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Pharmacogenomics – how close/far are we to practising individualized medicine for children?

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The translation of pharmacogenomics into clinical practice is a key approach for practising individualized medicine, which aims to maximize drug efficacy and minimize drug toxicity. Since the completion of both the Human Genome Project and the International HapMap project, the development of pharmacogenomics has been greatly facilitated. However, progress in translating pharmacogenomics into clinical practice, especially in paediatric medicine, is unexpectedly slow. Many challenges from different areas remain. This paper discusses the existing applications and the limitations to the implementation of paediatric pharmacogenomics, as well as possible solutions for overcoming these limitations and challenges.

Introduction

Individualized medicine may be described as being the selection of 'the right drug at the right dose for the right patient'. In paediatric therapeutics, as with adults, the age, body size, genome profile, concomitant drug use and organ dysfunction can all affect drug efficacy and safety [1, 2]. Lack of drug efficacy may result in a delay in successful therapeutic treatment, whereas adverse drug reactions (ADRs) may result in poor drug adherence, ultimately leading to a lower quality of life and sometimes life-threatening events.

Genetic factors have been found to account for a significant proportion of the individual variability in drug response [3, 4]. Genetic variation in individuals affects the activities of drug-metabolizing enzymes [cytochrome P450 (CYP) enzymes], hence the pharmacokinetics and pharmacodynamics of drugs. Poor ability to metabolize a drug may lead to accumulation of this drug in the body. Conversely, an individual patient who metabolizes a drug too rapidly may experience instances where the therapeutic level of the drug is not reached, due to enhanced metabolism or 'clearance'.The study and application of pharmacogenomics is thus important in order to optimize drug therapy, hence leading to individualized medicine.

Currently, translating pharmacogenomic knowledge and research into clinical practice remains the first priority in implementing individualized medicine. With advances in genotyping technology and gene mapping, a wealth of pharmacogenomic data and tests are readily available. However, uptake of the use of these resources in clinical practice is unexpectedly slow in all age groups. There are considerable obstacles to the practice of individualized medicine. In children, these obstacles are more challenging due to such factors as various developmental stages and ethical concerns, which make the progress of paediatric pharmacogenomics even slower than for adults. In this article, we discuss the current implementation of paediatric pharmacogenomic knowledge, limitations to this implementation and the possible solutions for overcoming these challenges.

Practising pharmacogenomics

In the last decade, the completion of the Human Genome Project [5], the International HapMap Project [6] and the advances in high-throughput genotyping technologies have facilitated the burgeoning development of pharmacogenomic studies. More than 100 drugs, some of

them are commonly used in children, such as thiopurine, warfarin and antipsychotic drugs, are mandated by the US Food and Drug Administration (FDA) to incorporate pharmacogenomic information in drug labelling under sections on Dosage and Administration, Warnings and Precautions and Indications and Usage etc. [7]. Most of the drug labels do not ask for a mandatory genotyping test, but the pharmacogenomic information provides additional guidelines for clinicians to design the drug therapy.

Examples applicable to both adults and children in clinical use

Carbamazepine and human leukocyte antigen (HLA) One of the promising examples of pharmacogenomics in practice is the genotyping test for human leukocyte antigen B (HLA-B) in patients with carbamazepine treatment. Carbamazepine, an anticonvulsant used to treat seizures and nerve pain, can cause severe cutaneous adverse drug reactions, such as Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). These adverse reactions are commonly found in Asian populations, and studies from China, Hong Kong, Malaysia, Taiwan and Thailand have reported that the *HLA-B*1502* variant allele is strongly correlated with carbamazepine-induced SJS/TEN [8–12]. In other populations, such as Caucasians and African-Americans, the prevalence of *HLA-B*1502* is almost absent, but study of European patients undergoing carbamazepine treatment has shown that another variant allele, *HLA-A*3101*, has a mild association with the increased risk of SJS/TEN [13].

In 2007, the US FDA included pharmacogenomic information on the drug label of carbamazepine, which recommended a genetic test for *HLA-B*1502* in high-risk patients prior to treatment with carbamazepine. Patients who are positive for *HLAB*1502* should not be prescribed with carbamazepine unless the benefits clearly outweigh the risks [14]. The screening for *HLA-B*1502* in patients from high-risk ancestry is routinely performed in clinical practice. The successful application of pharmacogenomics in carbamazepine treatment can be attributed to a number of factors. First, the allele variant has a high correlation with the adverse event. In the Taiwanese study, the odds ratio for developing carbamazepine-induced SJS/TEN among patients with a positive result to *HLA-B*1502* testing was 2504 (95% confidence interval 126–49 500) [8]. The odds ratios in other studies were also high [9, 10]. Second, the adverse events are severe and life threatening. There is a high mortality rate for SJS/TEN, ranging from 5% in SJS to 30% in TEN [15]. Third, other alternatives to carbamazepine, such as lamotrigine, are available. Therefore, based on the result of the genotyping test, clinicians can consider the best medication for the patient. For these reasons, pharmacogenomic information is very helpful and is widely used in carbamazepine treatment. Certainly, it is routinely used in many areas with a high Chinese population, such as Hong Kong, in both children and adults.

Thiopurine and thiopurine methyltransferase (TPMT) Thiopurine is commonly used to treat acute lymphoblastic leukaemia (ALL), in both adults and children. It is a prodrug that is metabolized by TPMT. To date, over 25 variants in the *TPMT* gene have been identified, most of these variants being associated with TPMT activity. It has been reported that >90% of ALL patients carry the *TPMT*2*, *TPMT*3A*, *TPMT*3B* or *TPMT*3C* allele in several populations [16–18]. A functional study showed that these variants enhanced proteolysis of TPMT and resulted in lower catalytic activity [19]. As a consequence, when patients carrying these variants receive standard dosage of thiopurine, cytotoxic molecules will accumulate, and it will subsequently lead to ADRs, such as myelosuppression and fatal bone-marrow toxicity [20–22].

A *TPMT* genotyping test has been shown to be highly specific and sensitive in ADR prevention. In 1214 German Caucasian patients, performance of genotype tests for the variant *TPMT*2* and *TPMT*3* alleles (*TPMT*3A*, *TPMT*3B*, *TPMT*3C* and *TPMT*3D*) achieved a sensitivity of 90% and a specificity of 99% in preventing ADRs [16]. With the observed high sensitivity and specificity, *TPMT* genotype testing has become commercially available. In 2004, the US FDA approved a *TPMT* genotype test and revised the drug labelling to recommend a prior *TPMT* genotype test for thiopurine [7]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released the guideline for the dose adjustment of thiopurines [23]. In the UK, the standard treatment protocol for ALL (UKALL-2003) includes the pharmacogenomic test for *TPMT* [24]. Patients with homozygous nonfunctional alleles of *TPMT* are required to reduce the standard dose by 90%, while a reduction of 30–70% of the standard dose is required for a heterozygous variant of *TPMT* (with one functional allele, **1*) [23, 25]. A prospective study on the *TPMT* genotype test showed that the dose-adjustment strategy can reduce drug toxicity without compromising efficacy [26]. The cost-effectiveness analysis in four European countries (Germany, Ireland, The Netherlands and the UK) showed that calculated cost per life-year gained by *TPMT* genotyping in ALL patients was €2100 (~£1820) [27]. This cost is much lower than £30 000 (~€34 700) per quality-adjusted life-year gained, which is the threshold value set up by the UK National Institute for Clinical Excellence (NICE) to indicate a cost-effective outcome [28]. Therefore, pretreatment *TPMT* genotype testing is a cost-effective approach in clinical practice.

Warfarin, CYP2C9 *and* VKORC1 Warfarin is the most frequently used medication in the long-term management of anticoagulation therapy in children. Individual dose requirements for warfarin are highly variable and subject to repeated dose adjustments. Age, body size, organ

dysfunction and diet are the main factors that affect the efficacy of warfarin treatment in adults and children [29–33]. Genetic factors that may also influence warfarin dosing have not been investigated thoroughly in children until recently.

A UK study showed that polymorphisms of *CYP2C9* (**2* and **3* alleles) and *VKORC1* (–1639G>A) were significantly associated with required dose adjustments of warfarin in children [31]. The mean warfarin daily dose requirement in children with the *VKORC1* GG genotype was significantly higher than for those with GA or AA genotype. *In vitro* and *ex vivo* studies showed that *CYP2C9*2* and *CYP2C9*3* cause a reduction of warfarin metabolism by 30–40 and 80–90%, respectively, indicating a lower dose requirement for children [34].

In 2007, the US FDA revised the label for warfarin with information pertaining to new pharmacogenomic data. An International Warfarin Pharmacogenetics Consortium algorithm was developed in 2011, and use of this algorithm was suggested to give a better prediction of the appropriate dose of warfarin than the other clinical algorithms or use of a fixed-dose approach [34]. However, this algorithm is based on data obtained from adults and may overestimate the dose for children [31]. Concerning the variability of response to warfarin, guidelines specific for paediatric patients would be preferable.

Examples more applicable to children

Psychotropic drugs and CYP2D6 Cytochrome P450 (CYP) is a well-known superfamily of drug-metabolizing enzymes involved in the metabolism of ~80% of drugs [35]. Cytochrome P450 2D6 is responsible for metabolizing many antipsychotic and antidepressant drugs. Polymorphisms of CYP2D6 have functional significance in drug metabolism and can be classified into the following four categories/drug-metabolizing phenotypes: poor metabolizer (PM); intermediate metabolizer (IM); extensive metabolizer (EM); and ultra-rapid metabolizer (UM) [36].

Atomoxetine, commonly used for treating attention-deficit/hyperactivity disorder (ADHD) in children, is metabolized by CYP2D6. Pharmacogenomic data have shown that CYP2D6 PM results in 10-fold greater area under the concentration *vs.* time curve of atomoxetine and higher than normal activity of CYP2D6, which poses risk of ADRs [37]. In US FDA-approved drug labelling, dose adjustment is recommended for CYP2D6 PM, which should be initiated at low dose and increased to the usual target dose if no improvement is observed and the initial dose is well tolerated [38]. A laboratory test for *CYP2D6* genotype is currently available. However, due to the lack of clinical utility and clear clinical guideline, a genotyping test is not routinely used by clinicians prior to the treatment of children with ADHD with atomoxetine. Details of limitations will be discussed the section entitled 'To what extent can we practise individualized medicine in children?'.

Cisplatin, TPMT, catechol-O-methyltransferase and ATP-binding cassette transporter C3 Cisplatin is one of the most effective chemotherapeutic agents for treatment of solid tumours. However, the use of cisplatin is limited by the high incidence of ototoxicity in children [39, 40]. This complication causes irreversible, bilateral hearing loss, which seriously hinders language and cognitive development in children [41].

Association studies in children with cisplatin-induced ototoxicity showed that genetic variants in *TPMT* (rs12201199) and catechol-*O*-methyltransferase (*COMT*; rs9332377) are associated with hearing loss [42]. The result was replicated by the same research group using an independent cohort of paediatric patients, and one more genetic variant, in ATP-binding cassette transporter C3 (*ABCC3*; rs1051640), was identified to be associated with hearing loss [43].

In clinical practice, the risk of cisplatin-induced ototoxicity is evaluated by clinical factors such as age, germ-cell tumour, cranial irradiation and vincristine treatment. A predictive model combining the variants of *TPMT*, *COMT* and *ABCC3* with clinical factors showed a significant improvement in predicting the risk of ototoxicity than using clinical risk factors alone [43]. This result illustrates the potential value of incorporating pharmacogenomics into clinical practice.

However, the association between *TPMT*, *COMT* and cisplatin-induced ototoxicity has been questioned because the result could not be replicated in another study and because the laboratory models did not support this association [44]. Therefore, more study should be done to validate the association.

In addition to the aforementioned examples, pharmacogenomic markers for drug efficacy and safety have also been identified for several paediatric antiepileptic drugs and immunotherapy drugs, such as abacavir, clobazam and phenytoin. The pharmacogenomics of these drugs have been discussed in previous review articles [45, 46]. Other common paediatric drugs with available pharmacogenetic tests are shown in Table 1.

Currently, there are only a few paediatric pharmacogenomic tests that are commercially available and used in clinical practice. However, with continuous support from national charity groups, healthcare support groups and regulatory agencies, it is expected that more paediatric pharmacogenomic tests will become available in the near future. In 2005, the US FDA released guidance to the pharmaceutical industry voluntarily to submit pharmacogenomic data for licensing. This guidance is intended to facilitate the use of pharmacogenomic data in drug development. In 2006, the European Medicines Agency (EMA) and the US FDA agreed to have a joint working initiative with respect to the data submission procedure. These efforts have raised awareness of the importance of pharmacogenomic study in drug development in terms of improving efficacy and reducing ADRs. Since

Table 1

Selected drugs with available pharmacogenomic tests for children*

Drug	Gene	Therapeutic class or indication	Genetic variant	Comment on genotype	Action recommended by US FDA-approved drug label
Abacavir	*HLA-B*	Human immunodeficiency virus therapy	*HLA-B*5701*	Increased risk of hypersensitivity	Abacavir is not recommended for people carrying *HLA-B*5701* allele
Atomoxetine	*CYP2D6*	Attention-deficit/ hyperactivity disorder	*CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6*	Alert to adverse drug effects in poor metabolizer	Start at 0.5 mg kg^{-1} day^{-1} and only increase to the usual target dose of 1.2 mg kg^{-1} day^{-1} if symptoms fail to improve after 4 weeks and the initial dose is well tolerated
Cisplatin	*TPMT*	Cancer	*TPMT*3B*, *TPMT*3C*	Increased risk of ototoxicity	Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose and for several years post-therapy
Clobazam	*CYP2C19*	Anticonvulsant	*CYP2C9*2*	Higher concentration of the active metabolite of clobazam	Initial dose should be 5 mg day^{-1} and titrated initially to 10–20 mg day^{-1}, and may be titrated further to a maximal daily dose of 40 mg if tolerated
Phenytoin	*HLA-B*	Anticonvulsant	*HLA-B*1502*	Increased risk of Stevens–Johnson Syndrome and toxic epidermal necrolysis	Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*1502*
Thioprines (azathioprine, mercaptourine, thioguanine)	*TPMT*	Acute lymphatic leukaemia	*TPMT*2*, *TPMT*3A*, *TPMT*3C*	Increased risk of myelosuppression	Substantial dosage reduction
Valproic acid	*POLG*	Anticonvulsant	*POLG* mutation	Increased risk of liver failure and death in patients with hereditary neurometabolic syndromes	*POLG* mutation testing should be performed in accordance with current clinical practice
Warfarin	*VKORC1*, *CYP2C9*	Anticoagulant	*VKORC1* (G-1639A), *CYP2C9*2*, *CYP2C9*3*	Increased risk of bleeding	A range of doses based on *VKORC1* and *CYP2C9* genotypes

*Drugs are selected from the British National Formulary for Children [66] and are listed in the table of the US Food and Drug Administration (US FDA) Pharmacogenomic Biomarkers in Drug Labeling [7].

then, additional clinical trials have incorporated pharmacogenomic tests in phases 2 and 3, and it is expected that pharmacogenomic data will be more commonly listed on drug labels.

To what extent can we practise individualized medicine in children?

A decade after completion of the Human Genome Project, individualized medicine is still in its infancy. Pharmacogenomic tests for children receiving medication are limited, and the progress of translating/incorporating pharmacogenomic data into clinical practice is unexpectedly slow. This poses a question: what obstacles slow down this progress of incorporation?

Gene expression and ontogeny in children

The gene expression profile and ontogeny in children is the biggest challenge for pharmacogenomic study. Most of the pharmacogenomic research identifies variation in the genetic sequence (e.g. single nucleotide polymorphism) as the marker to predict drug response. However, the level of gene expression can vary depending on changes in the environment, such as different developmental stages. The development of children can be subdivided into the stages of infancy, childhood and adolescence. During the developmental process, major organ systems involved in drug biotransformation are developing to reach maturity and, likewise, gene expression, particularly with respect to the drug-metabolizing enzymes, undergoes considerable changes throughout the developmental process [47].

In the study of ontogeny of drug-metabolizing enzymes, variable expression profiles of the enzymes can be observed. While some enzymes are expressed at the highest level in the fetus and become silenced (e.g. flavin-containing monooxygenase 1) or reduced to relatively low levels (e.g. CYP3A7) within a few days to 2 years after birth [48], in contrast, some enzymes (e.g. CYP2D6) are expressed at negligible or low levels in the fetus but increase significantly to high levels within a few weeks to 1 or 2 years after birth [49]. The change of enzyme activity across developmental stages greatly affects the drug response and tolerance in children.

When a genotype–phenotype relationship is identified in children, researchers have to consider the effect of developmental factors. However, the ontogeny of drug biotransformation in children remains unclear, which limits the predictive capacity of pharmacogenomic data for drug efficacy and safety.

Lack of pharmacogenomic information for use in paediatrics

Compared with adults, pharmacogenomic studies in children are scarce, hence pharmacogenomic information for paediatric use on drug labels is limited. Although numerous pharmacogenomic studies have been published, most have been performed in adults. Results from adult may not be applicable to children owing to differences in developmental stage, as discussed in the previous subsection. For example, the kidney and liver are the major organs responsible for drug metabolism and clearance/elimination. Developmental changes in these two organs, such as overall size, which will influence the total mass of drug-metabolizing cells and, in the case of the kidney, the glomerular function, will significantly influence drug metabolism in children. This is often markedly different from that observed in adults [50]. One example is the clearance of voriconazole, an antifungal agent, is ~3-fold higher in children than in adults [51].

With this limitation, paediatricians often remain sceptical and uncertain as how to use data derived from adult studies and apply them to clinical practice in children. In 2009, a survey study performed by The American Society of Pediatric Hematology/Oncology showed that most US paediatric haematologists are familiar with pharmacogenomic data and their application to the use in warfarin treatment. However, they refused to perform the genotype test prior to decision making for drug therapy in children [52]. The clinicians argued that there is a lack of data pertinent to the US paediatric population and most studies performed are retrospective in nature, with a small sample size. A prospective randomized clinical trial on the clinical effectiveness of pharmacogenomic tests in warfarin therapy has been conducted, but children were not included in the trial [53]. They urged a large prospective trial in children to provide a stronger evidence base for the current pharmacogenomic data.

Ethical concerns in paediatrics

The ethical concern of individualized medicine is of great importance, especially in children, and this also partly explains why only a limited number of pharmacogenomic studies have been conducted in children. A recent review discussed the ethical considerations for pharmacogenomic research in the paediatric population and its implementation in the care of children [54]. In paediatric research, acquisition of informed consent is one of the greatest challenges, especially in pharmacogenomic studies. Full disclosure of information is difficult, because the potential implications of pharmacogenomic data might be unknown at the time of the study. Given this uncertainty, risk–benefit assessment might not always be complete for children and their parents to make an informed decision on their participation in the research trial process.

In clinical practice, genetic discrimination and privacy are major concerns. In addition, pharmacogenomic testing may provide ancillary disease risk information, which might affect the ability of patients to obtain secure life insurance/protection [55]. The psychological burden to both children and parents should also be considered, because ancillary disease risk information implies the potential development of one or more diseases. In addition, privacy is also a concern in pharmacogenomic testing. A survey study conducted in 2007 showed that 66% of subjects had a fear of inadequate protection of their personal data if they were to undergo a pharmacogenomic test [56]. The survey did not involve children, but fear from their parents would probably result in a reluctance to allow any pharmacogenomic test to be performed on their child.

Lack of clinical utility and cost effectiveness

The key for translating pharmacogenomics into clinical practice is clinical utility and cost effectiveness. Currently, only a few pharmacogenomic tests are used routinely by clinicians, because the clinical utility is still being questioned. Atomoxetine is one of the examples. As discussed in the section of 'Examples more applicable to children', patients with *CYP2D6* variants have increased risk of adverse events, and dose adjustment is recommended by the US FDA. Regardless of CYP2D6 phenotype, the normal dose of atomoxetine should be initiated at 0.5 mg kg^{-1} day^{-1} and increased after a minimum of 3 days to a target total daily dose of 1.2 mg kg^{-1}. If the patient is CYP2D6 PM, the dose is recommended to be initiated at 0.5 mg kg^{-1} day^{-1} and only increased to the usual target dose of 1.2 mg kg^{-1} day^{-1} if symptoms fail to improve after 4 weeks and the initial dose is well tolerated [38]. In clinical management, a prescription starting with a low dose and titrating slowly is a basic practice and thus such recommendations seem not to be meaningful. Without knowing the *CYP2D6* status, clinicians are still able to dose atomoxetine to a safe and efficient level according to clinical assessment tools [57].

The prevalence of genetic variants among different ethnic populations also limits the clinical utility of some pharmacogenomics tests. For example, CYP2D6 PM are found in 7% of Caucasians but only 1% of Chinese populations [58]. In contrast, *HLA-B*1502* is commonly found in Chinese and other Asian populations but is almost absent in Caucasian and African-American populations. As a result, clinicians would be doubtful of using pharmacogenomic information based on other ethnic populations.

Apart from clinical utility, clinicians also consider the cost effectiveness of pharmacogenomic tests. Advances in genotyping technology will eventually reduce the cost of genotyping; however, performing routine pharmacogenomic testing in patients may still be expensive for individuals and the parent healthcare system. Therefore, both governments and clinicians are concerned about whether the cost of pharmacogenomic tests is justified by the clinical outcomes after performing them. However, there are only a few studies that demonstrate the cost effectiveness of performing pharmacogenomic tests, or show that the test is only cost effective in certain patient groups, such as with the case of testing prior to warfarin therapy [59]. Guidelines exist for economic evaluation of pharmaceutical products in the healthcare system, but they are rarely applied in pharmacogenomic study.

What should be done to facilitate the implementation of pharmacogenomics into clinical practice?

To overcome the challenges and facilitate the implementation of pharmacogenomics into clinical practice in paediatrics, different approaches can be worked on, and examples are given below. These suggestions are not limited to paediatric study and are applicable to all pharmacogenomic research.

Pharmacogenomics network for paediatric study

Drug metabolism in children is complex owing to differences in gene expression during physiological development. Therefore, in order to gain a better understanding of drug metabolism at the different developmental stages, adequate pharmacogenomic studies remain a prerequisite for improving paediatric individualized medicine. If a drug is required to be studied in an age-group-specific manner, we can envisage that subject recruitment will be a major challenge. In order to have sufficient power to detect any genetic effect/difference, nationwide pharmacogenomic networks for paediatric study and international collaboration are encouraged and essential to allow the collection of a representative sample size and to allow cross-comparisons of the results.

There are pharmacogenomic groups worldwide, but projects specific to paediatrics are limited. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is one of the few to have started a nationwide project on paediatric pharmacogenomics, namely the Genetic Approach to Therapy in Children (GATC) [60]. This project establishes a nationwide network for of surveillance ADRs in children and collects their biological samples for genotyping. They target three ADRs commonly found in children, i.e. cisplatin-induced hearing loss, anthracycline-induced cardiotoxicity and codeine-induced infant mortality. Thousands of ADR cases in children have been recorded, and pharmacogenetic markers have been successfully identified [42, 61]. The GATC may provide a framework of active pharmacogenomic study in children that can be adopted by other countries. In the USA, there is another paediatric pharmacogenomic project, termed 'PAAR4Kids: Pharmacogenomics of Anticancer Agents Research in Children', launched by National Institutes of Health's Pharmacogenomics Research Network (PGRN). This project studies only the pharmacogenomics of children with ALL and should be extended to other disciplines as well [62].

Guidelines for pharmacogenomics studies in children

Guidelines for conducting good pharmacogenomic studies in children should be developed. These guidelines could provide a framework for future investigators to be able to plan, conduct and evaluate pharmacogenomic analysis in paediatric studies. Several areas should be particularly addressed within these suggested guidelines, namely protocol development, ethical considerations in children, and the documentation of both research methods and results. With such guidelines, the quality and integrity of pharmacogenomic research can be maintained and, consequently, the results of such studies would be more robust.

Pharmacoeconomics in pharmacogenomics

The incorporation of pharmacoeconomic data into pharmacogenomic research will, it is expected, be the catalyst to full implementation of individualized medicine in modern society. Pharmacogenomic tests are not only beneficial to patients, but if they are also shown to be cost effective and to have positive cost–benefit, then their acceptance by physicians will be enhanced. Likewise, the willingness of individual governments/healthcare sponsors and private insurers to adopt and support pharmacogenomic technologies financially would be encouraged. There are few cost–benefit analyses of pharmaocogenomic studies, but they have adopted different methodologies and, consequently, the consistency of results is poor. A standardized pharmacoeconomic model for pharmacogenomics is favourable, but health economists are uncertain whether existing pharmacoeconomic models are sufficient to evaluate pharmacogenomic tests. Therefore, developing models for pharmcoeconomic analysis in pharmacogenomics should be one of the main focuses in future work on translational pharmacogenomics.

Integration programme for translational pharmacogenomics

In order for clinicians to integrate pharmacogenomics into clinical practice, they need support from various areas, including clinical guidelines, education and computational tools. An integration programme that works on these areas can greatly facilitate the progress of pharmacogenomics in clinical practice, including paediatrics.

An example is the translational pharmcogenomic programme led by St Jude Children's Research Hospital (St Jude). PG4KDS, a project launched by St Jude, aims to evaluate pharmacogenomic test results in children and selectively choose the tests that have strong evidence and closely link to drug response to incorporate into patient medical records. Clinicians will be alerted to any pharmacogenomic information about the patient when prescribing treatment [63]. In addition, St Jude is also developing protocols and computational tools to help clinicians to make prescription decisions based on the pharmacogenomic information [64]. To increase the use of pharmacogenomics, clinicians and pharmacists need to play an active role in decision making on the choice of pharmacogenomic tests and developing clinical protocols so that they have a better understanding of the pharmacogenomic tests and will be better able to use them. In addition, the project works on education by making videos and leaflets for parents and patients, as well as healthcare professionals. These materials are easily accessible in hospitals and online [65].

Conclusion

To date, full implementation of pharmacogenomics into clinical practice, and thus individualized medicine in children, is inadequate. There is a need to have more consortia that focus on paediatric pharmacogenomics and to encourage the reduction in the cost of genotyping in order to understand the ontogeny and gene expression in children. It can be foreseen that individualized medicine in children will be the future of paediatric medicine.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: ICKW was partly supported by the European Union Seventh Framework Programme FP7/2007–2013 under grant agreement no. 261060, the 'Global Research in Paediatrics Network of Excellence (GRiP)'; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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