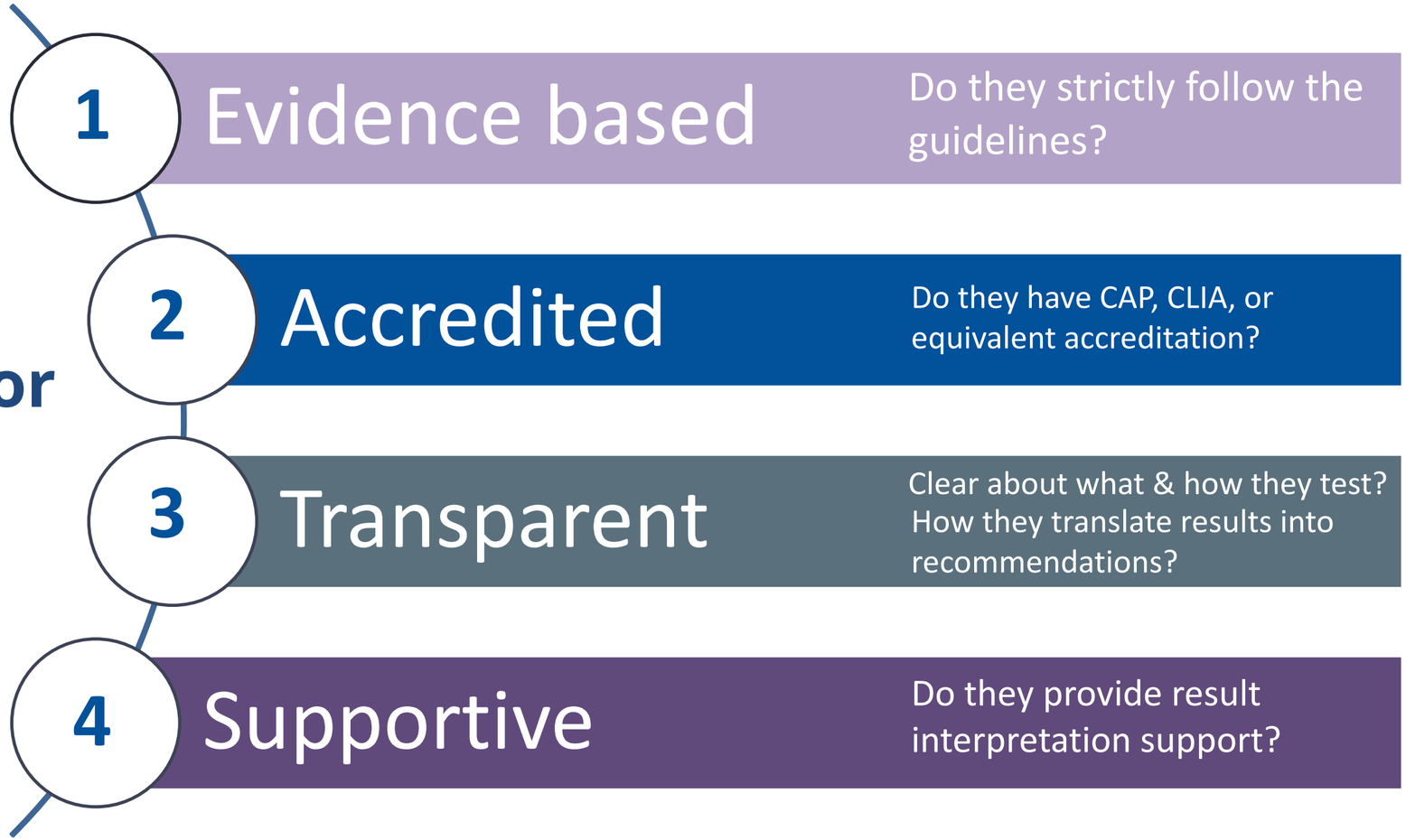


N = 40

Bousman et al., AJGP, 2022

Where to order a test?

Best Practices for choosing a lab



No lab is superior to all others

….but inferior labs exist

Bousman et al., Clin. Pharmacol. Ther., 106 (2), 2019

Where to order a test?

There are several private Canadian labs

Private Labs	Turnaround (days)	Cost (CAD)
Biron Genetique	5-10	$499
Dynacare	6-8	$495
DNALabs	10	$349
GeneYouIn	5-15	$599
Inagene	7-10	$399
Personalized Prescribing	7-10	$499
GenXys	7-10	$499

Where to order a test?

10 Canadian Insurance Providers Cover PGx Testing

	PGx testing benefits ($CAD)			Eligibility requirements for PGx coverage				
Insurer	Retail price	General member coverage	Condition-based coverage[a]	On disability leave?	Have extended health care coverage?	Physician diagnosis or prescription?	History of medication inefficacy or intolerability?	PGx testing lab partner
Beneva	$499	$0	$499	Yes	No	No	Yes	Biron Health Group
Canada Life	$599	Preferred pricing	$599	Yes	No	No	No	GeneYouIn Inc.
Desjardins	$499	$82	$499	Yes[b]	Yes[b]	Yes[b]	No	Biron Health Group
Empire Life	$599	$0	$599	Yes[c]	No	Yes[c]	No	GeneYouIn Inc.
Equitable Life	$499	$60	$499	No	Yes	Yes	Yes	Personalized Prescribing Inc.
Greenshield	$499	$0	$499	No	Yes	Yes	Yes	GenXys Prescribing Systems
Manulife	$499	$60	$499	No	Yes	Yes	Yes	Personalized Prescribing Inc.
Medavie Blue Cross	$599	Preferred pricing	$599	No	Yes	Yes	No	GeneYouIn Inc.
RBC Life	$499	$100	$499	Yes[b]	Yes[b]	Yes[b]	No	Personalized Prescribing Inc.
Sun Life	$499	$0	$499	No	Yes	Yes	No	Biron Health Group

Brubaker-Plitt & Bousman, *Pharmacogenetics and Genomics* , 2025

Where to order a test?

Free PGx Testing for Youth in Western Canada

PGx-STaR
Pharmacogenomics of Stimulant Treatment Response

Target population

- Age 6 – 24
- ADHD diagnosis
- Starting a methylphenidate

PGx-GAP
Pharmacogenetic-guided antidepressant prescribing

Target population

- Age 12 – 17
- Primary diagnoses of depression or anxiety
- Starting a new SSRI

Referrals should be sent to:
psychpgxlab@ucalgary.ca

Funding partner
Alberta Children's Hospital Foundation

Funding partner
CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

How to interpret test results?

Aripiprazole
Abilify®

CYP2D6 *9/*9
CYP2D6 : Intermediate Metabolizer

Gene linked to recommendation

Clinical Action:

Normal Exposure to Aripiprazole

The patient's genotype is associated with slightly increased aripiprazole exposure. Consider prescribing aripiprazole at standard la… recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

Daily dosing (oral): the daily maintenance and maximum recommended doses are 10-15 mg and 30 mg, respectively. Reduce dose by 50% if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered. Reduce the dose to 25% of the usual dose if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered. Double the dose if a strong CYP3A4 inducer is co-administered.

Monthly dosing (intramuscular): the starting and maintenance monthly recommended dose is 400 mg for *Abilify Maintena*. For *Abilify Maintena*, reduce the monthly dose to 300 mg if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered to patient… receiving aripiprazole at 400 mg, and reduce dose to 200 mg in patients receiving aripiprazole at 300 mg. For *Abilify Maint…* reduce the dose to 200 mg if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered to patients r… aripiprazole at 400 mg, and reduce the dose to 160 mg in patients receiving aripiprazole at 300 mg. If a strong CYP3A4 … is co-administered for more than 14 days, avoid using *Abilify Maintena*.

- Abilify Maintena [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2017.
- Aristada [package insert]. Waltham, MA: Alkermes; 2018.
- Aristada Initio [package insert]. Waltham, MA: Alkermes; 2018.
- Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2019.

Source of recommendation

Aripiprazole
Abilify®

HTR2C 114138144C>G G/G
HTR2C : Homozygous for the G allele (rs1414334)

Clinical Action:

Decreased Risk of Metabolic Syndrome with Aripiprazole

Genetic variations in the Serotonin 2C Receptor (HTR2C) gene in known to be partially involved in the adverse effects associated with atypical antipsychotic medications. The patient is homozygous for G allele of HTR2C variant rs1414334. The patient has low risk of developing metabolic syndrome when treated with aripiprazole.

- Risselada AJ, Vehof J, Bruggeman R, Wilffert B, Cohen D, Al Hadithy AF, Arends J, Mulder H. Association between HTR2C gene polymorphisms and the metabolic syndrome in patients using antipsychotics: a replication study. Pharmacogenomics J 2012 Feb;12(1):62-7.
- Mulder H, Cohen D, Scheffer H, Gispen-de Wied C, Arends J, Wilmink FW, Franke B, Egberts AC. HTR2C gene polymorphisms and the metabolic syndrome in patients with schizophrenia: a replication study. J Clin Psychopharmacol 2009 Feb;29(1):16-20.
- Mulder H, Franke B, van der-Beek van der AA, Arends J, Wilmink FW, Scheffer H, Egberts AC. The association between HTR2C gene polymorphisms and the metabolic syndrome in patients with schizophrenia. J Clin Psychopharmacol 2007 Aug;27(4):338-43.

Reports are not standardized nor are they regulated

Anti-Anxiety/Ant… Depression		
Amitriptyline (Elavil®)	✗	Elevated CYP2C19 …nzyme activity. Consider alternative drug NOT metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments. (CPIC)
Citalopram (Celexa®)	✗	Elevated CYP2C19 enzyme activity. Consider an alternative drug NOT predominantly metabolized by CYP2C19. Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. (CPIC)
Clomipramine (Anafranil®)	✗	Elevated CYP2C19 enzyme activity. Consider alternative drug NOT metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments. (CPIC)
Desipramine (desipramine®)	✓	Initiate therapy with recommended starting dose. (CPIC)
Doxepin (Sinequan, Silenor®)	✗	Elevated CYP2C19 enzyme activity. Consider alternative drug NOT metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments. (CPIC)

Patient Information Summary

This is a summary genetic report for your patient to share with other healthcare providers.

Gene	Genotype	Phenotype	Clinical Impact
CYP2B6	*1/*6	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2B6 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP2C19	*17/*17	Ultra-Rapid Metabolizer	Consistent with a significant increase in CYP2C19 enzyme activity. Exercise caution if CYP2C19 drug substrates are prescribed.
CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 enzyme activity.
CYP2D6	*9/*9	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2D6 enzyme activity.

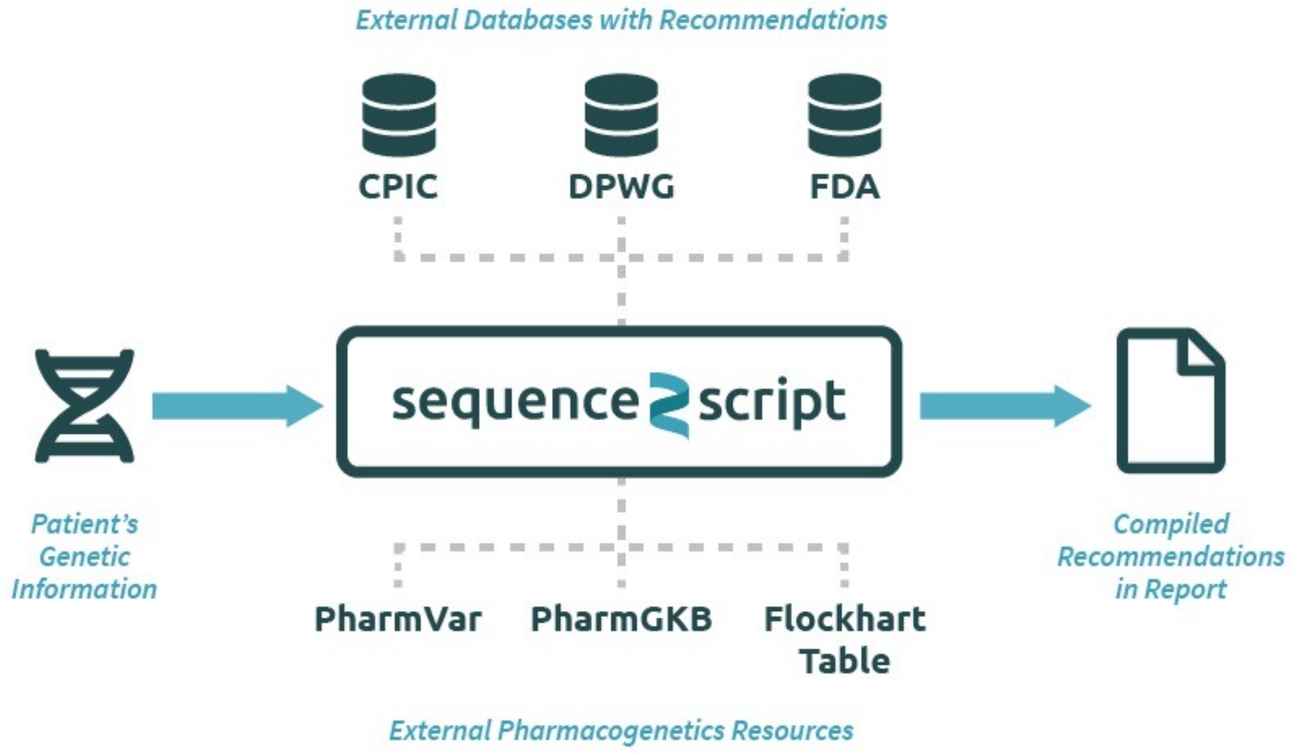
Genotype results

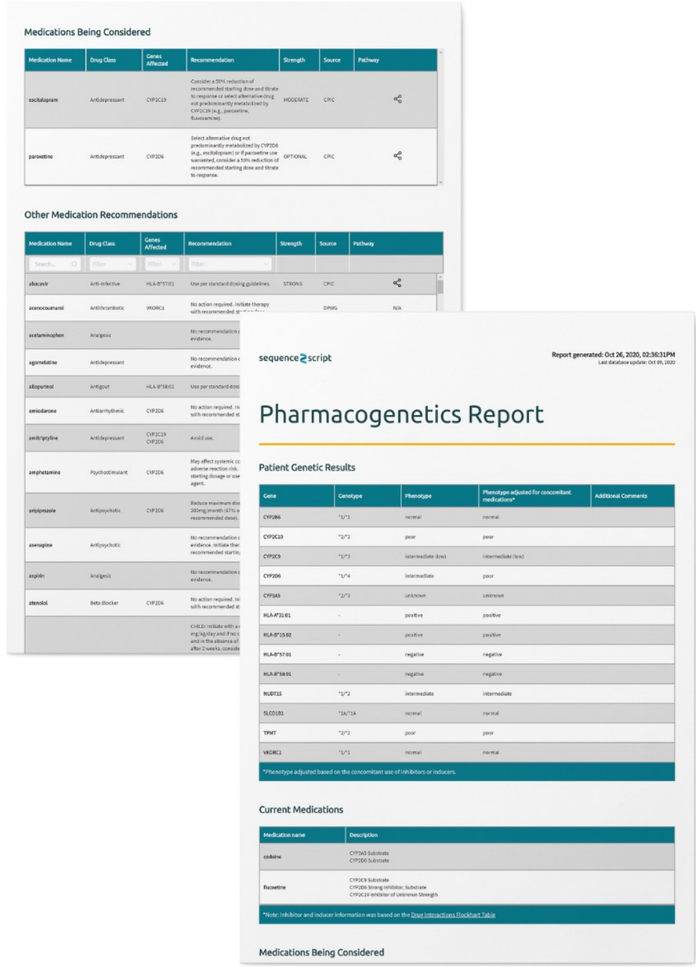
Genetic results:

Gene	Results
CYP2C19	One functional allele and one increased-function allele
CYP2C9	Two functional alleles
CYP2D6	One functional allele and one non-functional allele
CYP3A5	Two reduced-function alleles

How to interpret test results?

Get a Free Second Opinion





www.sequence2script.com

Bousman et al, 2021 *Front Pharmacology*

Take Home Points

1. PGx testing is an evidence-based strategy to inform prescribing of several psychiatric medications
2. The impact of PGx depends heavily on the quality of the testing and appropriate interpretation of results
3. PGx testing is a companion decision-support tool that can enhance not replace current prescribing strategies

Contact:

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UNIVERSITY OF CALGARY

Thank You!

Moraine Lake, Banff National Park, Alberta, Canada