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Pharmacogenomic testing: Enhancing personalized medication use for patients.

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Adverse drug reactions (ADRs) are an important clinical problem in modern medicine, sometimes resulting in debilitating and lethal consequences for patients. The burden of ADRs in Canada is underemphasized owing to most ADRs going unreported.[1] However, a 1998 study suggests that ADRs are between the fourth and sixth leading cause of death of hospitalized patients in the United States.[2] Genomic factors play a key role in drug response and contribute substantially to the risk of drug-induced harm. Pharmacogenomics—the determination of the genomic predisposition to a certain response to medication—is a key component in understanding how to use medication in a safer and more effective manner. Pharmacogenomic testing allows for the detection of genomic factors linked to differences in drug response before treatment, ensuring that the benefit of a medication is maximized without the unintended consequences of ADRs. While medication use in clinical practice is already personalized by considering clinical factors that contribute to variable drug responses, pharmacogenomic testing can explain why some patients experience unusual responses to medication and further enhances personalized medication use.

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS),[3] a group focused on incorporating pharmacogenomics into clinical practice, has identified genomic factors responsible for a number of ADRs, including but not limited to codeine-induced death in breastfed infants,[4,5] cisplatin-induced ototoxicity,[6,7] and anthracycline-induced cardiotoxicity.[8-10] To address these serious ADRs, pharmacogenomic tests have been developed to assess a given patient's risk of experiencing an ADR. Clinical practice guidelines have also been created to help clinicians develop better personalized therapy plans based on genomic risk.[11-13] As more genomic risk factors for ADRs are identified, pharmacogenomic testing can be optimized to provide better risk-benefit profiling for each patient.

The CPNDS and childhood cancer treatment

The CPNDS has worked to incorporate pharmacogenomic testing into childhood cancer treatment decisions to reduce the risk of developing ADRs such as anthracycline-induced cardiotoxicity. Anthracyclines, the most frequently used chemotherapeutic drug in Canada, can cause cardiac dysfunction leading to congestive heart failure in up to 20% of treated children.[13] Based on clinical factors alone, the predicted risk of experiencing this cardiac dysfunction (cardiotoxicity) generally falls in the range of a few percent to an almost 100% chance. Incorporating pharmacogenomic testing helps to better determine a patient's specific risk before treatment initiation. For instance, in 2 patients with the same diagnosis, one patient's genomic risk of serious cardiotoxicity might be below 20%, whereas the second patient's risk might be greater than 80%. Importantly, this ability to quantify pharmacogenomic risk provides a vehicle for patients and their families to dictate the level of risk they are comfortable with, in the paradigm of benefit-risk decision making in their cancer treatment. This exemplifies patient-oriented care, where an estimated risk of serious drug-induced cardiotoxicity of less than 20% might be acceptable given the considerable mortality that accompanies many cancer diagnoses. However, a predicted risk of drug-induced harm of more than 80% should require discussion of viable alternatives and pre-emptive preventive therapy. Together, this allows for better profiling for each patient to make informed treatment decisions.

Changes to drug labels

The CPNDS is not the only group focused on finding drug safety solutions through pharmacogenomics. Both the US Clinical Pharmacogenetics Implementation Consortium[14] and the Dutch Pharmacogenetics Working Group[15] also promote the use of pharmacogenomic information to enhance clinical decision making. The CPNDS found that the use of codeine for postpartum pain management in mothers with an extra copy of the cytochrome P450 2D6 isozyme gene *(CYP2D6)* can be lethal for their breastfed infants.[5] These findings have led to warnings and drug label changes by Health Canada, the US Food and Drug Administration (FDA), the European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency in Japan. Importantly, this research led to changes in the use of codeine worldwide.[11,15,16]

Pharmacogenomic information to inform clinical practice is included on more than 750 drug labels worldwide (**https://www.pharmgkb.org/labels**), a number that continues to rise as more pharmacogenomic discoveries are made. Currently, the FDA provides pharmacogenomic information on 335 drug labels, while Health Canada has been slower to incorporate such information (included in 105 labels). Given that drugs are used across all medical disciplines, pharmacogenomics should be the highest of priorities in both patient

care advancement and federal investment in research. To this end, the FDA facilitates the application of pharmacogenomics in clinical practice through initiatives driven by the Genomics and Targeted Therapy Group. A similar approach could be adopted by Health Canada as a first step toward improving awareness of pharmacogenomic information to guide prescribing decisions for Canadian physicians.

Integrating pharmacogenomic testing into clinical practice

Clinicians who want to integrate pharmacogenomic testing into their practices face considerable challenges that limit access. We propose an approach where pharmacogenomic testing is conducted only when a particular drug is being considered for treatment. The inclusion of only pharmacogenomic variants with clinical relevance, such as those appearing on drug labels or in pharmacogenomic clinical practice guidelines, or those replicated in at least 3 independent populations with strong associations (ie, odds ratios ≥3), allows for immediate and evidence-based application to prescribing decisions. Another possible avenue to improve accessibility is a screening approach where comprehensive pharmacogenomic information is collected and readily available for future prescribing decisions. This is an attractive strategy given the ever increasing affordability of genetic testing, and likely represents the future of pharmacogenomic testing,[17] but has obstacles for successful implementation. A pharmacogenomic screening approach must adhere to criteria outlined by Wilson and Jungner[18] that have been adapted to guide genomic screening approaches,[19] with particular emphasis placed on providing strong evidence for improved patient outcomes and cost effectiveness through formal program evaluations. Furthermore, deciding which variants should be reported and maintaining an updated list of variants with clinical relevance will require ongoing resources and management of the genomic data collected from screening.

Limitations of the health care system

Perceived resource constraints within the Canadian health care system might threaten adoption of pharmacogenomic testing. We therefore propose prioritizing serious ADRs where delays in access to tests put patients at risk of devastating consequences that also represent substantial cost burdens on the health care system. Pharmacogenomic testing for serious ADRs also holds the most promise for cost effectiveness. We have shown that cost savings associated with the prevention of one such ADR, anthracycline-induced cardiotoxicity, are predicted to outweigh the costs of testing.[20] Specifically, severe cases of anthracycline-induced cardiotoxicity cost more than $1 million owing to the need for heart transplants,[20] and incorporation of pharmacogenomic testing is estimated to save $495 per patient, representing a 5.7% reduction in costs associated with anthracycline-based cancer treatment.[20]

Several parameters must be optimized to improve access for our proposed approach to pharmacogenomic testing, including turnaround time for return of results; integration of sample collection and return of results into linic flow; and availability of pharmacogenomics training. By prioritizing serious ADRs, such as those encountered in childhood cancer treatment, the CPNDS is gaining understanding of how best to deliver pharmacogenomic testing to suit the needs of physicians, patients, and families, while also assessing the effect of such testing on the Canadian health care system by formally evaluating cost effectiveness. Importantly, lessons learned from these experiences will help family physicians incorporate pharmacogenomic testing for additional serious ADRs in the future. In particular, clinically relevant pharmacogenomic information informs the risk of experiencing the many serious ADRs encountered as a result of analgesics (eg, codeine- or tramadol-induced central nervous system depression or death), antibiotics (eg, rifampin-isoniazid-pyrazinamide–induced liver injury), and psychotropic medications (eg, carbamazepine- or phenytoin-induced skin reactions) that are commonly prescribed by family physicians. Given that these serious ADRs are typically rare, ordering pharmacogenomic testing will allow family physicians to continue prescribing highly effective drugs with well understood safety profiles in patients determined to be at low risk of experiencing ADRs, while choosing alternative drugs and avoiding potential harm in patients at high risk.

Conclusion

Ultimately, increasing accessibility to pharmacogenomic tests means better profiling risks of therapy before therapy begins and provides the potential to drastically affect the use of medication by making it safer, more effective, and personalized. It is an ethical responsibility for all of us—clinicians, hospital administrators, and policy makers—to provide access to this service to all Canadian families to help prevent serious ADRs when battling diseases and illnesses that require medication.

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