




# Pharmacogenomic testing in paediatrics: Clinical implementation strategies

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Pharmacogenomics (PGx) relates to the study of genetic factors determining variability in drug response. Implementing PGx testing in paediatric patients can enhance drug safety, helping to improve drug efficacy or reduce the risk of toxicity. Despite its clinical relevance, the implementation of PGx testing in paediatric practice to date has been variable and limited.

As with most paediatric pharmacological studies, there are well-recognised barriers to obtaining high-quality PGx evidence, particularly when patient numbers may be small, and off-label or unlicensed prescribing remains widespread. Furthermore, trials enrolling small numbers of children can rarely, in isolation, provide sufficient PGx evidence to change clinical practice, so extrapolation from larger PGx studies in adult patients, where scientifically sound, is essential.

This review paper discusses the relevance of PGx to paediatrics and considers implementation strategies from a child health perspective. Examples are provided from Canada, the Netherlands and the UK, with consideration of the different healthcare systems and their distinct approaches to implementation, followed by future recommendations based on these cumulative experiences.

Improving the evidence base demonstrating the clinical utility and cost-effectiveness of paediatric PGx testing will be critical to drive implementation forwards. International, interdisciplinary collaborations will enhance paediatric data collation, interpretation and evidence curation, while also supporting dedicated paediatric PGx educational initiatives. PGx consortia and paediatric clinical research networks will continue to play a central role in the streamlined development of effective PGx implementation strategies to help optimise paediatric pharmacotherapy.

## KEYWORDS

children, personalised medicine, pharmacogenetics, precision medicine

# 1 | PHARMACOGENOMICS: AN INTRODUCTION

Pharmacogenomics (PGx) relates to the study of genetic factors determining variability in drug response, in terms of both efficacy and toxicity.<sup>1</sup> It has long been known that individuals respond differently to medicines and, over the last two decades, numerous peer-reviewed publications have promised imminent benefits of *precision medicine*, with many highlighting pharmacogenomic strategies as a core component of this long awaited revolution in healthcare.<sup>2</sup> There is extensive literature dedicated to the clinical utility of PGx, which is largely focused on adult patients,<sup>3–5</sup> on whom the majority of PGx research is based. The challenges to implementation of pharmacogenomic testing within routine healthcare are well described.<sup>6–9</sup> The importance of PGx has been recognised by the drug regulatory agencies, with the European Medicines Agency (EMA) describing PGx as an “integral part of the development and post-authorization (marketing) phase for a number of medicines, with significant impact on the management of their benefits and risks in clinical use”.<sup>10–12</sup> However, the perceived relevance and familiarity of PGx to healthcare professionals working in paediatrics remain limited in most settings,<sup>13</sup> and the implementation of pharmacogenomic testing in paediatrics is also limited.<sup>14</sup>

This review paper discusses the relevance of PGx to paediatrics and considers the pros and cons of different implementation strategies from a child health perspective. Examples are provided from Canada, the Netherlands, and the UK, with consideration of the distinct healthcare systems, different approaches to implementation and its coordination at a national level, followed by future recommendations based on these experiences to date.

## 1.1 | Pharmacogenomic testing: An overview

The aim of a pharmacogenomic test is to improve either the safety or effectiveness of a pharmacological therapy, or both. This is achieved by using a patient's pharmacogenetic data (i.e., the elements of their genetic information that are of relevance to drug therapy) to inform prescription decision making.<sup>15</sup> To be deemed relevant to clinical practice, the genetic information obtained from a PGx test must be a robust predictor of drug response;<sup>1</sup> however, the degree of the genetically determined variability in drug response can vary considerably (ranging from 20–95% depending on the drug concerned<sup>16</sup>). In complex disease genetics (e.g., hypertension, type 2 diabetes, schizophrenia), there are multiple genes of interest, each producing small individual effects. However, exposure of the body to medication is a new event, in evolutionary terms, and there is evidence that genetic variants affecting medicines have, overall, larger effect sizes aiding their potential clinical utility.<sup>17</sup>

A PGx test result may detect a genetic predisposition to an adverse drug reaction (ADR), or differentiate between drug responders and drug non-responders, or it may indicate that a different dose of the drug—or in some cases a different class of drug altogether—is required (Table 1).<sup>1</sup> Actionable PGx results are those

**TABLE 1** Examples of PGx stratification of patient groups that are clinically relevant to paediatrics<sup>18</sup>

PGx patient group	Clinically relevant examples
Responders	Ivacaftor therapy for cystic fibrosis patients with specified <i>CFTR</i> mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R
Non-responders	CYP2D6 poor metabolisers: Limited conversion of codeine to morphine: Recommend prescription of alternative analgesic instead
Differential responders	CYP2C19 polymorphisms affect voriconazole pharmacokinetics: Genotype-guided dosing can help to optimise paediatric voriconazole therapy <sup>19</sup>  CYP2D6 ultra-rapid metabolisers have increased conversion of codeine to morphine, and this PGx variability is an important factor contributing to the EMA decision to make codeine use contraindicated in children under 12 years old <sup>20</sup>
At risk of severe ADR	<i>TPMT</i> genetic polymorphisms resulting in <i>TPMT</i> deficiency can predispose to potentially fatal myelotoxicity with thiopurine therapy (e.g., 6-MP; discussed further in text below)  <i>HLA-B*5701</i> allele predisposes to abacavir hypersensitivity: As the reaction is severe, the drug is contraindicated.  <i>HLA-B*15:02</i> allele predisposes to carbamazepine induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients from Southeast Asian countries <sup>21</sup>

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; EMA, European Medicines Agency; *TPMT*, thiopurine S-methyltransferase; 6-MP, 6-mercaptopurine.

that would alter the choices made by the prescriber, and that would significantly alter the balance of benefit to harm for the individual patient.<sup>22</sup> In many adult PGx panel-based studies, actionable PGx variants have been identified in more than 90% of patients.<sup>23,24</sup> Evidence-based classifications of actionability of drug/gene pairs are available from PGx practice guidelines consortia, which are discussed further below.

PGx testing can be either reactive or pre-emptive. Reactive testing occurs at (or close to) the point of prescription of a drug paired with a known pharmacogene (i.e., the gene of relevance to the clinical pharmacology of that particular compound). This process requires a prompt turnaround time to ensure the result is available in time to inform the relevant prescription.<sup>19</sup> In contrast, pre-emptive testing involves prospective PGx testing, before prescription of the relevant drug(s) is required. Here, results must be accessible within the electronic health record (EHR), and future prescribers need to be aware of the existence of actionable PGx results, and know what action to take.<sup>19</sup> In addition, when utilising an EHR, clinical decision support (CDS) systems are often also used. At least 20 different pharmacogenomic CDS systems have been, or are being, developed,

with the majority embedded within EHR systems.<sup>20</sup> An ideal CDS will inform the clinician of the clinically relevant PGx finding before they prescribe, including drug–drug interactions, while at the same time being sophisticated enough to work with dose range checking processes (as PG may require dose alteration to achieve clinical efficacy, while avoiding alert fatigue in the users). Some evaluation of CDS for pharmacogenomics has been presented, but more will be required.<sup>20</sup>

The approaches for PGx testing can include targeted genotyping technologies, which may focus on a single pharmacogene (if reactive testing is chosen) or a number of pharmacogenes within a PGx panel,<sup>21</sup> or may employ next generation sequencing techniques (e.g., whole exome or whole genome sequencing), which can be used with virtual (bioinformatics-based) PGx panels,<sup>18,25–29</sup> although the latter is largely restricted to research contexts at present.

## 1.2 | PGx practice guidelines consortia

The gap in the use of research discoveries to guide clinical practice—the so-called “Valley of Death”—is well known. To address this, and aid the dissemination of PGx data and implementation into clinical practice, a number of PGx consortia have evolved. These include CPIC, The Pharmacogenomics Knowledge Base (PharmGKB), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and the Dutch Pharmacogenetics Working Group.<sup>30–33</sup> Consortia members include representatives from many different disciplines, including physicians, pharmacists and clinical scientists, with relevant expertise in clinical pharmacology and therapeutics (CPT), genetics and numerous relevant subspecialty areas. These consortia disseminate evidence-based, peer-reviewed, updated and curated PGx practice guidelines, which consider all aspects of PGx including variation in risk according to ethnicity. Clear, well-referenced knowledge summaries are also published, for example those dedicated to so-called Very Important Pharmacogenes (VIPgenes: defined as genes with well-documented information regarding the relationship with a drug's pharmacokinetics/pharmacodynamics [PKPD]).<sup>33</sup> Notably, these consortia also provide information about when a PGx test should *not* be used to guide prescribing (denoted, for example, by CPIC assigning actionability levels C and D, which signifies that a specified gene/drug pair is *not* actionable).<sup>31</sup> There are methodological differences in the evidence appraisal approaches used by different consortia, which warrant more detailed consideration when they lead to differing recommendations regarding the actionability of PGx variants encountered in clinical practice.<sup>34</sup>

## 2 | THE RATIONALE FOR IMPLEMENTING PGX TESTING IN CHILDREN

While the rationale underlying PGx testing is largely equivalent for adults and children, the relevant principles are summarised here from the paediatric perspective. An actionable PGx result reported in a

child should change the choices made by a paediatrician (or a physician looking after the same patient in future during adulthood) *if* prescribing the relevant drug(s). Therefore, PGx information needs to be available and interpretable according to updated evidence-based paediatric PGx recommendations. While it is true that PGx will not be directly relevant for every child, nor will it be relevant for every prescription. This does not mean, however, that appropriate PGx testing should not be available as part of routine care for those children for whom it is relevant. It also should not matter if the prescribing clinician is the one who ordered the test, or is even located in the same institution, as these data should be shared to all prescribers to avoid unnecessary repetition of tests (which entails potential harms for the child and additional financial costs). Currently, the limited availability of PGx testing and clear paediatric PGx guidelines presents a major obstacle, in addition to the need for enhanced PGx evidence in children.

To overcome this, scaling up of new, validated testing strategies for routine implementation within healthcare systems is required, but can present numerous challenges. Traditionally, paediatric pharmacology research studies and implementation strategies to update drug labelling and evidence-based guidelines have often faced long delays in comparison to the equivalent timelines in adult medicine.<sup>35</sup> Typically, this delay arises due to various factors, including practical, ethical and financial barriers to research in children, many of which are now largely historical, thanks to coordinated global efforts to improve the pace of paediatric medicines research.<sup>36</sup>

The majority of prescriptions for children are prescribed in the community,<sup>37</sup> with medicines most commonly prescribed by a GP or Community Paediatrician. In contrast, the focus of interest for PGx, at least at first, is likely to be in prescriptions issued for medicines with narrow therapeutic ranges, variable efficacy, dose limiting toxicity, relatively frequent PGx-related ADRs, or intensive monitoring requirements. Therefore, the majority of paediatric prescriptions for which PGx is relevant will, at least initially, be in hospitals. In keeping with this, selected PGx testing is already routinely available in certain specialist settings, such as in paediatric haemato-oncology where thiopurine S-methyltransferase (TPMT) testing is routine (or mandatory) for patients due to receive 6-mercaptopurine therapy.<sup>38</sup> Relevant stakeholders from both primary and secondary care settings need to be prospectively involved in implementation planning, as discussed further below.

With the mainstreaming of genomic medicine rapidly changing the healthcare landscape,<sup>39</sup> increasing numbers of children and newborns are undergoing whole genome sequencing (WGS).<sup>40</sup> In particular, the role of diagnostic WGS (or WES [whole exome sequencing]) in paediatric and neonatal intensive care settings is growing,<sup>41,42</sup> and in addition, pre-existing WES/WGS data can be re-analysed to investigate PGx variants.<sup>43</sup> There have also been recent discussions about whether WGS may be introduced as part of routine newborn screening.<sup>44,45</sup> Since PGx testing can either be pre-emptively integrated into WGS for diagnostic reasons—or introduced as a separate “routine” (or reactive) test in its own right (e.g., when WGS is not available/required)—the concepts behind the development of a PGx

“passport”<sup>46</sup> with a lifelong PGx record<sup>47</sup> have become a reality that urgently needs further exploration within paediatric healthcare policy and practice. With appropriate data retention policies, WGS could represent the once in a lifetime test after which it would be possible to routinely access the PGx data at any point in a child's lifetime when they need a relevant drug prescribing. Such an approach would require the development of robust standard operating procedures (SOPs) that incorporate prospectively planned periodic data re-analysis to identify PGx variants which have since become clinically actionable (following new research findings), as this information would need to be updated in individuals' PGx records in a timely fashion.

Beyond the adoption of widespread genomic testing into healthcare services, there are other ways in which PGx testing for children is likely to emerge. Home PGx testing is already available to (adult) patients themselves via direct-to-consumer (DTC) routes<sup>48,49</sup> (although not all DTC results are consistent with regulatory guidelines). The utility of these services in children is not clear and it is likely that their availability (and related legislation) will vary in different jurisdictions, but it will be important to recognise that parents may seek to use them for their children.

## 2.1 | Assessing PGx evidence

Expert PGx consortia have researched and summarised much of the PGx evidence that is available to date,<sup>50,51</sup> considering data from the numerous previous randomised controlled trials (RCTs) in (mainly adult) patients that have demonstrated the clinical utility of PGx testing. As implementation initiatives progress, it will be important to synthesise and analyse the cumulative evidence from PGx studies involving children, which will require consideration of both the quantity and quality of evidence available. Requiring separate paediatric (or adult) RCTs to establish the clinical relevance of every single PGx gene/drug pair would prove impractical and unethical, as well as being unnecessary.<sup>52</sup> It also ignores the potential benefits of using either PGx panel or approaches based on next generation sequencing (NGS). It would be logical to approach PGx information (using data from either drug development or post-marketing studies) on the basis of sound pharmacological principles, to include appropriate prescribing actions according to specified PGx results, in the same way that drug dose recommendations are often adjusted for patients with renal or hepatic dysfunction, where necessary, without separate trials in these special populations.<sup>52</sup> Aronson et al. recently highlighted the inadequate appreciation and utilisation of mechanistic evidence in drug approval processes (where mechanistic evidence refers to evidence of different types, e.g. in vivo, ex vivo, in vitro, clinical, observational or simulation studies, that supports the existence or details of a particular pharmacological mechanism), in association with an overemphatic focus on the results of clinical studies/trials<sup>53</sup>; within a pharmacogenomic context, there is a risk that this same phenomenon exacerbates the ongoing delays in PGx implementation.<sup>54</sup>

## 2.2 | The need for separate paediatric PGx evidence

When reflecting on the need for more paediatric data in order to implement evidence-based PGx testing in children, it is important to consider two fundamental questions: firstly, is separate paediatric PGx evidence always needed? Secondly, if separate paediatric PGx studies are not always essential, when is it appropriate to extrapolate adult pharmacogenomic data to adolescents, children or even infants? In the field of paediatric clinical pharmacology, the traditional mantra had always been that ‘children are not small adults’,<sup>55</sup> although it has been increasingly recognised that, in terms of pharmacokinetics, it can be argued that “children are small adults, neonates are immature children”.<sup>56</sup> For those drugs where there is an actionable pharmacogene, this will typically be because of the pharmacogenetic effect on either the PK or PD of the drug in question.

Given that most PGx data have been generated in adult populations,<sup>14,57</sup> it therefore needs to be established, to what extent (if any) adult PGx data can safely be extrapolated to the paediatric population for each relevant drug/gene pair and the related prescribing indication(s). Several factors must be considered to determine the appropriateness of extrapolation, including the natural history of the disease progression and response to the proposed therapeutic intervention, the likely (or known) exposure–response profile, and the applicability of adult PD measures to children.<sup>58,59</sup> The EMA has acknowledged in its reflection paper on paediatric extrapolation that “gaps in knowledge of intrinsic factors related to organ maturation and ontogeny of enzymatic and transport functions or pharmacogenetics [...], particularly in the youngest age groups of the paediatric population are sources of uncertainties and can affect the reliability in the predictions”.<sup>60</sup> It will be essential for researchers to further characterise the role of ontogeny in relation to developmental PGx, particularly with respect to the age-related changes in expression of drug-metabolising enzymes (DME) and transporters, exploring how these dynamic processes influence the clinical relevance of known pharmacogenes from birth to adulthood.<sup>61,62</sup> This research will be especially important in the youngest age groups (i.e., patients under 2 years of age) where pharmacological variability—particularly that derived from DME ontogeny—is most pronounced, and also in those settings where the indication for a particular drug is unique to paediatrics.

Evidence should also be sought to validate known PGx associations in children<sup>57</sup> and, where possible, to demonstrate the conditions determining suitability of extrapolation using different PGx datasets including data from both adults and children. Given the paediatric PGx data that exist and the implementation programmes that have already evolved, it would be valuable to reach consensus regarding the acceptability of adopting (or adapting) paediatric PGx guidelines from other countries or institutions, when there are examples already demonstrating the effectiveness and utility of PGx testing in children.<sup>63</sup> Progress will improve when there is consensus regarding the definition of the threshold of PGx evidence needed for implementation.<sup>64</sup> This process would benefit from involvement of international specialist paediatric, clinical genetics and pharmacological societies,

developing collaborative guidelines together with associated educational materials and mutual endorsement, in order to help accelerate implementation processes, as has previously been achieved in other clinical areas.<sup>65–69</sup> Ethically, it is important to avoid unnecessary duplication of paediatric PGx research whenever possible<sup>70</sup>; it is therefore essential to synthesise existing evidence from PGx research and implementation, so that the lessons learned can enable adoption elsewhere to be streamlined and accelerated.

### 3 | IMPLEMENTING PGX TESTING IN PAEDIATRICS: STRATEGIES AND CHALLENGES

The translation of scientific knowledge into healthcare policy and practice is a complex process,<sup>71</sup> but strategic change is now supported by the ever-growing field of implementation science.<sup>72</sup> When planning paediatric PGx policy, healthcare leaders, managers and PGx experts must consider the issues described above in addition to

viewpoints of different stakeholders, expected benefits, unintended consequences and cost. Examples of key issues that need addressing are briefly summarised in Table 2. Rather than describing different implementation strategies and challenges conceptually,<sup>73</sup> specific examples are given below based on the paediatric PGx implementation experiences and future plans from three countries.

#### 3.1 | Implementation experience to date and lessons learned

The next section summarises relevant examples of PGx implementation from different countries, with reference to the structure of the healthcare system where relevant, and the key lessons learned.

##### 3.1.1 | Canada

Direct provision of healthcare in Canada is a provincial responsibility, with federal oversight of national issues such as drug and device

**TABLE 2** Logistics of implementing PGx testing in paediatrics

Issue	Challenge	Potential solution
Indication for PGx testing	Clinicians and pharmacists may feel uncertain when testing is required	Clear paediatric PGx guidelines with integration into electronic prescribing systems and protocols, with PGx champions in each clinical area
Reporting	Insufficient standardisation of PGx reports will impede interpretation and use of results	Standardised PGx report format, with educational modules to support prescribers, and local PGx web portal and helpline for queries
PGx result transfer	Inadequate mechanisms for data transfer/retention between different healthcare IT systems	Unified or interoperable EHRs between primary and secondary care and pharmacists in which PGx data is stored life long
Data retention	PGx results may get lost and the information will not be retained in the patient's lifelong EHR	Use of PGx cards or PGx QR codes linked to smartphone app (compatible with national health systems) and IT to enable linkage to local/centralised lifelong EHR
Data curation	Research updating PGx knowledge will not be checked against historical PGx results	PGx data repositories will allow original data to be revisited and reports updated periodically
Accountability	Prescribers including physicians, pharmacists, nurse prescribers, may not know how to use PGx information and it will be wasted	Proactive multidisciplinary education with CDS tools embedded in e-prescribing software alerting prescribers to actionable PGx variants
Coding	PGx testing and results are not linked to appropriate standardised clinical coding terms	Coding dictionaries need to be updated in discussion with PGx experts
Cost	It is unclear who should pay for PGx testing	Cost allocations need predefining during implementation planning
Cascade testing	There are ethical issues surrounding the implications for family members once actionable PGx results are known	Guidelines and SOPs should clarify when testing of a patient's relatives is recommended and how this will be communicated to relevant parties

Abbreviations: PGx, pharmacogenomics; EHR, electronic health record; QR, quick response; CDS, clinical decision support; SOP, standard operating procedure.

approval. Thus, it could be said that Canada has 14 healthcare systems, and consequently implementation of PGx strategies varies between provinces, with some provinces being much more active in this space than others, with the partial exception of diseases treated by national networks, for example children with cancer who are treated pursuant to national guidelines. It should be noted that, even with these guidelines in place and despite TPMT genotyping being considered a standard of care, availability still varies between provinces. As in many places, the initial push for pharmacogenetic testing came from academic researchers, who in the case of Canada have significant federal grant support.

Pharmacogenetic testing in broader clinical practice began based on discovery, replication and validation work completed by the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and with other research groups. Clinicians wanted to know why specific genes were being tested from the range of genetic variants reported in the literature. Development of peer-reviewed, multidisciplinary pharmacogenetic clinical practice guidelines based on systematic reviews and AGREE II<sup>74</sup> were developed for cisplatin<sup>75</sup> and anthracyclines,<sup>76</sup> and published thiopurine guidelines were used.<sup>77,78</sup> For the cisplatin and anthracycline guidelines, key questions to be answered were: (1) Who should be tested? (2) Which variants should be tested for? and (3) What therapeutic recommendations should be made if variants are found?

The CPNDS began the implementation of pharmacogenetic testing into clinical practice in 2012, focusing specifically on the implementation of tests in paediatric oncology at ten paediatric oncology

centres in seven of the ten provinces in Canada. TPMT variants strongly associated with hearing loss secondary to cisplatin therapy (rs1142345, rs1800460, rs1800462, rs56161402, rs6921269)<sup>79,80</sup> UGT1A6, SLC28A3 and RARG variants strongly associated with anthracycline-induced cardiotoxicity (rs17863783, rs7853758 and rs2229774)<sup>81-83</sup> and TPMT and NUDT15 variants for thiopurine-induced myelosuppression (rs1142345, rs1800460, rs1800462, rs56161402, rs6921269, rs116855232, rs147390019, rs186364861).<sup>77,78</sup> Currently, 827 pharmacogenetic tests have been ordered and results returned in paediatric oncology across Canada.

CPNDS also established a research programme to understand how best to return pharmacogenetic results for robust markers associated with drug outcomes within the three most commonly used classes of drugs: analgesics, antibiotics and psychotropic drugs. Robustness was defined as: information on pharmacogenetic variants included in the drug label by a regulator (e.g., Health Canada, the US Food and Drug Administration, European Medicines Agency); or published, peer-reviewed pharmacogenetic clinical practice guidelines from an established expert group (CPIC, DPWG or CPNDS); or variants with drug outcome associations with odds ratio  $\geq 3$  in at least three independent populations (see Table 3). To date, 222 pharmacogenetic tests have been ordered and results returned for these three classes of drugs in three provinces (British Columbia, Ontario, Quebec). Like in other countries such as the US, commercial pharmacogenetic panels are available and accessed throughout Canada by some patients. Some private insurers are paying for pharmacogenetic testing in specific instances.

**TABLE 3** CPNDS PGx testing panel for antibiotics, analgesics and mental health drugs

Drugs	Adverse drug reactions	Genes	Rationale
<b>ANTIBIOTICS PGx PANEL</b>			
Aminoglycosides	Hearing loss, deafness	<i>MT-RNR1</i>	
Dapsone/sulfonamides	Haemolytic anaemia	<i>G6PD</i>	
Rifampin/isoniazid/pyrazinamide	Serious liver injury	<i>NAT2</i>	
<b>ANALGESICS PGx PANEL</b>			
Codeine	CNS depression, therapeutic failure, death	<i>CYP2D6</i>	
Hydrocodone		<i>CYP2D6</i>	
Oxycodone	CNS depression, death	<i>CYP2D6</i>	
Tramadol		<i>CYP2D6</i>	
<b>MENTAL HEALTH PGx PANEL</b>			
<b>Mood disorders</b>			
Carbamazepine	Severe cutaneous reactions	<i>HLA-B, HLA-A</i>	
Phenytoin		<i>HLA-B, CYP2C9</i>	
<b>ADHD</b>			
Atomoxetine	Therapeutic failure	<i>CYP2D6</i>	
<b>Antidepressants</b>			
SSRIs (e.g., paroxetine)	Therapeutic failure	<i>CYP2D6, CYP2C19</i>	
SNRIs (e.g., venlafaxine)		<i>CYP2D6</i>	

Abbreviations: PGx, pharmacogenomics; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors.

### 3.1.2 | The Netherlands

A landmark event in the clinical implementation of pharmacogenetics in the Netherlands was made in 2005 when the Royal Dutch Pharmacist Association (KNMP) founded the Dutch Pharmacogenetics Working Group.<sup>32</sup> This multidisciplinary working group consisting of physicians and pharmacists writes pharmacogenetic guidelines based on systematic literature reviews of drug/gene pairs. To date, more than 100 different drug/gene pairs have been assessed and guidelines are available for 47 drugs. Recently, the DPWG guidelines were endorsed by the European Association of Clinical Pharmacology and Therapeutics<sup>84</sup> and the European Association of Hospital Pharmacists.<sup>85</sup>

Originally DPWG recommendations focused on patients with a known genotype. However, DPWG has also started to recommend testing, since the creation of the Clinical Implication Score, a system that identifies the drugs for which specific PGx testing is needed prior to prescribing.<sup>86</sup> The score is assigned to all actionable drug/gene pairs and has three categories for testing: “potentially beneficial,” “beneficial,” and “essential”. Currently the score “essential” is assigned to 14 drug/gene combinations comprising 11 drugs including clopidogrel (*CYP2C19*), azathioprine/6-MP (*TPMT*) and capecitabine/5-FU (*DPYD*). The utility of *DPYD* in paediatrics is limited as fluoropyrimidines are only used to treat rarer solid tumours in this population (e.g., naso-pharyngeal carcinoma). The clinical recommendations of the DPWG are available at point of care through incorporation in more than 90% of electronic prescribing systems and pharmacy order entry systems.

The most widely adopted PGx test in the Netherlands is testing for variants in *DPYD* to prevent fluoropyrimidine toxicity. A recent evaluation reported that over 85% of patients were tested prior to start of treatment.<sup>87</sup> Other PGx tests that are generally well accepted include *TPMT* (mercaptopurine and azathioprine in paediatrics), *CYP2C19* (clopidogrel) and *UGT1A1* (irinotecan), but the level of implementation is highly variable with specialised and academic centres having the highest adoption rates. PGx testing is mostly performed by 10–15 laboratories that are part of clinical chemistry, hospital pharmacy or clinical genetics departments. In recent years, the number of tests performed in primary care has expanded and in response the Dutch College of General Practitioners has issued a point of view on pharmacogenetics.<sup>88</sup> More recently also the Dutch Society for Psychiatry has released a PGx guidance document.<sup>89</sup>

Most PGx testing in the Netherlands is reactive, i.e. in response to the prescription of a drug with a potential PGx recommendation. However, in paediatric clinical genetics WES has become standard practice and, as mentioned above, this offers the opportunity to repurpose existing diagnostic WES data for pharmacogenomics to enable pre-emptive testing. Recently it was shown that meaningful pharmacogenetic profiles for seven of 11 important pharmacogenes can be successfully extracted,<sup>43</sup> although there were limitations with this technique, with some variations in established pharmacogenes (e.g., *CYP2C19* and *CYP2D6*) not identified.

### 3.1.3 | United Kingdom

Currently paediatric PGx testing in the UK mainly takes place in specialist contexts or research studies, examples of which are given below.

In paediatric haemato-oncology, *TPMT* PGx testing is now routine for patients due to receive mercaptopurine as part of the chemotherapy regime for childhood acute lymphoblastic leukaemia (ALL).<sup>38</sup> The implementation of routine testing followed many years of research,<sup>90</sup> which had investigated *TPMT* genetic polymorphisms in relation to clinically relevant endpoints, including the prevention of potentially fatal myelotoxicity associated with *TPMT* deficiency, optimal dosing of mercaptopurine,<sup>91</sup> ALL clinical outcomes<sup>92,93</sup> and the importance of genotype–phenotype correlation.<sup>94</sup> The details of *TPMT* pharmacogenomics are reviewed elsewhere<sup>77</sup> and the significance of standardising nomenclature has been emphasised.<sup>95,96</sup> Notably, the infrastructure to conduct this *TPMT* research efficiently in the UK was in place because of the pre-existing clinical trials networks for childhood cancers; paediatric oncology has been recognised internationally as the “subspecialty in which research defines the standard of care”.<sup>97</sup> Testing of *NUDT15* is not currently standard of care in the UK, but testing can be accessed if required. A pre-existing paediatric clinical research network which fully integrates medical research into routine patient care, with ongoing trials into which PGx studies can be incorporated, is invaluable.<sup>98</sup> Similar trials networks and collaborative clinical groups will remain pivotal in facilitating PGx research and also provide a robust infrastructure within which to disseminate and implement new PGx recommendations.<sup>99–101</sup>

Some research studies aim specifically to implement PGx within defined routine care settings, such as the Pharmacogenetics to Avoid Loss Of Hearing (PALOH) study.<sup>102,103</sup> PALOH is a clinical implementation study aiming to investigate a new point-of-care (POC) PGx testing device to identify neonates at risk of aminoglycoside-induced hearing loss (secondary to the genetic variant m.1555A>G).<sup>102</sup> This study is recruiting in Liverpool and Manchester, but the findings will be of relevance to neonatal units across the country, particularly if they support the introduction of the new POC PGx test as part of standard neonatal care. PALOH is funded by the NIHR Invention for Innovation (i4i) programme, which is focused on early-stage collaborative studies, involving academic, NHS and industry partners, and deemed to have commercial potential with scope for future implementation within the NHS.<sup>104,105</sup> The study is also supported by the NIHR Manchester Biomedical Research Centre (BRC)<sup>103,106</sup> in partnership with a charity<sup>107</sup> and a local small–medium enterprise (SME). The NIHR BRCs all involve collaborative partnerships between universities and NHS teaching hospitals, with the aim of translating scientific research into patient benefit.<sup>108,109</sup> This example again demonstrates the importance of appropriate research networks with an adequately resourced infrastructure to support delivery of PGx studies.

Historically, PGx testing approaches and availability within the UK were somewhat heterogeneous and non-standardised.<sup>110</sup>

However, there have recently been large changes to the Genomic Medicine infrastructure in the NHS, which will impact upon future PGx testing implementation. NHS England delivered a report in 2015 describing its focus on “improving outcomes through personalised medicine”, which included the aim of delivering whole genome sequencing for specific conditions by 2020.<sup>111</sup> To support this aim, a series of multidisciplinary genomic education initiatives have been implemented, which are discussed further below. A dedicated PGx working group has been created composed of national experts aiming to prioritise actionable gene/drug pairs.<sup>112</sup> At the time of writing, the formal recommendations of this working group are expected to be published in the near future and, while initial phases are understood to have focused on implementation of PGx testing in adults, it is anticipated that consideration of paediatrics will follow soon afterwards. The infrastructure provided by the NHS Genomic Medicine Service, underpinned by a coordinated national network of Genomic Laboratory Hubs and a National Genomic Test Directory, into which PGx testing can be integrated, has the potential to support delivery of an efficient, cost-effective national paediatric PGx testing programme.

## 4 | RECOMMENDATIONS FOR PGx IMPLEMENTATION APPROACHES IN PAEDIATRICS

The adoption of PGx guidelines into normal clinical practice will require careful orchestration of national, regional and institutional implementation strategies; these should ideally include CDS tools fully integrated into the electronic health record (EHR),<sup>113</sup> delivered in parallel with a specialist PGx consulting service. Recommendations regarding paediatric PGx needs and implementation strategies do not necessarily need to be segregated from the activities of PGx consortia dedicated to developing PGx practice guidelines and the approaches used for adult patients; for example, in the United States, three children's hospitals were involved from August 2012 in phase II of the Electronic Medical Records and Genomics (eMERGE) Network,<sup>114,115</sup> which includes extensive PGx implementation research.<sup>116</sup> A review of the integration of PGx into the US system has also recently been published.<sup>117</sup> There are clear advantages of integrating paediatric PGx implementation into nationwide approaches, rather than postponing paediatric initiatives until an unknown future point, in order to avoid children experiencing unnecessary delays in receiving the benefits of pharmacogenomics in practice.

It is recommended that paediatric PGx implementation planning in different nations is informed by the available evidence, experience and implementation science. Programme delivery should be continually monitored for clinically relevant outcomes, evaluating predefined metrics of success and cost-effectiveness. As the costs of genomic testing have diminished,<sup>118</sup> PGx testing has become more affordable and therefore more accessible. This apparent affordability does not alone guarantee cost-effectiveness or clinical

utility, and the pharmacoeconomics of proposed paediatric PGx implementation strategies will need detailed evaluation.<sup>119,120</sup> Prompt information sharing, either through peer-reviewed publications or paediatric PGx networks, will enable the collaborative PGx community to learn together to build adaptable, responsive implementation models that can be applied to different healthcare systems.<sup>121,122</sup> Implementation initiatives should consider paediatric drug utilisation patterns in different countries and how these will impact upon the practical relevance of PGx recommendations. It will also be important to continue to share lessons learned about implementation across borders so that paediatric PGx benefits can become available globally when resources permit, as previously advocated by the Pharmacogenetics for Every Nation Initiative.<sup>123,124</sup>

Effective implementation will require early input from key stakeholders, some of whom will vary depending on local and institutional contexts. Our recommendations for stakeholders to invite to PGx planning teams are summarised in Table 4. The importance of advocacy for implementation from experts within the relevant specialty fields needs to be recognised and incorporated into planned educational strategies, together with identification of PGx champions in each discipline who can help to support implementation on the front line. Suggested members for the paediatric PGx multidisciplinary team are shown in Figure 1.

### 4.1 | Embedding education in PGx programmes

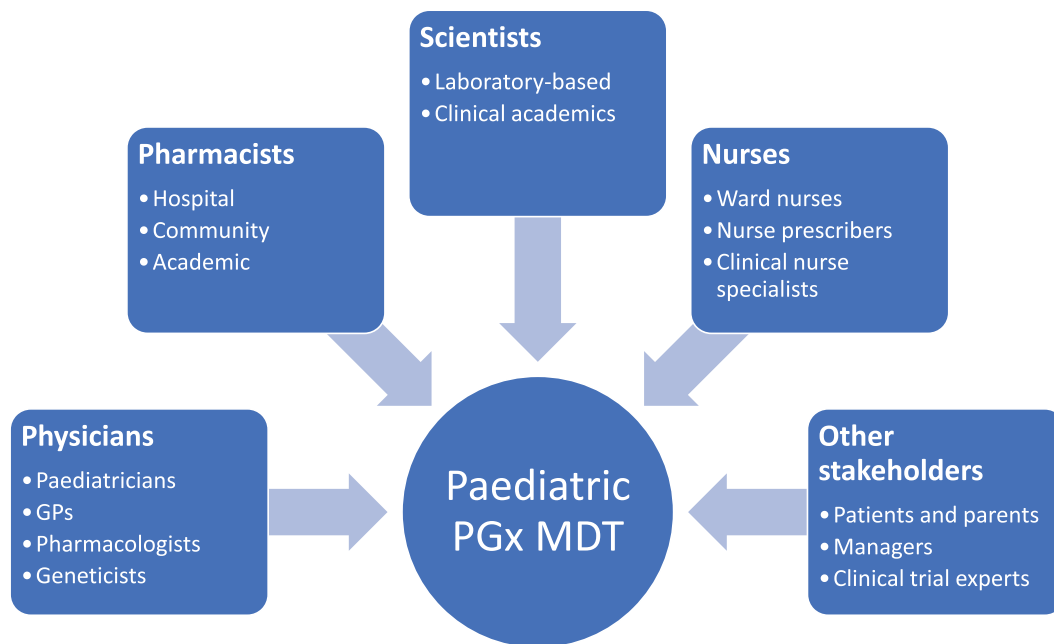
A critical aspect of implementing and “mainstreaming” paediatric PGx testing will be ensuring that concise educational material is developed for all stakeholders in parallel with the implementation plan. Relevant stakeholders will include practising paediatricians (including hospital consultants, registrars/residents and community paediatricians), general practitioners, hospital/community pharmacists, nurses and PGx analytical laboratory scientists. Educational programmes need to provide adequate information about the principles behind the new testing recommendations, indications, cost and, most importantly, the clinical relevance to patients. Inadequate or ill-timed multiprofessional education could jeopardise the success of implementation, for example through contributing to inappropriate use of PGx testing, lack of uptake or misinterpretation of results, and therefore a well-planned education strategy must be embedded within the implementation plan. The importance of this extends beyond pharmacogenomics alone, and to improve “genomic medicine preparedness” (in its broadest sense) among healthcare professionals, interprofessional, interdisciplinary educational programmes should be developed<sup>126</sup> and the material should concomitantly be adapted for undergraduate students in each discipline.

Inspiration can be taken from various pre-existing educational initiatives, including, for example, the Health Education England (HEE) Genomics Education Programme, which has developed high-quality educational modules targeted towards professionals and students from different disciplines, and these educational programmes



**TABLE 4** Stakeholders to invite in paediatric PGx implementation planning

Group	Examples of inclusion or recommended representatives
<b>Physicians</b>	
Paediatricians	Both subspecialist consultants and general paediatricians should be involved in implementation planning
Clinical geneticists	Geneticists and genetic counsellors with PGx expertise <sup>125</sup>
Clinical pharmacologists	Physicians and pharmacists with expertise in paediatric clinical pharmacology and/or PGx
GPs and community doctors	General GPs and those with a special interest in child health
<b>Pharmacists</b>	
Hospital	Including representation from specialist hospitals and local hospitals
Community	Representatives from general community pharmacies
<b>Academic and laboratory experts</b>	
Scientists	PGx experts from genomic laboratories and clinical academia
<b>Nurses</b>	
Nurse prescribers	Advanced nurse practitioners and clinical nurse specialists who prescribe for children in relevant contexts
<b>Other groups</b>	
Patients	Lay representation on PGx working groups and committees
Funders	Include management representation and engage early with commissioners
Trial coordinators	Research network leads and trial coordinators can advise on integrating planning PGx studies into existing paediatric research networks

**FIGURE 1** Healthcare professions and other stakeholders who could contribute to a paediatric pharmacogenomics multidisciplinary team (MDT) meeting

have been formally recognised as a core component of implementing Genomic Medicine within the NHS.<sup>127</sup> The Ubiquitous Pharmacogenomic (U-PGx) e-learning platform also provides open access online learning materials.<sup>128</sup> Furthermore, there is a wealth of educational literature relating to pharmacogenomics programmes in

many different settings,<sup>129–134</sup> including undergraduate curricula,<sup>135</sup> and it will be important to tailor pre-existing material specifically towards paediatrics in order to keep it relevant and to make it suitable for CPD (continuing professional development) at a postgraduate level.

## 4.2 | Integrating research with implementation

In addition to education, PGx research needs to be similarly embedded in any paediatric implementation strategy. The evidence based supporting PGx recommendations will constantly grow and protocols will, as always, need to be regularly updated. Demands for ever more research prior to implementation, in order to increase the quantity of evidence available to inform the implementation process, need to be weighed against the risks of further delays to implementation and the right balance must be struck.<sup>54</sup> Integrating research into implementation, for example through prospective ethical approvals for gathering PGx data into curated repositories, can help to overcome this barrier and develop a systematic infrastructure for improving the population PGx evidence base.

## 5 | THE FUTURE

Continued international collaboration and cooperation will enable the PGx community to realise the potential of precision medicine to contribute meaningfully to optimal pharmacotherapy for children.<sup>136</sup> As the omics scientific technologies continue to grow, the remit of PGx will expand to incorporate understanding of new domains such as pharmacotranscriptomics and metabolomics.<sup>137</sup> Updated, curated data-sharing initiatives underpinned by robust information governance will prove invaluable in advancing paediatric PGx science. Ultimately, evidence-based PGx in practice will aim to provide clear and timely PGx results to paediatric prescribers, supported by high quality genomic education resources, and continually informed by a cycle of improvement incorporating the latest results of research, audit and stakeholder feedback. It will also be important to work towards harmonisation of paediatric recommendations across the PGx consortia and regulatory agencies to help build internationally recognised PGx standards.<sup>34,138</sup>

## 6 | CONCLUSIONS

Children deserve the benefits of genomic medicine including PGx-informed therapies based on strong evidence coupled with affordable implementation. It is inevitable that there are many challenges when introducing new paediatric pharmacogenomic testing strategies into any complex healthcare system. However, with international collaboration and evidence curation, to synthesise implementation success stories from different countries, we can avoid unnecessary duplication of research and develop streamlined approaches to pharmacogenomic implementation strategies. As the genomic medicine revolution is well underway, collaborative efforts of the pharmacogenomic community will continue to bring PGx benefits to the bedside, supported by the infrastructure of well-funded paediatric research networks. It is essential that a pro-active dialogue with the paediatric workforce continues to be nurtured, to ensure children benefit from improved access to

pharmacogenomic testing delivered with a cost-effective, evidence-based and sustainable strategy.

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### COMPETING INTERESTS

G.G. holds a Genomic Applications Partnership Program grant from Genome Canada and Genome British Columbia with required matching funding from a commercial partner provided by Dynacare.

A.H.M. has received research grants outside the submitted work from GSK, Boehringer Ingelheim and Vertex, is the PI of a P4O2 (Precision Medicine for more Oxygen) public private partnership sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (Boehringer Ingelheim, Breathomix, Fluida, Ortec Logiqcare, Philips, Quantib-U, Roche, Smartfish, SODAQ, Thirona, TopMD and Novartis), and she has served on advisory boards for AstraZeneca, GSK and Boehringer Ingelheim with money paid to her institution.

M.R. holds the CIHR-GSK Chair in Paediatric Clinical Pharmacology at the University of Western Ontario and is a co-investigator on a Genomic Applications Partnership Program grant from Genome Canada and Genome British Columbia with required matching funding from a commercial partner provided by Dynacare. M.R. holds unrelated grants from the National Science and Engineering Council, the Canadian Institutes of Health Research and the Academic Medical Association of Southwestern Ontario.

B.C. holds a Genomic Applications Partnership Program grant from Genome Canada and Genome British Columbia with required matching funding from a commercial partner provided by Dynacare. B.C. is also an advisor for pharmacogenetic testing at the UnitedHealth Group.

All the other authors declare they have no conflicts of interest.

### CONTRIBUTORS

This study was conceived by C.I.S.B. All authors contributed to the writing, editing and overall content of the manuscript.

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