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REVIEW

Pharmacogenomic Testing In Pediatrics: Navigating The Ethical, Social, And Legal Challenges

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Abstract: For the past several years, the implementation of pharmacogenetic (PGx) testing has become widespread in several centers and clinical practice settings. PGx testing may be ordered at the point-of-care when treatment is needed or in advance of treatment for future use. The potential benefits of PGx testing are not limited to adult patients, as children are increasingly using medications more often and at earlier ages. This review provides some background on the use of PGx testing in children as well as mothers (prenatally and post-natally) and discusses the challenges, benefits, and the ethical, legal, and social implications of providing PGx testing to children.

Keywords: pharmacogenetic testing, education, benefit, risk, consent, children, maternal health

Introduction

The expanded interest and implementation of pharmacogenetic (PGx) testing have raised both challenges and excitement alike. As with some other testing applications in personalized or precision medicine, PGx testing can be used for patients and healthy individuals. The scope of testing has evolved from single gene to large gene panels. As with any new clinical application, the development of the clinical delivery infrastructure, education, and clinical decision support of providers and patients, and evidence basis are critical for successful implementation and utilization. In the paper, the ethical, legal, and social issues associated with PGx testing for children are considered in light of the scientific and clinical evidence, particularly during pregnancy and for newborns.

Overview Of PGx Testing

PGx testing involves the analysis of variants of genes associated with drug metabolism and transport or medication targets. The knowledge of potential differences in drug metabolism impacted by genetic variants can inform drug selection or dosing over a patient's lifetime since the results will not change with age and many of the variants occur in genes involved in the pathways for multiple medications. In particular, the genes encoding liver enzymes in the cytochrome P450 family, including CYP2D6 and CYP2C19, are involved in the metabolism of a wide range of commonly used drugs and are highly polymorphic. Genetic variants impact enzyme activity, resulting in phenotypes defined as ultra-rapid, normal (extensive), intermediate, or poor metabolizer. Thus, knowledge of a patient's PGx genotype in combination with other clinical information can inform appropriate medication and dosing decisions.[1]

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Some of the early successes with PGx were developed in children, such as with the TPMT gene and acute lymphoblastic leukemia.[2–4] The spectrum of potential applications of PGx testing in children ranges from post-transplant[5] to pain management[6] to psychiatric illness.[7–11] Ongoing trials of PGx in pediatric populations continue to gather evidence of clinical utility.[12–14] There are a wide range of clinical PGx tests currently available,[15] typically including multiple genes (multi-gene panels), though not specific to age group but rather medication class or disease.

PGx testing can either be ordered at the point-of-care (at the time a drug is needed) or preemptively. There is an ongoing debate about the use of preemptive testing and clinical utility.[16,17] Clinical benefits will only be accrued if a therapeutic need arises for a medication known to be impacted by PGx variant and if the prescribing decision was informed by the test results (to increase likelihood of therapeutic response or reduce likelihood of an adverse response). Thus, it is likely that not all of the information from a multi-gene panel test will be of benefit to the patient. However, it may be the same or costlier to order a PGx test for a single gene as a panel test since the addition of more genes may not substantially change the effort or cost of testing (economies of scale). Another consideration for ordering PGx testing at the point of care (i.e., when treatment is needed) is the delay in treatment while testing is being completed. Many labs offer a short turnaround time (48 hrs), but that still may not be quick enough for some clinical needs.

It is unclear what the attributable fraction of genetics is to non-response or an adverse response. Clearly, multiple genes encode the many proteins involved in the multiple pathways from drug absorption to drug excretion, some of which have yet to be identified. Furthermore, other factors such as the gut microbiome,[18–20] diet, age, concurrent medication use, and co-morbidities all contribute to drug response.[21] Thus, for such a complex phenotype as drug response is, it is likely that a single gene only accounts for a small proportion of variability observed in drug response, except in rare cases that mirror a Mendelian disease.

Medication Use In Children

Data from analysis of 2013–14 data from the National Health and Nutrition Examination Survey (NHANES) demonstrate medication use throughout childhood, with about 20% of the children having had at least one prescription medication in the past year.[22] Adolescents (13–19 years) had the highest medication use (23%) and infants/toddlers (0–5 years) had the lowest (15%).[22] Use of prescription medications in children has declined from 25% in 1999–2002 to 22% in 2011–2014.[23] The most commonly prescribed groups of medications were respiratory agents (i.e., bronchodilators), followed by psychotherapeutic agents and antidepressants.[22]

Adverse drug response (ADR) in children is a major concern,[24] due in part to drug use based on limited evidence and the complexity of pharmacokinetic and pharmacodynamic changes that occur during development. It has been estimated that about 8% of the children on medications are at risk for drug–drug interactions.[22] Emergency room visits for ADRs in children are primarily due to overdoses (45%), but 13% were due to adverse effects.[25] About half of these visits were in children between one and four years of age.[25] Children and adolescents may have greater risk of ADRs related to psychotropic medications compared to adult patients.[26]

Prenatal And Newborn Period

Newborns undergo a battery of tests including those for inherited genetic diseases. Called newborn screening, testing for a suite of inherited conditions can identify affected newborns that, with early intervention, the condition can be prevented or outcomes substantially improved.[27] These tests are performed by state public health laboratories, and the number and type of diseases tested vary from state to state. PGx variants are not currently included in any state newborn screening panels. The primary criterion to expand a newborn screening or add a new disease to the screening panel is clinical utility, and specifically, demonstration of the clinical benefit of an early diagnosis.

Newborns may require treatment or be exposed to medications through maternal use during pregnancy and/or the post-partum period through breastmilk.[28] Maternal use of medications during pregnancy varies by country, ranging from 28% in Australia,[29] 97% in the US,[30] about 60% in Canada,[31,32] 79% in the Netherlands,[33] 85% in Scotland,[34] and 95% in France.[35] Canadian data show an increase in maternal medication use over the past decade, with 10% more women prescribed medications during pregnancy between 2002 and 2011.[36] Common medication classes used during pregnancy include antibiotics, anti-emetics, oral contraceptives, asthma drugs, vitamins, and antidepressants.[31] In addition, the burgeoning problem of opioid dependence and substance abuse during pregnancy presents a substantial risk for neonatal abstinence syndrome (NAS), fetal alcohol syndrome, low birth weight, and other conditions.[37,38] Treatment with methadone or buprenorphine do not appear to increase risks to fetal development.[39–41]

There is also a wide range in estimates regarding maternal medication use during the post-partum period, from 34% to 100%,[42] with as many as three to four medications used during breast-feeding.[43] Many women request pain medications, particularly in the first-week postpartum for discomfort due to episiotomy, perineal laceration, uterine involution from vaginal delivery, or a cesarean section. The most commonly prescribed drug classes are oral analgesics, antibiotics, and vitamins during the postpartum period.[44] Mothers and providers may be uncertain about medication use due to concerns about the adverse impact on the newborn's health; decisions not to initiate or stop treatment may pose risks to the mother's health.[45]

PGx variants can impact both safety and efficacy of medications for the mother's health as well as fetus/newborn's health.[46,47] In addition, physiological changes associated with pregnancy can alter pharmacokinetic states,[48–50] including for the cytochrome P450 or CYP genes.[51–55] Thus, the combined effect of pregnancy-related changes and genetic variation could potentially result in unpredictable activity levels of key proteins associated with drug response.

In the fetus/newborn, the metabolic pathways are subject to developmental changes, and thus, enzyme activity levels are in flux. A number of medications reportedly used during and after pregnancy are known to be impacted by PGx variants, including medications for nausea,[56] prevention of preterm labor,[57] opiate maintenance such as methadone,[39] and pain.[58–60] Predictive models of transfer into human milk thus far have not accounted for maternal PGx variants.[28,61,62] Drug toxicity is likely to be more common during the newborn period due to slow metabolism and elimination by the infant.[63] Although all medications can enter breast-milk, serum concentration will vary due to characteristics of the drug.[64] For example, psychotropic medications are shown to be present at low levels in breastmilk and no data have indicated harm to the infant.[65] Low molecular weight and lipophilic medications can easily move through the lipid membranes of cells, and therefore, the concentration of these types of medications in breast-milk is higher than other types of drugs.[63]

Harms to the newborn associated with exposure through breast milk have been reported infrequently.[66] One example of the adverse impact of PGx and medication exposure during nursing is with the enzyme CYP2D6 enzyme, which converts codeine to the active metabolite morphine. The prevalence of CYP2D6 genetic variations linked to ultra-rapid metabolism ranges from 1 to 28 per 100 individuals, varying between racial/ethnic groups.[67] Thus, a nursing mother who is an ultra-rapid metabolizer may expose the infant to toxic levels of the active morphine metabolite.[68] The use of codeine for pain relief during the post-partum period has decreased,[36] likely due in part to knowledge of the impact of CYP2D6 variants on drug metabolism and the reported newborn deaths associated with maternal codeine use during breast-feeding and PGx variants,[69,70] and the subsequent US Food and Drug Administration warnings.[71]

In addition to PGx variations, there are several other factors that impact drug response in children, which can affect dosing and exposure levels.[72–75] One of the primary challenges to the use and interpretation of PGx testing in children is the developmental changes in gene expression.[76–80] Within the span of a few weeks to months after birth, the levels of drug absorption, transport, and metabolism alter significantly.[81] Further complicating treatment decisions and prediction of the impact of PGx variants on drug response, physical changes (body weight, height) and environmental factors, such as maternal smoking, and the child's diet, polypharmacy, and co-morbidities can affect drug response.[24,82–85] Prior medication use also may impact expression of drug metabolism enzymes through epigenetic modifications.[86] Given the multitude of factors impacting drug response and ontological fluctuations, it may be helpful to perform both PGx testing (DNA-based) and pharmacometabolomic analysis to generate a more comprehensive dataset for drug response predictions.[87,88]

PGx Programs In Children

The implementation of PGx testing into practice requires a multi-faceted approach and dedicated delivery team.[89,90] There are several ongoing clinical PGx programs in the US, mostly at academic medical centers, in both inpatient and outpatient settings.[91–93] Some programs have also been implemented at community health centers.[94] PGx programs that are devoted exclusively to children include Medi-Map at the Inova Hospital Center in Fairfax, Virginia,[95] Cincinnati Children's Hospital Medical Center,[96] and St Jude Children's Hospital.[97] In addition, other programs are investigating the benefits and risks of implementing newborn sequencing programs, in affected infants in neonatal intensive care units (NICU)[98,99] and healthy newborns,[100] though PGx genes are not typically included (e.g., the BabySeq program reported including SLCO1B1, associated with response to statins[101]). PGx results may also be generated from whole exome or genome sequencing tests ordered for diagnostic purposes (a secondary finding).

Weighing The Benefits And Risks Of PGx Testing In Children

Much has been written regarding genetic testing in children in general.[102–111] However, fewer papers have been published specifically about the appropriateness of PGx testing in children.[76,112–114] Guidelines from professional organizations focus on the benefits of testing to the child[103,115] and support the use of PGx testing, particularly when the clinical utility has been demonstrated in pediatric studies.[102] For example, the American Academy of Pediatrics states "When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent".[115] PGx testing could be argued to straddle the definition of predictive testing and predispositional testing,[103] since with exposure to a specific medication, the phenotype may or may not manifest depending on the extent of the clinical and genetic heterogeneity (and in the absence of exposure to a specific medication therapeutic, the phenotype will not manifest). Post-ADR, PGx testing may be considered diagnostic.

Public attitudes toward PGx testing are generally positive, though familiarity with or awareness about testing has not been reported high.[116–118] In weighing the benefits and risks of PGx testing in children, a wide range of factors should be considered including test characteristics, benefit and risk to pregnant mothers, benefit and risk to the fetus/newborn/child, testing logistics including sample collection, storage and portability of test results in the medical record, access to testing, provider preparedness and clinical decision support, and patient education and informed consent. The testing scenarios – whether testing is medically necessary (at the point of care) versus optional/elective (preemptive testing) – will impact the balance of benefit and risk and decisions regarding the appropriateness of testing in children.

Benefit/Clinical Utility

Evidence supporting the use of widespread PGx testing of children has not been reported, but rather, reports of specific medications or classes have suggested some benefit of PGx testing for children.[119–123] If evidence continues to accumulate for different pediatric medications, it is likely that this will be used to support the use of preemptive PGx testing in children along with data documenting the increasing use of medications in children. Thus, currently, the benefit(s) of PGx testing in children with respect to specific medications in need are more straightforward than preemptive testing of healthy children since the time to benefit and the benefit for the medications to be prescribed are not known. To date, no studies have demonstrated benefits of PGx testing of the mother prior to or early in pregnancy, but such knowledge may inform medication use during pregnancy. Although the occurrence of severe infant drug toxicity due to transfer of drug metabolites via breast milk appears limited,[66] PGx testing to prevent even these uncommon events and alleviate maternal concerns of newborn drug toxicity may be worthwhile given the long-term benefits of breast-feeding. In addition, maternal PGx status will also be useful during the post-natal period. However, the utility of this information may be limited without knowledge of the infant's PGx status and also due to limited lactation studies regarding drug concentration in human milk and milk-to-plasma concentrations.

In addition, psychologically, parents may benefit from reduced anxiety regarding risk of ADRs and efficacy of treatment plans for their child and increase compliance with the prescribed regimen, thereby improving likelihood of desired health outcomes.

Risks

There are currently 261 drugs listed on the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling); 136 (52%) are approved for pediatric use.[124] However, an earlier study reported a small proportion of the 65 of 150 with medications approved for pediatric use between 1945 and 2014 and that included with PGx information in the approved drug labeling was based on data collected through pediatric PGx studies (9 of 65).[125] To further demonstrate the limited availability of data from pediatric PGx studies, a recent search (conducted 9 June 2019) of the US National Library of Medicine's PubMed database shows that the majority of PGx clinical trials (1028/1297 or 79%) are conducted in adults compared to children.

Therefore, the largest risk is the inability to interpret PGx results given the limited amount of evidence to interpret the clinical significance on risk of ADR or likelihood of response. Similarly, for some medications, there are less data regarding pharmacodynamic and pharmacokinetic properties in children compared to adults. The interpretation of PGx data may be more challenging in children due to developmental changes in gene expression and physiological changes that impact other drug absorption, transport, and excretion children.[126] Gene expression or enzyme activity assays may provide more additional insight to inform treatment rather than DNA-based testing. In addition, much of the research conducted on PGx has been with individuals of European ancestry, and therefore, there are limited data for minority populations,[127] though it has been demonstrated there are differences in allelic prevalence between groups.[128] As a result, the clinical utility of PGx testing may be lower in minority populations as the prevalence and clinical significance of PGx variants are still being investigated in these groups.[129–133] Depending on the type of testing platform used or choice of variants to include, some rare variants or variants that are more prevalent in certain populations may not be captured or included in a clinical PGx test. In addition, although some medications are used in both pediatric and adult populations, evidence of PGx testing benefits generated in an adult study population may not extrapolate to a pediatric and caution should be taken to develop a pediatric PGx program based on adult findings.[11] With the rapidly changing test technologies, the scope of testing may not be limited in the future.

Sample collection may also be a concern for children. Parents may not consent to blood draws for their children and/or providers may not recommend testing because of the blood draw.[96] Many labs now offer testing on buccal swab or saliva samples. At this time, prenatal PGx testing of drug metabolism genes would likely require a fetal specimen from chorionic villus sampling or amniocentesis. Given the risks of these invasive procedures, prenatal PGx testing should be limited unless there are known serious adverse consequences associated with maternal medication use. However, with the rapid expansion of non-invasive, cell-free fetal DNA testing,[134] single gene or multiple gene PGx panel testing may be possible in the near future. Some data have indicated that maternal medication use may impact the quantity of cell-free fetal DNA available.[135]

Children and family members may be at risk of psychological harms resulting from learning of a PGx variant that can affect how the child responds to medication. Parents may experience anxiety, stress, and feelings of hopelessness if their child is found to have an extreme phenotype (e.g., ultra-rapid or poor metabolizer) or not have the genetic variation indicated for an available medication. Heightened concern for adverse exposure could lead to poor adherence or avoidance of medical care in extreme situations. Additionally, misconstrued fears that the child will not benefit from medications may also affect parents' behavior toward their child, treating them as highly vulnerable or at risk and potentially limiting interactions or participation in childhood activities to reduce the likelihood of illnesses that require treatment.[136] Since the effects of a PGx variant may never manifest without exposure to certain drugs, curtailing childhood activities may cause more harm than benefit. Furthermore, feelings of stigmatization and anxiety may be experienced by family members and the child, even though the phenotype may never manifest due to other clinical and genetic factors (some unknown) or lack of exposure to medications impacted by that genetic factor. It is important to note that no evidence to date has reported on any of these potential risks with PGx testing in either pediatric or adult populations. Positive PGx results will also have implications for siblings and parents, potentially leading to PGx testing of family members.

In the absence of immediate benefit, some may argue that preemptive testing should not be ordered for healthy children (in line with recommendations for predictive testing[103]). Alternatively, if treatment is not needed, preemptive PGx testing could be deferred until the child is of an age and maturity level that they may participate in decisions regarding testing.[102] However, if treatment is needed and impacted by a PGx variant, it could be worthwhile to order a panel test that would provide benefit both for the immediate and long-term health of the child.

Another risk that has been raised with PGx testing is the association of some genes with unrelated disease risk or phenotype. For example, the ApoE4 gene is associated both with cholesterol metabolism and response to statin medications as well as Alzheimer disease.[137,138] The American Academy of Pediatrics states that "If a pharmacogenetic test result carries implications beyond drug targeting or dose-responsiveness, the broader implications should be discussed before testing",[115] echoed by the American Academy of Pediatrics and American College of Medical Genetics and Genomics joint statement.[103] The potential for genetic discrimination also exists, although discriminatory actions by employers and health insurers are prohibited by the federal Genetic Information Non-Discrimination Act (GINA).

Informed Consent And Patient Education

Given the novelty of PGx testing, informed consent or physician assent/acknowledgment that the parents have provided consent for testing is typically required.[139] For adolescents and young adults, their preferences regarding testing may not always be supported.[140] Thus, some discussion and educational resources should be available to parents to promote informed decision-making as well as for older children that have reached a level of maturity to provide assent. For example, Cincinnati Children's Hospital has developed patient education sheets for each test offered (www.cinncinnatichildrens.org/gpsinfo). Other groups have developed videos to convey some of the complex scientific and medical concepts.[141] In particular, given the multitude of factors that can impact drug response, parents and children should understand that PGx testing will provide some insight about drug response, but that the results should not be considered absolute in most cases. Furthermore, the ongoing research may alter the interpretation of PGx results. If considering preemptive testing, testing could be delayed until late adolescence or adulthood when the patient can provide assent or full consent, respectively. Various educational tools used for genetic testing could be adapted for PGx testing to promote parental awareness and decision-making.[142]

Provider Support

Several studies have reported limited knowledge of providers regarding precision medicine and PGx, though none have specifically evaluated knowledge of obstetricians or pediatricians.[143–150] While some literature indicates inclusion of precision medicine and PGx in medical curricula,[151–153] it is unclear how consistent or to what depth this subject is taught. In some cases, patients may share PGx results ordered by specialists with their general pediatrician, who may not be prepared to integrate the findings into practice, and online resources about PGx are not easily located through search queries.[154] Thus, to address knowledge gaps and acknowledge varied learning styles, multiple modes of information delivery are likely needed to increase providers' knowledge and comfort in delivering PGx testing, such as immersive learning opportunities and traditional continuing medical education (e.g., workshops, online modules, print).[155,156]

While there are a number of comprehensive PGx resources, these may be overly technical for general practitioners.[157–160] At the point-of-care, clinical decision supports have been developed at several medical centers to inform providers about the availability of PGx testing for certain drugs that are prescribed or alert providers of the patient's test result if testing has already been performed.[96,161–166] PGx testing reports can also be a source of information, including treatment recommendations based on genotype.[167]

Beyond physicians, nurses and pharmacists can also play important roles in the delivery of PGx testing, patient education, and insuring appropriate use of results. Nursing and pharmacy educators and schools have recognized training needs and are working towards integrating content into curricula and other learning opportunities.[168–171] Pediatric pharmacists can help integrate PGx results into therapeutic decision-making and work with both providers and families.[172] In some places, clinical PGx consultation services have been established.[96,173] It is unlikely that genetic counselors will play a central role in the delivery of PGx testing given the limited number of counselors available and the different clinical settings in which they are traditionally accessible. However, counselors will likely encounter PGx results in sequencing and should be prepared to discuss these with patients and patients with complex results should be referred for counseling.[174]

Storage And Portability Of Results

Particularly for children and the anticipated recurrence of the use of PGx information throughout their life, the storage and portability of PGx results are critical. The integration of PGx information into electronic health records has been investigated over the past several years and several groups have developed standardized nomenclature[175,176] and test results reporting. As the child reaches adulthood, it will be critical to insure that the PGx results are transferred to the adult care providers.

Regulation And Reimbursement

While the evidence regarding drug safety and efficacy in children has increased due to more regulatory requirements and incentives, there are still challenges in conducting and completing pediatric trials.[177,178] The oversight of clinical laboratory testing has also been the subject of much debate and scrutiny over the past several decades. Many genetic tests, including PGx testing, are considered a 'laboratory-developed test' (LDT) and at this time, the FDA typically does not enforce premarket review[179] and only a few test manufacturers or laboratories of proprietary tests have obtained FDA approval for PGx testing. In addition, the direct-to-consumer company 23andMe received FDA approval in 2018 to market a multi-gene PGx test panel,[180] though this has been available in the UK.[181] However, the agency is taking more interest in the clinical validity of PGx testing and potential risk for harm through issuance of safety alerts and warning letters to a clinical laboratory. In November 2018, the agency released a safety alert to patients about PGx testing and the limited evidence basis, urging patients not to make any changes to their medications without consulting a health provider.[182] In April 2019, the FDA issued a warning letter to Inova Genomics Laboratory, which was providing PGx testing to newborns among other PGx tests.[183] The agency raised concern about the evidence of clinical validity and potential harms to patients if results are used to inform treatment decisions. All testing laboratories based in the US must comply with the Clinical Laboratory Improvement Amendments (CLIA) that require documentation of analytical validity, quality controls and assurance, personnel qualification and some evidence of clinical validity.

At this time, in the US, reimbursement for PGx testing is inconsistent and guided by the availability of clinical trials data and clinical guidelines, which are still lacking for most tests.[184] A few cost-effectiveness studies have been performed for PGx testing for children[185] and mothers,[186] although the majority have focused on adult applications. There are no national coverage decisions for PGx testing in the US. Preemptive PGx testing is often not covered by insurers[187] and, therefore, is an out-of-pocket expense, resulting in limited access and disparities. Patients have expressed willingness-to-pay for testing to reduce risk of serious adverse drug responses, though the amount was impacted by their overall interest in testing.[118,188–190]

Conclusion

The short and long-term benefits to children (and potentially expectant mothers), the growing body of evidence, and the declining costs of testing technologies for multiple genes should positively influence uptake of (or utilization) testing. However, the clinical utility of PGx results is likely to remain limited until more pediatric PGx trials are conducted and a greater understanding of the multiple factors that can impact drug response is attained, especially in younger children who have not attained stable expression of many genes important to drug metabolism and transport. PGx test results may inform the safe use of medication during pregnancy and post-partum, and increase mothers' confidence that breast-feeding is safe for their infant. As PGx testing is still novel to many providers and patients, more efforts are needed to improve awareness about testing, promote informed decision-making, and insure appropriate utilization and access.

Disclosure

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