CES presentations are meant to provide general information about child and youth health and wellness and are for educational purposes only. The information provided is not intended to be a substitute for seeking medical advice. Please contact your Family Physician and/or licensed healthcare professional/team for follow-up on appropriate diagnoses, and or treatment for the child/youth in your care.

Here are some useful resources within Alberta:

Emergency	911	Addiction Helpline	1-866-332-2322
Health Link	811	Kids Help Phone	1-800-668-6868
211 Alberta	211	Distress Centre	1-403-266-4357
Access Mental Health	1-844-943-1500	Suicide Line	1-888-787-2880
Mental Health Helpline	1-877-303-2642	Togetherall	https://togetherall.com/en-ca/

Territorial Acknowledgement

Community Education Service acknowledges that the land on which we virtually gather today is the traditional territories of the people of the Treaty 7 region in Southern Alberta. The City of Calgary is also home to Métis Nation of Alberta, Region 3.

2021

Starting or changing medication for your child/youth's mental health?

An introduction to genotype-guided prescribing

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University of Calgary

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The Mathison Centre for Mental Health Research & Education

Objectives

- Overview of the rationale & evidence for using genotype-guided prescribing
- Explain who can benefit from it
- Highlight current research examining genotype-guided prescribing

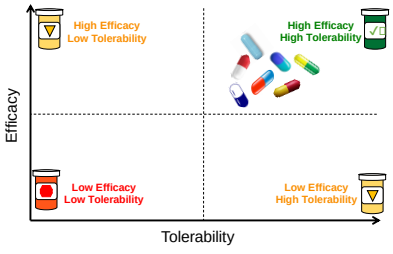
The Rational

No drug is good
No drug is bad
Every drug is both

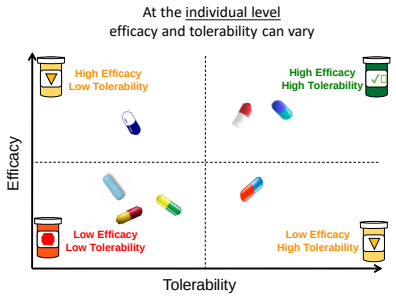
-Thomas Hager, *Ten Drugs*, 2019

The Rational

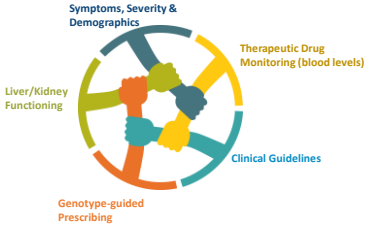
At the population level
medications are efficacious and tolerable



The Rational

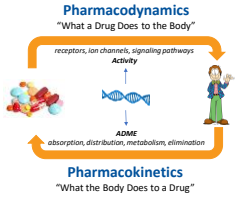


Personalized Prescribing Strategies



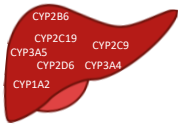
Genotype-guided prescribing

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



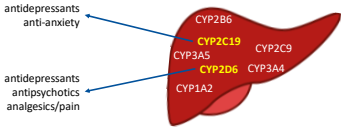
Drug Metabolizing Enzymes

Cytochrome P450 family of enzymes are responsible for the metabolism of the majority of drugs

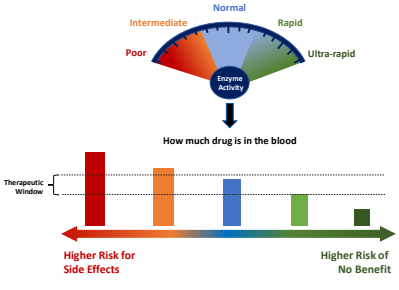


Drug Metabolizing Enzymes

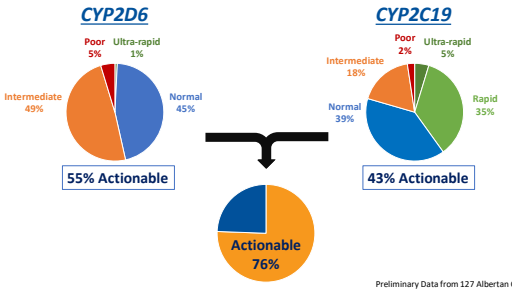
Cytochrome P450 system is responsible for the metabolism of the majority of drugs



Metabolism Groups

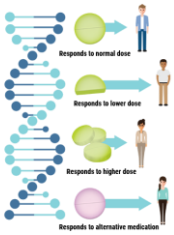


How many children are at risk?



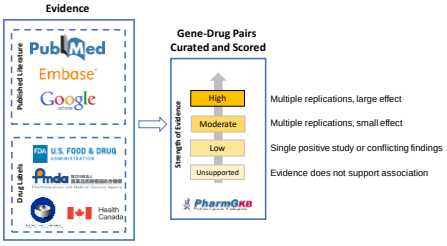
Preliminary Data from 127 Albertan Children, 2021

Who Can Benefit?

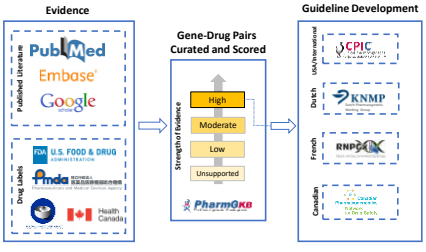


The Evidence

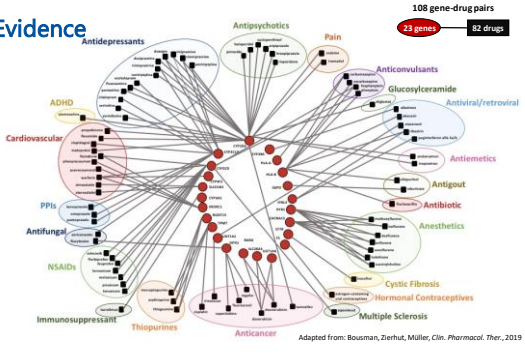
The Evidence



The Evidence

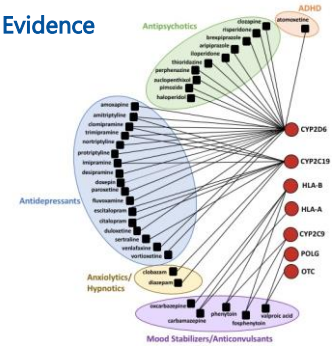


The Evidence



Adapted from: Bousman, Zierhut, Müller, *Clin. Pharmacol. Ther.*, 2019

The Evidence



44 gene-drug pairs

7 genes — 34 drugs

Bousman et al, *Pharmacopsychiatry.*, 2020

Consensus Recommendations

ISPG
INTERNATIONAL SOCIETY OF PSYCHIATRIC GENETICS

The current evidence supports genotype-guided prescribing for specific:

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

Bousman et al, Pharmacopsychiatry (2021)

Clinical Example

Age: 23
Sex: Male

Clinical Presentation: Patient presented with repetitive and obsessive behaviors, anxiety related to visual and auditory stimuli, and difficulties with transitions. He was prescribed quetiapine and fluvoxamine. On these therapies he began to exhibit regressive behaviors (e.g., severe apathy, catatonia, lack of focus on tasks, aggression). His part-time employment was terminated and he was required to return to his family home. A full clinical work-up (e.g., brain scan, CSF analysis, muscle biopsies, full blood panels) found nothing outside the normal range. At this stage, the patient's psychiatrist recommended PGx testing.

Gene	Genotype	Predicted Phenotype
CYP2B6	*1/*6	Intermediate Metabolizer
★ CYP2D6	*4/*4	Poor Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*3	Intermediate Metabolizer

*Based on a case published by: Mitra et al., *Mol Genetics & Genomics Medicine*, 2017 5(2)

Clinical Example

Evidence & Guidelines

CYP2D6 Substrates
(examples)

atomoxetine
aripiprazole
paroxetine
fluoxetine
fluvoxamine
quetiapine (norquetiapine)
venlafaxine

Dosing Guidelines
(fluvoxamine)

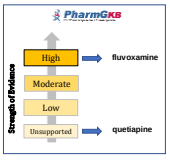
CPIC

"Consider 25-50% dose reduction or an alternative drug not predominantly metabolized by CYP2D6."

Drug Labels mention CYP2D6
(fluvoxamine)

U.S. FOOD & DRUG ADMINISTRATION

swissmedic



Clinical Example

Case Conclusion:

- Quetiapine and fluvoxamine were discontinued
- Olanzapine and desvenlafaxine were commenced (neither is primarily metabolized by CYP2D6)
- Progressive improvements in all behaviors and sleep; returned to supported living home and commenced working again

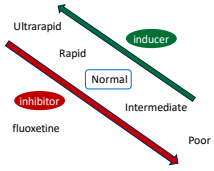
Take Home Message:

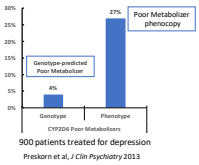
- PGx testing could significantly reduce these types of experiences & avoid unnecessary medical procedures

Things to Consider

Non-genetic factors can impact interpretation of PGx test results

Phenoconversion: A phenomenon that converts:
- Normal/intermediate metabolizers → poor or rapid metabolizers
- Rapid/ultrarapid metabolizers → normal, intermediate, or poor





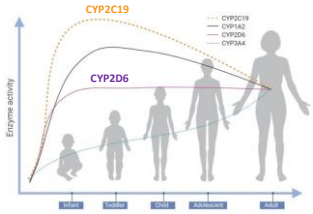
900 patients treated for depression
Preskorn et al, *J Clin Psychiatry* 2013

Things to Consider

Developmental factors can affect how children process and react to medications

CYP2C19: Returns to adult levels in adolescence

CYP2D6: Reaches adult levels soon after birth



Ramsey et al, *JAACAP*, 2020

Take Home Points

1. Genotype-guided prescribing is an evidence-based strategy for several commonly used psychotropics
2. Genotype-guided prescribing should adhere to available guidelines and consider non-genetic factors
3. Genotype-guided prescribing is a companion tool that can enhance not replace other prescribing strategies.

Development of Genotype-Guided Prescribing in Alberta

Core Components

Partnerships

Primary Care Networks

Alberta Health Services
Strategic Clinical Networks™

ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

ALBERTA INNOVATES

Alberta Children's HOSPITAL FOUNDATION

UNIVERSITY OF CALGARY

Core Components

Genetic Test

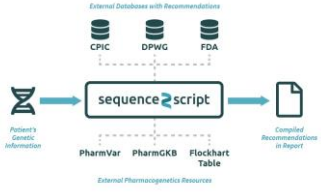
CYP2B6
CYP2C9
CYP2C19
CYP2D6
CYP3A5
NUDT15
SLCO1B1
TPMT
VKORC1

VeriDose Custom Array

Agena MassARRAY

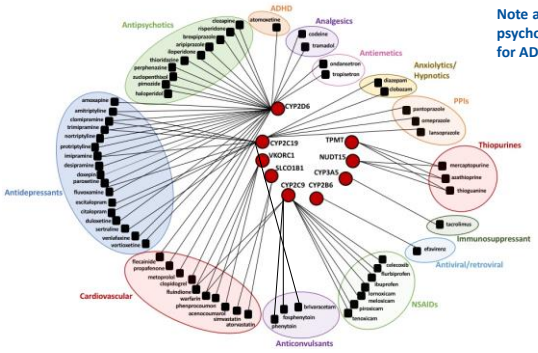
Core Components

Decision-support tool



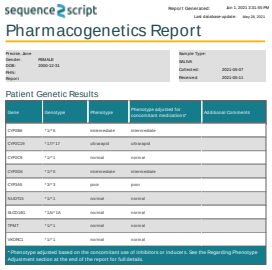
www.sequence2script.com

Bousman et al, 2021 *Front Pharmacology*



Note absence of psychostimulants for ADHD

Pharmacogenetics Report



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Pharmacogenetics Report

Patient Genetic Results

Gene	Genotype	Phenotype	Phenotype adjusted for concomitant medication*	Additional Comments
CYP2B6	*1/*1	intermediate	intermediate	
CYP2C19	*17/*17	ultrarapid	ultrarapid	
CYP2C9	*1/*1	normal	normal	
CYP2D6	*1/*5	intermediate	intermediate	
CYP3A5	*3/*3	poor	poor	
NUDT15	*1/*1	normal	normal	
SLCO1B1	*1A/*1A	normal	normal	
TPMT	*1/*1	normal	normal	
VKORC1	*1/*1	normal	normal	

*Phenotype adjusted based on the concomitant use of inhibitors or inducers. See the Regarding Phenotype Adjustment section at the end of the report for full details.

Medication Name	Drug Class	Genes	Recommendation	Strength of Recommendation	Source	Pathway
citalopram	Antidepressant	CYP2C19	Consider an alternative drug not predominantly metabolized by CYP2C19 (e.g., paroxetine, fluvoxamine)	MODERATE	CPIC	pathway
escitalopram	Antidepressant	CYP2C19	Consider an alternative drug not predominantly metabolized by CYP2C19 (e.g., paroxetine, fluvoxamine)	MODERATE	CPIC	pathway
fluoxetine	Antidepressant	CYP2D6	No action required. Initiate therapy with recommended starting dose (10-20 mg/d). Titrate dose depending on indication and age).		DPWG	pathway
fluvoxamine	Antidepressant	CYP2D6	Initiate therapy with recommended starting dose (Children ≥8 mg/d; Adults≥ 50 mg/d)	MODERATE	CPIC	pathway
paroxetine	Antidepressant	CYP2D6	Initiate therapy with recommended starting dose (20 mg/d)	MODERATE	CPIC	pathway
sertraline	Antidepressant	CYP2C19	Initiate therapy with recommended starting dose. If patient does not respond to recommended maximum dose, consider another drug not predominantly metabolized by CYP2C19 (e.g., paroxetine, fluvoxamine).	OPTIONAL	CPIC	pathway
venlafaxine	Antidepressant	CYP2D6	Select alternative drug not predominantly metabolized by CYP2D6 (e.g., escitalopram) or reduce the dose and monitor patient's plasma metabolite level	OPTIONAL	DPWG	pathway

The strength of a recommendation is based exclusively on pharmacogenetic information published in guidelines. They do not reflect the strength of a recommendation based on phenotypes that have been adjusted due to the presence of concomitant inhibitors or inducers.

Patient Wallet Card

Pharmacogenetics Information

sequence2script

What is this card?

For use by healthcare professionals only

sequence2script

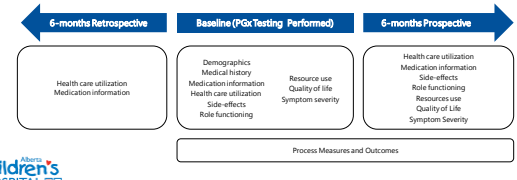
Personal Pharmacogenetics Information Card

Genotype-Guided Prescribing Research in Alberta

PGx-SParK: Pharmacogenetic-Supported Prescribing for Kids

Primary Objective

Implement Canada's first PGx testing service to improve drug treatment outcomes in children receiving mental health care



PGx-SParK: Pharmacogenetic-Supported Prescribing for Kids

INCLUSION

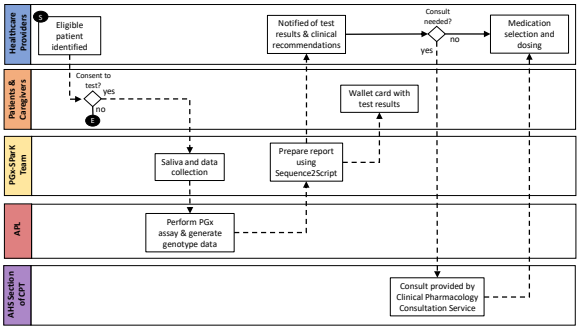
- Age 6 – 17
- Start, switch, dose change, or augmentation of psychiatric medication is indicated
- Treating doctor requests pharmacogenetic testing

PGx-SParK: Pharmacogenetic-Supported Prescribing for Kids

EXCLUSION

- Unable or unwilling to provide a saliva sample
- History of liver or bone marrow transplant

Genotype-Guided Prescribing Workflow



Pharmacogenetics of Antidepressant-Induced Disinhibition

PGx-AID

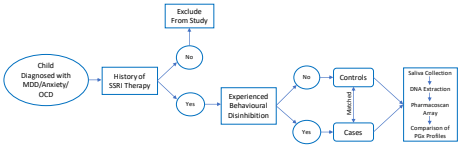
- 10% – 20% of children experience behavioural disinhibition or activation after taking an selective-serotonin reuptake inhibitor (SSRI)
  - aggression, agitation, impulsivity, hyperactivity.
- No clinical markers/tools to identify those at risk.

Bridge *et al.*, JAMA, 2007.
Elbe *et al.*, Clinical Handbook of Psychotropic Drugs for Children and Adolescents, 2015.
Luft *et al.*, Curr Probl Pediatr Adolesc Health Care, 2019.

PGx-AID: Study Design

PGx-AID

To identify and validate a panel of genetic variants that could be used to pre-emptively detect children at-risk for developing SSRI-induced behavioural disinhibition.



Philanthropic Donation: 90,000$

Pharmacogenetics of Antidepressant-Induced Disinhibition

PGx-AID

Inclusion:
- Aged 6 – 17 years
- Diagnosis of MDD, anxiety disorder, or OCD
- Current or past history of SSRI therapy

Exclusion:
- Unable or unwilling to provide a saliva sample
- History of liver or bone marrow transplant
- Attention deficit hyperactivity disorder
- Oppositional defiant disorder
- Conduct disorder
- Bipolar disorder
- Psychotic disorder
- Pervasive developmental disorder

Two Easy Ways to Refer

Patient/family gives consent to email their information (name, email, phone) to us

psychpgxlab@ucalgary.ca

You give our contact information to the patient/family.

psychpgxlab@ucalgary.ca

Referring physicians receive a brief 2-minute online survey

THANK YOU

Contact
chad.bousman@ucalgary.ca

Website:
https://www.psychpgxlab.com/projects/pgx-spark

PROJECT TEAM

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