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Gene-based drug therapy in children

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Position Statement

Gene-based drug therapy in children

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ABSTRACT

The past two decades have seen enormous advancements in medical knowledge around the role of genetic factors of variability, both in human disease and drug response. This knowledge is increasingly being translated into guidelines that inform drug dosing, monitoring for efficacy and safety, and determining the suitability of specific agents to treat patients. Health Canada and the U.S. Food and Drug Administration have recommended using genetic information to guide dosing for more than 20 drugs. There are no current, comprehensive paediatric guidelines to assist health care professionals in the use of genetics to inform medication dosing, safety, and efficacy in children, and such guidance is urgently needed. This statement helps to guide clinician understanding of the role of pharmacogenetics and how to use this information when prescribing medications in paediatrics.

Keywords: Adolescents; Adverse drug reactions; Child; Pharmacogenetics; Pharmacogenomics.

Individual response to medications can vary markedly from person to person, both as to efficacy and toxicity, and while the reasons for variable response are many, the role of genetic factors in influencing outcomes for many drugs is increasingly well recognized. Adverse drug reactions (ADRs) are a major unsolved problem of modern medicine because of their debilitating, and sometimes lethal, consequences for patients. ADRs are the fourth to sixth leading cause of death in Canada and the USA, and a significant contributor to morbidity and hospitalization rates (1–4).

Pharmacogenomics establishes the role of genetic variation(s) in an individual's response to medication, both in terms of efficacy and safety. Pharmacogenetics (relating to a single gene) and pharmacogenomics (relating to multiple genes) are key to understanding how to use medications more safely and effectively, ensuring better compliance, and avoiding ADRs. Indeed, the field of pharmacogenomics has been identified as one of great promise for personalized or precision medicine (5). Rapid technological advances in genomics and a sharp reduction in the costs of testing have produced a new generation of studies focused on drug variability and helped to introduce personalized or precision medicine into clinical practice. However, findings from such research can create problems for clinicians who have not yet been

trained to evaluate results, a knowledge gap further compounded by the relative lack of training in pharmacogenomics in undergraduate medical education and paediatric residency programs in Canada.

This position statement reviews the current evidence for the role of genomics in paediatric medications and outlines the steps that need to be taken to improve drug efficacy and safety for children and adolescents.

PHARMACOGENETIC STUDIES IN PAEDIATRICS

The study of pharmacogenomics in children often lags behind comparable research in adults, where large studies have incorporated pharmacogenetic and pharmacogenomic dimensions into clinical practice, most notably for warfarin, clopidogrel, abacavir, and simvastatin. However, the studies which have involved children have shown that adult models are often inaccurate when applied to children, and many of the medications studied have limited paediatric indications as a result (6). Awareness is growing that children are not simply small adults, and human development produces profound changes in drug disposition throughout the life course due to changing

genetic expression (7). For example, metabolic enzyme activity and pathways change throughout childhood, which complicates the role of pharmacogenomics in paediatrics, especially in younger children, compared with adults. Applying pharmacogenomics in paediatrics means considering changes in the expression of proteins during development, including phase I drug biotransformation enzymes (e.g., the cytochrome P450 family of enzymes), phase II conjugating enzymes (e.g., glucuronosyltransferases), and drug transporters and receptors. This complex of influential factors highlights that paediatric-specific studies of pharmacogenomics are needed for medications commonly prescribed to children.

Some early pharmacogenetics research studied the variability of response to purine analogues (mercaptopurine and azathioprine) in children. Thiopurine S-methyltransferase (TPMT) is the primary pathway for inactivating these drugs. Up to 11% of the children studied, who were of European descent, were found to be heterozygote carriers of one low-functioning allele, while 1 in 500 was homozygous for both alleles being low-functioning variants. Reduced TPMT function was found to cause slower inactivation of the medication, leading to greater toxicity and, more specifically, to prolonged myelosuppression and increased risk for infection (8). Further studies have demonstrated that dose reduction of medication to 10% for homozygous risk variants, and 50% dosing for heterozygotes, resulted in improved efficacy, more predictable drug concentrations, and reduced toxicity (9). Despite common use of mercaptopurine in paediatric oncology, nephrology, and gastroenterology, and the clear benefits that precision medicine can provide, genotyping is not offered to most subjects before initiating therapy (10).

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) (11) was initiated in 2004 with the goal of identifying genomic factors responsible for severe ADRs in paediatrics. Using case-control studies, they have identified the genetic variants associated with codeine-induced infant and toddler death (12–15), cisplatin-induced ototoxicity (16,17), and anthracycline-induced cardiotoxicity (18–21). To address these serious ADRs, pharmacogenomic clinical practice guidelines and tests have been developed that assess individual patient risk for specific ADRs before starting treatment, such that a more personalized therapy plan can be developed based on a drug's benefit/risk profile for each patient (22–24).

The Food and Drug Administration in the USA had included pharmacogenomic information in the labels of more than 330 drugs at time of writing. This number will continue to rise steadily as discoveries are made linking risk for ADRs with specific genetic markers. A current, more international list of drug labels annotated to include pharmacogenomic information can be found on the [PharmGKB website](#), which is supported by the U.S. National Institutes of Health and maintained by Stanford University (25).

Drugs are commonly used across all paediatric specialties, making it easy to justify why pharmacogenomics should become a prioritized research area. In some paediatric care areas, both research and timely implementation are critically important, including the following:

- 1) **Transplantation:** Studies have shown that individuals who have CYP3A5 variants that are extensive or intermediate metabolizers have lower trough concentrations of tacrolimus compared with those who have CYP3A5-poor metabolizing variants. This difference can delay reaching target blood levels of tacrolimus and raise concerns for graft rejection in solid organ transplants or for increased graft versus host disease in stem cell transplantation settings (26,27).
- 2) **Paediatric pain:** Codeine is a common opioid used to treat pain in children. Its analgesic properties hinge on conversion to morphine and morphine-6-glucuronide, and this process depends in turn on metabolism pathways that include CYP2D6 and UGT1A1 (28). Ultra-rapid metabolizers of codeine can rapidly convert codeine to morphine, leading to severe or even fatal results following administration of standard codeine doses to children (e.g., post-tonsillectomy) (29).
- 3) **Mental health:** Fluoxetine is an anti-depressant from the selective serotonin reuptake inhibitor class that is often used to treat children and adolescents. However, a significant proportion of paediatric patients, estimated at up to 40%, do not respond to this therapy. Polymorphisms in a few specific genes, including CYP2C9 and CYP2D6, have been shown to influence serum drug levels in adults. However, changes in drug concentrations alone may not lead to differences in efficacy or toxicity, and these results have not been consistently replicated in children's studies, and further work in this area is needed (30).
- 4) **Epilepsy:** The use of anticonvulsants is challenged by rare but potentially fatal hypersensitivity reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Human leukocyte antigen (HLA) genetic variation has been associated with severe cutaneous adverse reactions (SCARs) to anticonvulsants such as carbamazepine. Specific variants, such as HLA-B*15:02 and HLA-A*31:01 have been associated with SJS, TEN, and SCARs, and their differential expression in children from different ethnicities explains higher rates of this particular ADR in children of Chinese ancestry, for example (31).
- 5) **Asthma:** Numerous studies have investigated the role of genetics in the efficacy of response to medications such as beta-agonists, which are commonly used to treat asthma (32). One recent systematic review identified 33 studies looking at the response to long-acting beta agonists, and 8 of these were paediatric studies involving 6051 children. An included meta-analysis found increased risk for asthma exacerbations in children (but not adults) who carried a particular variant in the ADRB2 gene (32).
- 6) **Oncology:** The use of highly toxic medications is commonplace in paediatric oncology, with most children experiencing significant negative effects from chemotherapeutic agents (33). Because many treatment-related toxicities are life-threatening or cause permanent disability, numerous studies have investigated the pharmacogenetics of drug toxicity in children with cancer. Key associations have been found with anthracyclines (heart failure), cisplatin (hearing loss), vincristine (neuropathy), methotrexate (mucositis, cognitive effects), and steroids (avascular necrosis) (34).
- 7) **Hematology:** The use of warfarin to treat children and adolescents with thrombosis, anticoagulation for heart

valves, or congenital heart disease is common. Adult studies have shown that variants in *CYP2C9* and *VKORC1* genes are critical for determining response and can be used in treatment algorithms to predict the doses required to reach therapeutic levels. One paediatric study of warfarin found that 21.1% of variability in dosing is accounted for by these two genes, and that the risk of significant major bleeding while on warfarin was associated with a specific *CYP2C9* variant (35).

- 8) **Infectious disease:** Antibiotics are frequently prescribed to children, and while they are typically well tolerated, some children are at risk for significant toxicities. Ongoing research is investigating the role of genetics in predisposing children to such toxicities, which include hearing loss from aminoglycosides (associated with mitochondrial genes), liver injury from amoxicillin-clavulanate (with HLA variants) or from rifampin and isoniazid (associated with the *NAT2* gene), or SJS/TEN from sulfonamides (with HLA variants) (36).

The indications for pharmacogenomics testing are evolving so rapidly in the literature that it is challenging to capture the latest research in clinical practice guidelines. However, multiple international working groups are publishing up-to-date clinical pharmacogenetic drug dosing guidance, including the Clinical Pharmacogenetics Implementation Consortium, the Dutch Pharmacogenetics Working Group, and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). Clinical guideline annotations from these and other groups are updated online at PharmGKB. A summary of select medications that may be prescribed for children and youth by a general paediatrician is listed in Table 1.

RESEARCH CHALLENGES

Paediatric pharmacogenetic and pharmacogenomic research faces many obstacles, and study results focused on children and youth lag far behind data for adults. Rigorous phenotype

identification is key for both populations, but because definitions of toxicity have not been standardized, studies frequently diverge regarding case–control definitions and results. Also, the number of cases for many ADRs of interest is small. Severe ADRs are rare in paediatrics, and paediatric clinical trials often involve much smaller sample sizes than adult trials, making their results less compatible with genome-wide association studies, where large numbers of well phenotyped subjects are required.

Further, children or youth living with severe ADR effects typically are not enrolled in studies where their DNA information is collected systematically for specific pharmacogenetic or pharmacogenomic research. Many paediatric studies perform multiple tests across their cohort, a practice that can lead to false-positive results based on chance, which is why replication studies and validation cohorts are especially critical in paediatrics. Replicating pharmacogenetic and pharmacogenomic findings in more than one independent cohort of subjects is crucial yet fraught with challenges, including variable populations, inadequately powered follow-up studies, and divergent methodologies. Moreover, conflicting laboratory results have undermined clinical confidence in pharmacogenetic and pharmacogenomic research. Finally, there is the ethical problem of performing genetic research in minors who cannot provide informed consent to treatment. However, many position statements from prominent ethicists and leading organizations have affirmed the importance of *not* excluding children from genomic research. They maintain that studies can be conducted ethically and provided with oversight and ongoing support from international drug regulatory agencies.

CLINICAL CHALLENGES

Clinicians wishing to integrate pharmacogenomic testing into their practice face many challenges. Lack of access to rapid, easy tests means not knowing a child or youth's genetic risk at the point when a medication is being prescribed. This limitation can be especially significant in the acute care setting (e.g., with ordering codeine or prescribing antibiotics). In other treatment

Table 1. Key pharmacogenetic medications for the general paediatrician

Medication	Gene	FDA label	Toxicity or efficacy
Abacavir	HLA-B	Required	Toxicity
Carbamazepine	HLA-B	Required	Toxicity
Valproic acid	POLG	Required	Toxicity
Ivacaftor	CFTR genotype	Required	Efficacy
6MP, 6TG, Azathioprine	TPMT, NUDT15	Recommended	Toxicity
Ondansetron	CYP2D6	Recommended	Efficacy
SSRIs	CYP2D6, CYP2C19	Recommended	Toxicity and efficacy
Amitriptyline	CYP2D6	Recommended	Toxicity and efficacy
Codeine	CYP2D6	Actionable	Efficacy
Phenytoin	CYP2C9, HLA-B	Actionable	Toxicity
Warfarin	CYP2C9	Actionable	Toxicity
Inhalational anesthetics, succinylcholine	RYR1, CACNA1S	Actionable	Toxicity

FDA Food and Drug Administration; 6MP 6-Mercaptopurine; 6TG 6-Thioguanine; SSRIs Selective serotonin reuptake inhibitors.

Note: 'Actionable' refers to pharmacogenetic associations for which the data indicate a potential impact on safety or response but further evidence is required to make a recommendation.

settings, however, there is sufficient time to order a diagnostic test before initiating therapy.

In Canada, most pharmacogenetic and pharmacogenomic tests, even when supported by convincing evidence, are not funded by provincial/territorial health care plans. Individual requests for test approval can be obtained, but this extra step can be a barrier to timely testing. Pharmacogenetic and pharmacogenomic testing should be both accessible and affordable, and preventive testing on a large scale is documented to be cost-effective (37). Many of the ADRs being prevented through testing are costly for individuals and families living with the consequences as well as for society at large. As a final challenge, many health care providers must be trained to make optimal use of gene-based tests and dosing.

RECOMMENDATIONS

Canadian governments should:

- Fund pharmacogenetic and pharmacogenomic tests that have been trialed and recommended by leading international regulators, especially when they are commonly used in paediatrics.
- Provide funding and reimburse for pharmacogenetic and pharmacogenomic tests that help predict drug response in children and adolescents.
- Support pharmacogenetics and pharmacogenomics research in paediatrics, especially for common medications and treatment modalities.

Health Canada should include testing recommendations in drug labelling for pharmacogenetic and pharmacogenomic testing when this is demonstrated to have a significant effect on efficacy and/or safety.

Clinical labs should make accessing tests easy and ordering them simple for prescribing clinicians, while ensuring rapid turnaround times to ensure real-time use of gene-based drug dosing.

Researchers in Canada should replicate adult pharmacogenetic and pharmacogenomic studies using paediatric cohorts to ensure that results hold true in younger populations, and conduct pharmacogenetic and pharmacogenomic testing for disorders unique to (or with special characteristics in) infants, children, and youth.

Continued medical education programs should develop clinical tools and training to optimize effective use of pharmacogenetic and pharmacogenomic testing in various practice settings, and provide regular updates on labelling from curated websites, such as PharmGKB.

Medical schools and residency programs must train future clinicians, and the next generation of investigators, on appropriate and imminent use of pharmacogenetic and pharmacogenomic testing as part of the regular curriculum.

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