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Ethical considerations for pharmacogenomic testing in pediatric clinical care and research

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Abstract

The information gained from pharmacogenomic testing is becoming increasingly recognized as an opportunity to improve our current dosing strategies for children. The identification of gene polymorphisms that influence drug disposition and effect can be used to help predict a child's susceptibility to toxicity and/or response to a particular drug or therapeutic regimen. However, the potential consequences of performing genomic analysis in children raise important ethical considerations. Although the level of risk introduced remains partially hypothetical, awareness of the ethical concerns and protective legislation will be an important part of fully informing patients, families, clinicians, and researchers about the risks and benefits of pharmacogenomic testing in children. Where it can be done without loss of benefit, risk reduction is a moral imperative, and so the ethical complexities related to pharmacogenomics must be addressed in an ongoing way as we continue to learn more about the value of the technology to children.

Keywords

child; DNA; pharmacogenetic; pharmacokinetic; SNPs

Pharmacogenomic (PGx) testing is being increasingly studied and used in children to improve pediatric dosing strategies. The hope is that by identifying the specific genetic determinants involved in drug absorption, distribution, metabolism, excretion and drug response throughout a child's development, pediatricians and clinical investigators can choose the best drug for a child and more accurately determine safe and effective dosing. However, as PGx technology evolves in pediatrics, several key ethical issues unique to children will need to be considered. In this article, we address three main types of questions that arise in pediatrics: should PGx testing be performed in children, and if yes, what are the specific benefits and risks to the child? What are the ethical considerations of pediatric PGx testing in the context of research and how are they similar to other forms of pediatric research in terms of informed consent, assent and research risk assessment? How do these

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general ethical concerns translate into pediatric-specific issues and guide actions that are ethically sound for the practitioner prescribing a drug with potential PGx variability, for the clinical research physician considering whether to study novel PGx markers in children, and for the investigator whose nontherapeutic PGx study may pose some risks? Broad ethical and political issues of PGx testing have been extensively addressed in the adult population [1]. When the patient or research participant is a child, however, the issues become more complex in part because pediatric participants range from neonates who do not participate in the decision-making process to older adolescents who often participate more, but not with the complete autonomy of an adult. The PGx examples and issues outlined below primarily refer to testing based on DNA sequence analysis to identify gene-expression patterns and genetic polymorphisms that lead to variable functional protein levels and/or enzyme activity that lead to altered drug responses and variable drug pharmacokinetic (PK) profiles. The starting point for this discussion will involve a brief overview of current applications of PGx testing in pediatrics. While the examples explored are most relevant to hematology and hemato-oncology, the fundamental aspects of testing can be applicable to any area of pediatric practice or research where PGx testing is involved. It should be noted that the ethical and regulatory issues presented in this article are specific to the American health system. It should also be emphasized that these challenges are not static. The considerations change as a child grows, as our knowledge of PGx evolves and as legislative responses mature in response to these new technologies.

PGx testing in pediatric practice

Individualized genome-based therapy has the potential to impact drug efficacy, reduce rates of toxicity and improve overall outcomes for children with a variety of medical disorders. When 70% of medications used in children today have not been adequately studied in children [2], the use of PGx technology to better understand drug effects is especially promising in pediatrics. PGx data, coupled with an understanding of the nongenetic factors that impact pediatric drug disposition, including organ function, concomitant medications and underlying diseases processes [3], can improve our current dosing practices for children. Specific applications and benefits include: pharmacogenetic-guided dosing for children instead of a trial-and-error approach; improved medication effectiveness by appropriate dosing strategies and patient population selection; decreased adverse events by identifying those children at risk of enhanced susceptibility to drug toxicity and variable systemic exposures; an improved understanding of treatment nonresponse; facilitation of drug approval for effective agents by determining drug response and adverse drug reactions in specific patient cohorts; and an improved understanding of pediatric PK and pharmacodynamics (PD) [4]. PGx testing can provide critical information to explain or describe those factors that influence drug disposition in children including variable absorption (e.g., membrane transporter SNPs [5], metabolism (e.g., genetic variants encoding drug-metabolizing enzymes such as CYP450 enzymes) [3], and excretion [6]. Furthermore, identifying genetic variation in drug targets (e.g., drug receptors) and key regulatory proteins (e.g., ion transporters), which can lead to both direct and indirect effects on drug action [3], may help to explain a child's drug response to a particular medication. Importantly, pediatric PGx data, in comparison to with that of adults, needs to be interpreted in the context of the ontogeny of gene products (e.g., drug-metabolizing enzymes and transporters) throughout a child's development, which will also impact drug disposition and drug effect [6,7]. PGx data may also be used to classify children into prognostic categories as demonstrated by the Taiwanese pediatric acute lymphocytic leukemia (ALL) study [8]. Individual genomic polymorphisms can also be used to better understand the PK/PD variability of drugs used in children; this is well described in pediatric organ transplantation, asthma and attention deficit disorder [9]. There are also ongoing clinical PGx studies to understand the PGx of adverse drug reactions and how they can be predicted for children

with psychiatric and neurodevelopmental disorders, atopic dermatitis, HIV, asthma, sickle cell disease, venous thrombosis and ALL – devastating diseases that afflict many children and demand improved therapies [10]. While challenges of PGx testing remain, including the incorporation of polygenic determinants of drug effects into an individualized dosing regimen [3] and the difficulty interpreting several SNPs at the same time, PGx testing holds great promise as a method to improve drug safety and efficacy for children.

One noteworthy example of PGx testing in pediatrics is the use of the thiopurine methyltransferase (*TPMT*) genotype and/or enzyme assay results in children with ALL to predict chemo therapy sensitivity. The activity of *TPMT*, a key enzyme in the metabolic pathway of thiopurines, impacts the safety and efficacy profile of mercaptopurine and thioguanine, two drugs used in the standard treatment for childhood ALL. *TPMT* genetic polymorphisms can at least in part explain the considerable differences in toxicities, such as myelosuppression, experienced by children with *TPMT* variants that result in reduced expression and activity of this enzyme [11]. PGx testing can then be used in practice to guide appropriate dosing, a practice which has been demonstrated to impact outcomes for children with ALL [12]. Another example of PGx in children includes *VKORC1* and *CYP2C9* testing in children initiating warfarin treatment [13]. While these examples illustrate how genotype analysis for drug metabolism can help guide therapy in children, the application of PGx testing is far from universal in this population. In fact, leukemia protocols usually only recommend *TPMT* testing for children who experience severe myelosuppression, and PGx algorithms for warfarin dosing have not yet been validated in children [14]. There are many concerns that need to be addressed before the full implementation of PGx testing in children occurs including, but not limited to, the expense of testing, privacy, insurance denials for the cost of testing, unknowns related to the use and storage of genetic information, the failure of genomic testing to predict outcomes and one which is receiving possibly the greatest attention with respect to predictive pediatric PGx testing; the threat of discrimination.

The specific elements related to potential discrimination are based on the following considerations: the ability to afford PGx testing [15,16]; the possibility of ethnicity-based testing rather than individualized testing [17–19]; and the risk of denials for disability, long-term care and life insurance as a result of testing [20]. In light of these concerns, should physicians obtain genotype analysis for children when the results may uncover predispositions to adult-onset disease or resistance to specific therapies when these findings might impact a child's ability to get insurance later in life? Fortunately, steps to protect patients who have PGx testing performed have been taken by the US federal government. Specifically, in 2008 the Genetic Information Nondiscrimination Act (GINA) was passed and went into effect in 2009 [21]. The intent of this legislation was to protect patients from discrimination by their insurance company or employer based on genetic testing results or family history [21]. However, it can be difficult for clinicians to maintain up-to-date knowledge of PGx policy and legislation, some of which is rather complicated. For example, while the passage of GINA was critical for the protection of adults and children and the advancement of the field of PGx, notable gaps in broad protection exist [21]. Specifically, it does not protect against discrimination when applying for life or disability insurance [21], a gap which may have significant implications. In addition, once genetic information of any kind is available, many worry that such information might be used to the detriment of a child sometime in the course of his or her life should legislative protections be weakened. Though the level of risk introduced by such issues remains partially hypothetical, the risk being demonstrable only if they occur in the context of legal and policy development, it is critical to acknowledge these concerns.

Another important concern with PGx testing is how to proceed with secondary or ancillary genomic information. Ancillary information is defined as additional information pertaining to the predisposition to diseases, prognostic information, or information relevant to other classes of drugs for a disease that the individual is not currently seeking treatment [22]. Ancillary information may also have implications for family members when considering inherited variations. Some test results can also provide information on health events that will occur much later on in a person's life. For instance, testing for the apolipoprotein E genotype could guide warfarin dosing or statin selection, but may also inform individuals regarding their risk of disease, such as Alzheimer's disease [23]. Recommendations should be developed to help guide pediatricians on how best to disclose and manage this clinical information in children. It should be emphasized, however, that while PGx testing may provide secondary information, the primary PGx test should not be discriminatory; rather, the primary information should be used to improve drug therapy.

Despite the benefits of PGx testing in children, challenges remain for both patients and clinicians. For instance, a primary issue in the USA relates to reimbursement and associated healthcare costs. Because third-party payers may refuse to provide PGx testing, it might be available only to those who can afford the costs. The financial impact of the testing will require considerable further study, including cost analysis that attends to such variables as the cost of PGx testing compared with, for example, days in the hospital from neutropenia induced by inappropriately high doses of mercaptopurine. As PGx testing increases in children, clinicians and investigators must continue to explore all the risks and benefits related to pediatric PGx testing in order to inform policy-makers and guide further implementation in routine care and research. Even when patients are willing to accept risks for the sake of potential benefits, they may still be confronted with the additional burden of testing that does not remove or even impact the need to monitor drug safety and efficacy through pre-existing standard of care methods [24]. Other challenges include the lack of readiness of the healthcare delivery system for personalized medicine, the gap between the genomic medicine technology available and the health system knowledge regarding this technology [25], and the lack of site-based testing for quick test turnaround time, which can lead to treatment delays. Lastly, pediatricians remain mindful of the fact that genomic analysis performed for a child may have unforeseen implications for the individual once they reach adulthood.

Although PGx testing, which aims to improve drug safety or efficacy, is distinct from predictive genetic testing and mandatory newborn genetic screening, the experience we have gained with traditional genetic testing in children can be instructive. For example, the incorporation of PGx testing may involve a similar approach to that applied to other genetic tests, with integration into pediatric clinical care only after tests have been demonstrated to have analytic validity, clinical validity and clinical utility in adult studies and once evidence-based guidelines for test utilization have been developed [26]. Some find this level of caution and demonstrated certainty excessive, with the potential harm of delayed PGx benefits to children. In any case, the guiding aim of PGx is ultimately to optimize therapy, and to do so while decreasing unnecessary risk to children.

PGx testing in pediatric research

Without appropriate evidence, physicians often use products in children for unapproved indications (off-label) and with limited or no pediatric PK data, potentially exposing them unnecessarily to adverse drug effects [27]. This lack of pediatric-specific drug information and limited knowledge regarding PK/PD in children should facilitate further PGx research as the identification of individual genomic polymorphisms encoding key metabolic proteins can offer the opportunity to improve our current dosing strategies in children with a variety

of pediatric diseases. While a comprehensive overview of the ethical framework that guides all pediatric research lies beyond the scope of this article, the pivotal events and policy that have impacted the proper conduct of pediatric research as well as the general principles of bioethics most relevant to the introduction of pediatric PGx research will be reviewed here.

The overarching goal of the ethical decision-making process involved in all pediatric research includes three basic elements: informed consent; assent when appropriate; and full disclosure of information [28]. Informed consent or permission giving is challenging not only because these technologies are complex to explain, but also because they hold the potential for hidden future implications. The possibility of achieving meaningful informed consent can seem remote in these cases. Furthermore, as is often the case with advanced medical technologies, full disclosure of information regarding PGx testing requires the introduction of complex terminology. Thus, one important challenge for clinicians is to overcome this knowledge gap and ensure that patients and parents are informed with a language that serves to protect the child and is age-appropriate, whilst also being understandable to the parents, a goal which is not always easy to achieve.

The requirement to provide full disclosure of information stems from several events in the history of bioethics in the US. Specifically, significant ethical issues raised by the Tuskegee study led the US Congress in 1974 to form The National Commission for the Protection of Research Subjects of Biomedical and Behavioral Research [28]. This resulted in the *Belmont Report* [29], which outlined three fundamental principles as particularly important for research involving human subjects: respect for persons, beneficence, and justice [28]. The concept of respect for persons comprises the two principles that individuals be treated as autonomous agents and that those with less autonomy are entitled to added protections. This latter aspect of the concept is especially relevant in pediatric disciplines and is somewhat fluid in its definition owing to changes in the degree of autonomy held by pediatric patients as they approach adulthood. The National Commission's report, *Research Involving Children*, outlined specific criteria for the conduct of research in children including that the research conducted should be scientifically sound and significant; that when appropriate, studies are first conducted on animals and then adult humans; that risks are minimized using safe procedures; that provisions are in place to protect the privacy of children and their parents; and that permission from the parent and assent of the child be obtained [30].

In the context of complex pediatric research, especially for younger children, the process of 'consent' is generally conceived as a process of 'permission giving' in the best interest of the child [31]. In pediatrics, the issues are more complex because there is not a single level of developmental capacity, and irrespective of developmental capacity, there are important legal constraints on the manner in which children participate in medical or research decision-making, with some variation existing between states. One can identify at least three categories of minors with respect to their capacity to participate in treatment decisions: minors without the capacity to participate in the decision in any meaningful way; minors with a developing capacity to participate in decision-making; and minors such as mature minors who have the capacity to make most healthcare decisions. The second category is the one for which the concept of assent is most appropriate. Assent involves assessing a minor's understanding of the factors influencing their decision and obtaining the child's agreement, free of coercion, to participate in research [28]. However, in PGx research studies, as with other pediatric research, the requirement to seek assent from a child with developing capacity can be overridden if the child's participation in the research involves a prospect of benefit to the child such that the child's welfare would be significantly jeopardized by failing to participate, and the benefit in question cannot be obtained otherwise. For this reason, understanding when a child has the potential to benefit from a PGx trial and when

that potential is less certain is critical in determining when parental permission is sufficient for proceeding with the trial or intervention, and when the child's assent is required.

Because pediatric research involving PGx testing will inevitably involve children who do not have complete autonomy, and many of whom will not be capable of making their own decisions, testing raises ethical issues that are unique to the pediatric population. Many genomic medicine companies that provide PGx testing allow legal guardians to sign consent for their children [32]. The fact that the child recipient of the risk or benefit is often not the same person who makes the decisions must be taken into account when developing ethically optimal processes for decision-making in pediatrics. Parents make decisions for their child, but including children in the decision-making process is reasonable, and sometimes obligatory, if the child is developmentally mature and has been given the opportunity to consider all options. This enables the child to impact their parents' and caregivers' decision-making process in a developmentally appropriate way. That said, the minor providing assent may not be capable of understanding the information sufficiently to meaningfully participate in the process of decision-making. A child's capacity to meaningfully assess their involvement in research studies and understand what counts as their 'best interest' are issues that vary and depend on many factors, including age, developmental stage and past experience with medicine and research.

A central ethical concept that guides decision-making for pediatric research is risk assessment. In the course of developing ethical policies that are flexible enough to allow PGx research and advances that benefit children, while being restrictive enough to protect them, some uncertainty regarding risk will be inevitable. Parents can give permission for children to participate in studies that do not have the prospect of direct benefit only if the study carries no more than minimal risk or, in the case of a study that contributes to general knowledge related to children who suffer from the same condition being addressed in the study, a minor increment over minimal risk [28]. What is minimal risk? The *Belmont Report* defined minimal risk as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children" [28,29]. However, risks encountered in the course of 'daily life' vary widely among children. With relatively new technologies, such as PGx, where the potential benefits and risks are still being tested, both in terms of clinical risks and benefits, and in terms of social and legal ramifications of the technologies, assessment and clear articulation of risks and benefits are especially challenging.

Given the uncertainty regarding the risks of genomic testing for individuals, family members and the larger society, permission giving related to PGx testing in pediatrics must begin with consideration of the potential benefits of genomic analysis in guiding drug dosing. In addition, in order for parents to adequately assess whether a given test is in the 'best interest' of their child, the clinician must explain the disease/drug, the proposed test and intervention and the likelihood that a child will receive benefit from testing. As PGx advances, the potential benefits to individual children will become more apparent; however, these benefits may not be easy to define. In cases where PGx testing allows rational adaptation of therapies to a particular child in such a way that therapeutic efficacy is retained while risks from the intervention are decreased, the benefit is easy to define. Such benefits will accrue as experience is gained with PGx testing and techniques are refined. That said, any discipline that is relatively young will often advance in clinical trials that may or may not hold the prospect of direct benefit to their participants. One of the challenges with PGx research in areas where we truly do not know the implications of testing, is how to define direct benefit early in the use of a new technology. Should research only be permissible when there is a clear prospect of direct benefit to the child and less than a minimal risk? How is 'direct benefit' defined in cases where a genomic variant may have prognostic implications but no

clear therapeutic solution? It is not always clear if subjects should be informed of research results of genetic analysis [33,34]. Should the decision to inform children/parents of test results depend on the risk–benefit relationship? Risks and benefits are never stable, but rather change with every advance in knowledge, meaning that the ethical dimensions of PGx will require frequent re-evaluation.

One last aspect of PGx testing in research relates to its impacts on the pediatric drug-development process. An improved understanding of the impact of developmental changes and PGx on drug disposition and effect early in the drug-development process could help guide proper dosing recommendations throughout childhood [6]. One example is how the characterization of TPMT activity on drug tolerability led to changes in labeling for mercaptopurine, which now includes TPMT testing in dosing guidelines [35]. Therefore, other potential ethical issues relate to the responsibility of pharmaceutical companies to conduct pediatric PGx research. For instance, if a drug is effective in only a small fraction of the population owing to PGx variability, this information needs to be available to patients and providers. For this reason, pharmaceutical companies are being asked to include genetic studies during drug development [35], which may impact drug labeling. Otherwise, drug companies may profit by dispensing the drug to large numbers of patients in whom no benefit may be seen [35]. This emphasizes a concern that PGx testing may place patients and pharmaceutical companies at odds with one another since such testing might narrow the number of potential users of a drug based on PGx, while the drug company wants to maximize the number of users. Furthermore, if PGx testing reliably limits the number of people who might rationally benefit from a drug, the drug companies might be less inclined to invest in the production of such a drug. A further moral challenge which is of substantial ethical concern to society, is the weight of such financial aspects of healthcare compared with the potential benefit to children, issues that have come to the forefront in recent public debates and discussions of US healthcare reform.

Future perspective

While the full therapeutic potential of PGx for children remains to be seen, it is reasonable to expect that PGx testing will become an important part of both standard pediatric clinical care and research studies in the future. A clear consensus on the specific use of PGx testing in children remains to be established. The incorporation of PGx testing into pediatric treatment strategies will need to be extensively validated for each therapeutic application, and for individual racial and ethnic groups to ensure the accurate assessment of genetic determinants of drug response [3], and to guide translation into pediatric care. Guidelines will not be static and will be increasingly derived from an improved knowledge of the actual predictability of PGx test results and the successful incorporation into care. In the process of achieving these advances, there will continue to be areas of uncertainty in which ethical, policy and legislative issues will have important implications for how clinical studies and trials are constructed and informed consent, permission giving and assent are structured in light of risks and benefits. As PGx testing evolves in pediatrics, it is critical that pediatricians and investigators understand the facilitators and barriers to testing to enable the development of appropriate policy and clinical resolutions, to address the concerns of stakeholders and to enable the field to move forward. Ongoing multidisciplinary discussions, including input from scholars in ethics and law, are warranted. Lastly, we can expect that these ethical considerations will need to be re-evaluated as novel issues arise from the discovery of new genotype–drug response associations and new technologies and demand a case-by-case approach. It will remain an active topic of discussion especially as US healthcare reform legislation continues to evolve. The growing availability of PGx testing, the establishment of pediatric DNA research databases and the unforeseen future

implications of identifying genomic variability in individual children makes the ethical issues surrounding genome-based testing of critical importance for children today.

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Executive summary

- The benefits of pharmacogenomic (PGx) testing in children are likely to continue to accrue as experience is gained and the techniques are refined.
- Before the pediatric community considers incorporating genomic analysis into standard medical practice or research, all potential risks and benefits need to be considered.
- There is a moral dimension of reducing risks to children through the application of PGx testing.
- As technology evolves, multidisciplinary policy discussions specific to pediatric PGx testing will be critical to ensure the ongoing protection of children.
- The ethical dimensions of PGx testing in children will require frequent re-evaluation.