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Practice Point

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Gene-based drug therapy for children and youth treated with psychoactive medications

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ABSTRACT

Psychoactive medications are increasingly used to treat children and youth with mental health conditions, but individual variations in response highlight the need for precision medicine. Pharmacogenetic (PGx) testing is a key component of precision medicine. The number of commercial pharmacogenetic testing companies promoting PGx, with the promise of achieving individualized and effective treatment of mental health conditions, has grown exponentially in recent years. Scientific evidence supporting the use of PGx to manage mental health conditions is limited, especially for paediatric populations. This practice point outlines steps guiding the use and interpretation of PGx testing for psychoactive medications in clinical settings, along with key supportive resources. Practice guidelines have been developed for variants in pharmacogenes encoding cytochrome P450 drug-metabolizing enzymes (e.g., *CYP2C19*, *CYP2D6*, *CYP2C9*) as one determinant of drug concentrations in blood, which can support both drug choice and dosing strategy for certain anti-psychotics, anti-depressants, and anti-epileptics. Adverse drug reactions to some anti-epileptic drugs (e.g., carbamazepine and phenytoin) have been associated with certain human leukocyte antigen types and variants in DNA polymerase gamma (*POLG*; valproic acid). Evidence remains limited for genetic variants of drug target proteins, making it challenging to identify patients with altered treatment responses at a therapeutic blood concentration.

Keywords: Child and youth mental health; Child psychiatry; Pharmacogenetic testing; Precision medicine.

BACKGROUND

Mental health conditions affect at least 1 million children and youth in Canada, and psychoactive medications are increasingly used for their management (1). At present, an estimated 9% of young people (aged 3 to 19 years) are receiving an antidepressive, anti-anxiety, or antipsychotic medication (2), while an additional 3.6% receive psychostimulants for attention-deficit hyperactivity disorder (ADHD) (3). These medications can improve symptom management and quality of life for both patients and families (4–6). However, medication inefficacy and adverse drug reactions (ADRs) can also occur that negatively affect quality of life and delay attainment of illness control (4–9).

Precision medicine aims to maximize treatment efficacy and prevent ADRs by identifying specific patient characteristics that influence such outcomes, which in turn may offer diagnostic and treatment approaches that decrease cycles of 'trial and error.' A prime example of precision medicine is pharmacogenetic (PGx) testing, where known relationships between gene variants and drug-related outcomes (i.e., drug–gene associations) are used, along with other patient factors, to guide pharmaceutical treatment.

PGx testing in the paediatric population has been discussed in the CPS position statement "Gene-based drug therapy in children" (10). This document focuses on PGx testing for children with mental health conditions. It acquaints clinicians with the indications and principles underlying PGx testing and provides easy-to-use charts to guide and interpret PGx testing for psychoactive medications. Importantly, this document does not recommend or endorse PGx testing for all children with mental health illnesses.

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TERMINOLOGY

Pharmacogenomics and pharmacogenetics

PGx investigates genetic variations that help explain differences among individuals related to drug disposition, treatment response, and the occurrence of ADRs via drug–gene interactions. More specifically, PGx targets genes influencing pharmacokinetics or pharmacodynamics. While the term 'pharmacogenomics' implies genome-wide investigation of genetic effects on drug disposition and effects rather than specific focus on one gene or the small group of genes involved in pharmacogenetics, these terms have come to be used almost interchangeably.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic (PK) genes encode proteins that affect the processes of what the body does to a drug, such as absorption, distribution, metabolism, and elimination. In the context of PGx, these processes mainly involve: (a) drug metabolism genes that influence drug-metabolizing enzymes such as cytochrome P450 (e.g., *CYP2C19*, *CYP2D6* and *CYP2C9*) and (b) transporter genes (e.g., *SLCO1B1*) that facilitate drug transport over a cell membrane, which influences drug uptake in the liver, for example. In contrast, pharmacodynamics (PD) refers to what the drug does to the body, such as direct biologic effects on a cellular level (e.g., receptor activation), clinical effects on illness (e.g., mood, behaviour), or risk for developing specific ADRs, which are different from PK-based effects. For example, PD genes may code for drug target receptors (e.g., serotonin receptors *HTR1A* or *HTR2A*) or human leukocyte antigens (HLA) (e.g., *HLA-A*31:01* or *HLA-B*15:02*). The anticonvulsant carbamazepine has been linked to severe cutaneous adverse reactions such as Stevens-Johnson syndrome (toxic epidermal necrolysis) via HLA variants, for example.

CLINICAL PRACTICE GUIDELINES IN PGx

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Canadian Pharmacogenomics Network for Drug Safety (CPNDS) in North America, and the Dutch Pharmacogenetic Working Group (DPWG) in Europe are continually translating PGx evidence into guidance for clinical practice. These guidelines identify high-quality evidence supporting indications for PGx tests, their relation to a specific outcome (i.e., drug–gene associations), and how treatments should be adjusted to improve medication efficacy and safety. While the level of evidence is a leading standard of practice, the effects of a particular PGx variant on clinical outcomes often vary in size. For example, to avoid adverse events, smaller effect sizes are sometimes integrated into clinical guidance while drug–gene associations relating to efficacy require stronger proof of impact. An example of the CPIC recommendations for *CYP2C19* and citalopram/escitalopram dosing is shown in Table 1 (11).

Drug manufacturers are increasingly providing PGx data in product monographs, which are approved by regulatory agencies such as Health Canada or the Food and Drug Administration (FDA) in the United States. Guidance provided as part of drug labelling can vary considerably, from general information regarding a drug–gene association (e.g., "poor metabolizers for *CYP2C19* may lead to increased rates of adverse drug reactions") to specific treatment recommendations. Occasionally, regulatory agencies include a requirement for PGx testing before prescribing a medication. Importantly, information on a drug label may not fully reflect available data, but rather, or primarily, that generated by the pharmaceutical company.

CURRENT LEVEL OF EVIDENCE

Paediatricians can request PGx testing for children and youth who might benefit from a psychoactive drug for a mental health condition, but the value of testing depends on the strength of evidence for the drug–gene association. While data based on PGx associations relevant to mental health are growing rapidly, the number of variants for which the level of evidence is sufficient to include them in clinical PGx guidelines is relatively small. Established drug–gene associations pertinent to psychoactive medications are shown in Table 2, which lists medication names, the relevant genes,

Table 1. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for citalopram/escitalopram

CYP2C19		**Impact**	**Therapeutic recommendation**
Genotype	**Phenotype**		
*17/*17	Ultrarapid metabolizer	Increases metabolism when compared with normal metabolizers. Lower plasma concentrations increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by *CYP2C19*.
*1/*17	Rapid metabolizer		
*1/*1	Normal metabolizer	Normal metabolism.	Initiate therapy with recommended starting dose.
*1/*2, *1/*3, *17/*2, *17/*3	Intermediate metabolizer	Reduces metabolism when compared with normal metabolizers.	Initiate therapy with recommended starting dose.
*2/*2, *2/*3, *3/*3	Poor metabolizer	Significantly reduces metabolism when compared with normal metabolizers. Higher plasma concentrations may increase risk for side effects.	Consider a 50% reduction of recommended starting dose and titrate to response OR select an alternative drug not predominantly metabolized by *CYP2C19*.

Data drawn from reference (11). Note: The genotype column shows the genetic states of both copies of the gene, which is based on the star-allele annotation where *1 represents wild-type and each variant affecting enzyme production or function is assigned a standardized numeric code.

Table 2. Drug–gene interactions and dosing recommendations in clinical practice guidelines and drug labelling

Drug	Gene(s)	Guideline source
Anti-psychotics		
Aripiprazole	*CYP2D6*	DPWG
Brexpiprazole	*CYP2D6*	DPWG
Haloperidol	*CYP2D6*	DPWG
Pimozide	*CYP2D6*	DPWG
Quetiapine	*CYP3A4*	DPWG
Risperidone	*CYP2D6*	DPWG
Thioridazine	*CYP2D6*	FDA
Zuclopenthixol	*CYP2D6*	DPWG
Tricyclic antidepressants (TCA)		
Amitriptyline	*CYP2D6, CYP2C19*	CPIC, DPWG
Clomipramine	*CYP2D6, CYP2C19*	CPIC, DPWG
Desipramine	*CYP2D6*	CPIC
Doxepin	*CYP2D6, CYP2C19*	CPIC, DPWG
Imipramine	*CYP2D6, CYP2C19*	CPIC, DPWG
Nortriptyline	*CYP2D6*	CPIC, DPWG
Trimipramine	*CYP2D6, CYP2C19*	CPIC
Selective serotonin reuptake inhibitors (SSRIs)/ serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Atomoxetine (SNRI)	*CYP2D6*	CPIC, DPWG
Citalopram	*CYP2C19*	CPIC, DPWG
Escitalopram	*CYP2C19*	CPIC, DPWG
Fluvoxamine	*CYP2D6*	CPIC
Paroxetine	*CYP2D6*	CPIC, DPWG
Sertraline	*CYP2C19, CYP2B6*	CPIC, DPWG
Venlafaxine	*CYP2D6*	CPIC, DPWG
Vortioxetine	*CYP2D6*	CPIC, FDA, Health Canada
Anti-seizure medications		
Carbamazepine	*HLA-A*31:01, HLA-B*15:02*	CPIC, CPNDS, FDA
Clobazam	*CYP2C19*	FDA
Lamotrigine	*HLA-B*15:02*	DPWG
Oxcarbazepine	*HLA-B*15:02*	CPIC, CPNDS, FDA
Fosphenytoin	*CYP2C9, HLA-B*15:02*	CPIC
Valproic acid/divalproex sodium	*POLG*	FDA, Health Canada
Other		
Tetrabenazine	*CYP2D6*	FDA, Health Canada

CPIC Clinical Pharmacogenetics Implementation Consortium; CPNDS Canadian Pharmacogenomics Network for Drug Safety; DPWG Dutch Pharmacogenetic Working Group; FDA U.S. Food and Drug Administration. Notes: Drug labelling for amoxapine, brivaracetam, clozapine, dronabinol, perphenazine, and protriptyline includes pharmacogenetic data, but because no dosing recommendations are given, they have been excluded from this table. Medications not listed in this table had no clinical guidelines available at time of writing. Up-to-date clinical guidance can be found in the Pharmacogenomic Knowledge Base (PharmGKB's), Clinical Guideline Annotations (https://www.pharmgkb.org/guidelineAnnotations)

and sources for clinical guidance and/or drug labels. If a medication is not listed, it means no clinical guidance yet exists. Note that except for HLA and DNA polymerase subunit gamma (*POLG*) variants, only PK genes are practice-ready at the present time. Remember also that the paediatric data underlying PGx guidelines are generally small. However, because the expression of most drug-metabolizing genes reaches adult values before age 1, the use of these guidelines in paediatric populations is allowed. Note also that inclusion in a clinical practice guideline does not mean that testing is recommended for all patients; rather, that there is sufficient evidence to include PGx test results into clinical decision-making. PGx testing is strongly recommended or required before starting a child or youth on the anti-seizure medications carbamazepine or valproic acid (<2 years of age), or on tetrabenazine, which is used for movement disorders.

For some psychoactive medications, drug–gene associations are too weak to guide clinical practice and no treatment adjustments based on PGx variant status are proposed or required. Table 3 lists medication names, the genes evaluated in clinical practice guidelines, and the source. Sometimes drug–gene interactions are omitted from guidelines because even if the PGx variant has been associated with drug concentration differences, active metabolites may also be involved in the therapeutic effects. Finally, some

Table 3. Drug–gene interactions without clinical implications

Drug	Gene(s)
Anti-psychotics	
Clozapine	*CYP2D6, CYP1A2*
Flupentixol	*CYP2D6*
Fluphenazine	*CYP2D6*
Olanzapine	*CYP2D6, CYP1A2*
Quetiapine	*CYP2D6*
Selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitor (SNRIs)	
Citalopram	*CYP2D6, SLC6A4*
Escitalopram	*CYP2D6, SLC6A4*
(Des)venlafaxine	*HTR2A, SLC6A4*
Duloxetine	*CYP2D6, HTR2A, SLC6A4*
Fluoxetine	*CYP2D6, HTR2A, SLC6A4*
Fluvoxamine	*CYP2C19, HTR2A, SLC6A4*
(Levo)milnacipran	*HTR2A, SLC6A4*
Paroxetine	*HTR2A, SLC6A4*
Sertraline	*CYP2D6, HTR2A, SLC6A4*
Vilazodone	*HTR2A, SLC6A4*
Vortioxetine	*HTR2A, SLC6A4*
Other	
Alpha-agonist—Clonidine	*CYP2D6*
Central nervous system stimulants—Methylphenidate	*CYP2D6, COMT*
Tetracyclic antidepressant—Mirtazapine	*CYP2D6, CYP2C19*
Monoamine oxidase (MAO) inhibitor—Moclobemide	*CYP2C19*

Notes: Based on evidence, drug–gene combinations listed here have been included in clinical guidelines, but no treatment recommendations can be made. Therefore, PGx testing is not recommended. Up-to-date clinical guidance can be found in the Pharmacogenomic Knowledge Base (PharmGKB's) Clinical Guideline Annotations (https://www.pharmgkb.org/guidelineAnnotations)

medications may have drug–gene interactions that warrant both clinical use (e.g., sertraline and *CYP2C19*) and avoidance (e.g., sertraline and *CYP2D6*, *HTR2A*, and *SLC6A4*).

Table 4 lists drug–gene associations with a low level of evidence. Many of these involve PD genes that were studied in small (selected) populations or in an uncontrolled manner. While lack of evidence does not imply absence of effect, treatment decisions should not be based on such limited data.

PRACTICAL CONSIDERATIONS FOR PGx TESTING

Many commercial companies offer PGx testing, with prices ranging from $200 to $400 CDN. No provincial/territorial health care plan reimburses test costs, although some coverage may be provided by private insurers and individual tests are sometimes covered publicly (e.g., HLA typing for carbamazepine hypersensitivity, and *POLG* for valproic acid in children younger than 2 years old). Having no universal funding for clinically relevant PGx testing will further disadvantage underserved populations in Canada, which highlights the need for strong advocacy.

Testing is mostly conducted using buccal swabs, which minimizes the patient burden and allows for home sampling. However, testing can still be challenging for a child or youth with oral aversion. Many companies work with laboratories based in the US, which has raised privacy concerns. The turnaround time for results, upon receipt of the sample at the laboratory, can be 1 to 3 weeks.

Companies have different test panels, and many target mental health conditions by including a large number of genes, sometimes more than a hundred, most of which are not included in clinical practice guidelines. Nevertheless, test results are reported along with the company's interpretation of relevance to treatment, risk for adverse reactions, and, sometimes, specific treatment recommendations. For some medications, more than one gene may be listed, sometimes yielding conflicting recommendations.

A physician should never rely on test results that are not reflected in current guidelines (as per Tables 3 and 4). However, if such results are acted upon clinically, discussing their off-guideline status with patients and families becomes a critical step in quality care. Avoiding a first-line treatment based on PGx testing might lead to using a medication that has less safety and efficacy data specific to children and youth.

TIMING AND ROLE OF PGx TESTING

PGx testing can be pre-emptive, conducted before starting a medication, or *post hoc*, to help interpret drug response. Testing may lead to dosing recommendations and, occasionally, to avoiding a medication due to an unsafe or unpredictable PK profile. PGx information alone will not identify a preferred medication but may exclude treatment options. The choice of medication should always be based on a full clinical picture, including PGx data.

When a child or youth is treated with a medication and responds well, there is limited value to PGx testing, whatever

Table 4. Drug–gene associations implicated in some research but insufficient evidence for use in clinical practice

Gene	Medications	Reported associations
ABCB1	SSRI, anti-psychotics, lithium, carbamazepine	PK, PD (efficacy, toxicity)
ADGRL3 (LPHN3)	Methylphenidate	PD (efficacy)
ADRA2A	SSRI, methylphenidate	PD (efficacy)
AKT1	Risperidone	PD (efficacy)
BDNF	SSRI, anti-psychotics	PD (efficacy, toxicity)
CACNG2	Lithium	PD (efficacy)
CES1	Methylphenidate	PK
CNR1	Anti-psychotics, cannabis	PD (toxicity)
CNR2	Cannabis	PD (toxicity)
COMT	SSRI, anti-psychotics, methylphenidate	PD (efficacy, toxicity)
CYP1A1	Olanzapine, anti-epileptics, cannabis	PK, PD (efficacy, toxicity)
CYP3A5	Midazolam, carbamazepine, olanzapine, quetiapine	PK, PD (toxicity)
DRD3	SSRI, anti-psychotics, methylphenidate	PK, PD (efficacy, toxicity)
EPHX1	Carbamazepine, phenytoin	PK, PD (toxicity)
FKBP5	Antidepressants, anti-psychotics	PD (efficacy, toxicity)
GRIK2	Citalopram	PD (toxicity)
GRIK4	Antidepressants	PD (efficacy)
HTR1A	SSRI, anti-psychotics	PD (efficacy)
HTR2C	SSRI, anti-psychotics	PD (efficacy, toxicity)
MC4R	Anti-psychotics	PD (efficacy, toxicity)
MTHFR	Anti-psychotics, anti-epileptics	PD (toxicity)
NEFM	Anti-psychotics	PD (efficacy)
RGS4	Anti-psychotics	PD (efficacy)
SCN1A	Anti-epileptics	PD (efficacy)
UGT1A4	Risperidone, lamotrigine, valproic acid	PK, PD (efficacy)
UGT2B15	Benzodiazepine	PK

PK Pharmacokinetics; PD Pharmacodynamics; SSRI Selective serotonin reuptake inhibitors. Note: Up-to-date clinical guidance can be found in the Pharmacogenomic Knowledge Base (PharmGKB's) Clinical Guideline Annotations (https://www.pharmgkb.org/guidelineAnnotations)

the dose. When a treatment has failed, *post hoc* testing might provide limited insight or help explain why the treatment did not work. In patients for whom multiple medications have failed, history is rarely explainable based on PGx variants alone because different drug-metabolizing pathways are often involved. PD factors may have a role, but they are not yet well understood.

ADDRESSING PGx TEST RESULTS IN CONSULTATION

Increasingly, families are bringing the results of PGx testing to paediatric appointments. Sometimes testing was undertaken at the recommendation of a health care provider but often too, families have decided on and arranged testing for themselves.

To help patients and families understand the value of test results, paediatric care providers must be able to answer these four questions:

1) *Was testing conducted for a drug–gene association covered by a clinical PGx guideline?*

Tables 2–4 can be used to answer this question. When test results include several different genes and recommendations, counselling families concerning the claims that are supported and unsupported by evidence becomes key to quality care. As PGx testing evolves, current clinical guidance can be found in the Pharmacogenomic Knowledge Base (PharmGKB's) Clinical Guideline Annotations (https://www.pharmgkb.org/guidelineAnnotations). Also, expert opinion can always be sought from clinical pharmacologists or clinical pharmacists via electronic or in-person consultation.

2) *Is this child or youth's current treatment being affected by PGx test results?*

Ongoing treatment with a psychoactive medication that is well-tolerated and efficacious usually does not require further intervention based on PGx test results. However, a young person's metabolizer status can help explain a treatment that has failed, or an ADR. In all such cases, the full clinical picture should be considered when determining whether a dose adjustment or alternative treatment suggested by PGx results is indicated.

3) *Can PGx testing guide future care for this child or youth?*

While PGx test results alone cannot identify what treatment is best, they can inform decisions about medications to avoid or optimize dosing. Clinical factors and patient preference are the first and best guides when choosing a medication to manage

child or youth mental health conditions. Evidence-based PGx information or recommendations in clinical guidelines can then be used to help adjust dosing or when seeking an alternative treatment.

It is relatively common for a child or youth to experience adverse effects in response to one or more psychoactive agents that cannot be explained by increased drug exposure due to genetic variations affecting drug metabolism. If patients receive PGx recommendations that suggest prescribing a higher dose compared with standard treatment, careful clinical judgement is needed. Because adverse events are more likely to result from variations in PD, patients would benefit from starting at a lower dose and gradual titration.

4) *Are non-psychoactive medications this child or youth is taking being affected by the PGx results?*

PGx test results can sometimes provide guidance for medications unrelated to mental health. Common examples are proton pump inhibitors and the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs). More information can be found in the Pharmacogenomic Knowledge Base (PharmGKB's) Clinical Guideline Annotations (https://www.pharmgkb.org/guidelineAnnotations).

CONCLUSION

PGx testing is a promising method of providing safer, more efficacious, and individualized medication choices for children and youth with mental health conditions. While testing is currently recommended for carbamazepine, valproic acid (in children younger than 2 years old), and tetrabenazine, not all provincial/territorial health plans cover costs. Physicians are increasingly presented with PGx test results and must bear in mind that current best evidence is sufficient for only a select few drug–gene associations in paediatrics. Knowing when to initiate testing, interpret or reject test results, and consult with experts in the field for guidance are becoming key components of quality mental health care for children and youth.

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