Considerations of pharmacogenetic testing in children

“With minimal risks of pharmacogenetic testing and potential benefits, pharmacogenetic availability can help reduce pediatric adverse events and treatment failure.”

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Approximately 60% of US children currently take a prescribed medication [1]. Medication errors and biological differences in children increase the risk of adverse events (ADRs). Knowledge of pharmacogenetic (PGx) variants that impact ADR risk or drug efficacy may reduce these events by informing therapeutic decision-making and in turn reduce healthcare costs associated with suboptimal outcomes. Thus, the pediatric population may greatly benefit from pre-emptive PGx testing. We explore advantages and risks of pre-emptive PGx testing in newborns.

Drug response is a complex phenotype that warrants continued study to understand drug–drug, drug–gene and interactions with other clinical biomarkers. For example, recent work indicates that a child’s PGx profile and mother’s smoking habits contribute to response to methylphenidate for attention deficit hyperactivity disorder [2]. However, randomized clinical trials are unlikely to provide evidence of clinical utility for PGx; therefore, ‘practical trials’ may be an acceptable alternative, particularly for children and the elderly, who are under-represented in drug studies [3]. The impact of PGx variants for medications used in pediatric populations has been reviewed elsewhere [4], but includes codeine, atomoxetine, warfarin and voriconazole.

The advantages of providing PGx testing pre-emptively compared with the point-of-care are unclear [5]. Several hospitals and clinics are exploring implementation of prospective PGx testing [6]. St. Jude Children’s

Research Hospital (TN, USA) provides a PGx panel for all children admitted to their hospital, and Vanderbilt University tests all adult patients who consent to participate in their hospital-based biobank program for several PGx genes. The University of Maryland (MD, USA) and University of Florida (FL, USA) also offer PGx testing for adults undergoing catheterization.

Pre-emptive PGx testing in children

Current policies recommend that genetic testing of children only be considered if there is benefit to the child [7,8]. To respect autonomy, genetic testing of no benefit during childhood should be deferred until the child reaches legal age or attains maturity to assent. However, recent initiatives such as BabySeq (sequencing of healthy newborns) and professional recommendations to return secondary, disease-related genetic risk to all patients who undergo clinical sequencing [9] contradict these testing criteria.

Based on recommendations, PGx testing should only be ordered if useful during childhood. Imminent benefit or clinical utility of pre-emptive PGx testing has been exemplified by analyses indicating that over 90% of adult patients carry at least one PGx [10] and other groups have found that a substantial proportion of adult patients will be prescribed a medication with a known PGx interaction [11] and could benefit from pre-emptive testing.

While no similar analysis is yet available for pediatric populations, we find that 63 of

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144 medications included in the US FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling [12] are approved for pediatric uses. Sing *et al.* [13] identified eight drugs included in the British National Formulary for Children that are also listed in the FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling. One of those drugs is codeine, a drug associated with several deaths in children found to be *CYP2D6* ultra-rapid or extensive metabolizers [14]. This triggered a black-box drug label warning advising against pediatric codeine use following tonsillectomy and/or adenoidectomy. Based on the prevalence of ultra-rapid and poor metabolizers in the USA, and the estimated number of patients prescribed codeine, more than 300,000 pediatric patients each year may be at risk for drug toxicity or ineffective treatment [15].

Furthermore, pre-emptive PGx may be particularly beneficial for acute care. In 2013, 18% of children (0–18 years) and 24% of children under the age of 6 years sought care at an emergency department at least once [16]. Pre-emptive PGx testing could prevent treatment delay in these cases.

Risks & limitations of pre-emptive PGx testing

Risks and limitations of pre-emptive testing must be addressed to ensure benefit to pediatric patients. Like all genetic tests, PGx testing may have familial implications such as revealing non-paternity. However, family members may benefit from learning a child's PGx results or be motivated to seek testing themselves. For example, codeine is prescribed to about 10% of postpartum mothers for pain management [17] and knowledge of the newborn's and mother's *CYP2D6* status can inform treatment decisions.

Another risk to consider is the potential for psychosocial harms. Presumably, there will be no benefit and no harm in the absence of a drug exposure, similar to the evidence of minimal harms of carrier screening that only provides benefit if two carriers decide to have children. Some have suggested that PGx test-

ing raises fewer concerns than disease susceptibility testing [18].

Informational needs for a newborn PGx program

PGx testing at a young age will require educational resources and applications to promote result portability between providers and in transition to adult care. Parents have expressed interest in PGx testing but need educational resources to promote informed decision-making [19]. This will enable understanding of potential lifetime benefits and promote result sharing with providers. Resources such as PharmGKB, the FDA's PGx Table, and commercial laboratories will support widespread PGx use. Informed consent may also address informational needs and support understanding. Similarly, clinical decision tools are needed to facilitate the use of PGx results [20]. Clinical utility may be realized and increased portability of results may be achieved by integrating results from pre-emptive PGx testing into the EHR.

Conclusion

Children account for a substantial proportion of drug expenditures and related care. With minimal risks of PGx testing and potential benefits, PGx availability can help reduce pediatric ADRs and treatment failure. However, as the level of evidence has not reached a threshold for inclusion in routine newborn testing, the option for PGx testing should be discussed with parents, informational tools should be made available, and written consent should be obtained.

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