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Analyses of Adverse Drug Reactions–Nationwide Active Surveillance Network: Canadian Pharmacogenomics Network for Drug Safety Database

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Abstract

Adverse drug reactions (ADRs) are a major problem in modern medicine, representing up to the fourth-highest cause of mortality. Pharmacogenomic tests are 1 of the most promising methods to tackle the challenge of ADRs. The objective of this study was to analyze the clinical and demographic information of the pan-Canadian active surveillance network, Canadian Pharmacogenomics Network for Drug Safety (CPNDS). Information entered into the database by trained active surveillors between May 15, 2005 and May 9, 2017 was collected and analyzed. Specific data included for analysis were number of ADR reports, reports of drug use without ADRs, date of onset of ADR, suspected drugs, concomitant drugs, and fatal ADR cases. The CPNDS database consisted of 93,974 reports of medication use, including 10,475 reports of ADRs, of which 72.6% occurred in pediatric patients (≤21 years old). Self-reported ancestries were predominantly Europe (38.2%), Canada (9.6%), and East Asia (4.9%). The 5 most frequent ADRs were cutaneous ADRs, peripheral neuropathy, cardiotoxicity, central nervous system toxicity, and ototoxicity. The 5 drugs most commonly suspected to cause ADRs were methotrexate, vincristine, doxorubicin, cisplatin, and L-asparaginase. The CPNDS database is a valuable resource to identify clinical and genomic predictors of ADRs. The database also highlights our candidate ADRs for pharmacogenomic discovery research to identify additional ADR biomarkers. Additionally, the database provides information that can be used for developing strategies to prevent ADRs and raises awareness of ADRs among Canadian healthcare professionals.

Keywords

adverse drug reaction, pharmacogenomics, active surveillance, network

Pharmacotherapy is one of the keystones of contemporary medical care; as an example, 41% of the Canadian population aged from 6 to 79 years took at least one prescription medication within 2 days of their interview

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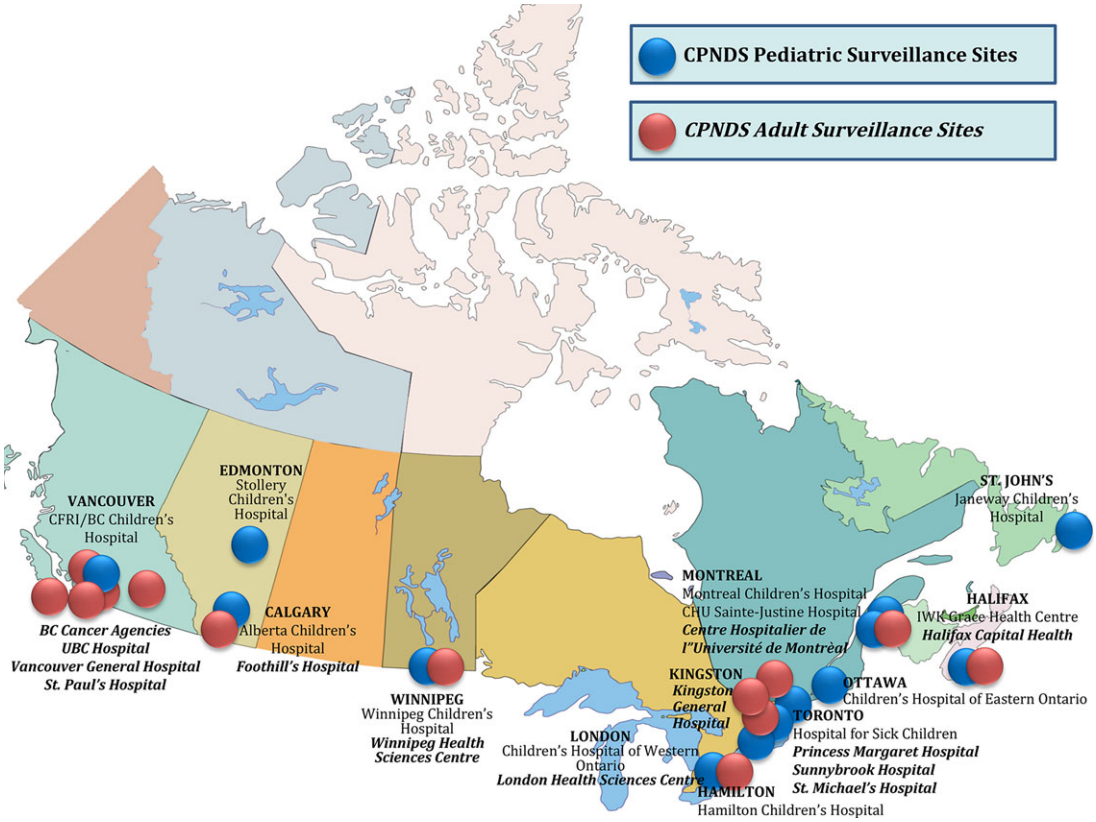

Figure 1. Active surveillance sites that form part of the Canadian Pharmacogenomics Network for Drug Safety in Canada. These sites include 13 pediatric and 13 adult institutions. Adult surveillance sites are *italicized*.

by national survey.[1] Treatment outcomes of potentially fatal diseases have improved dramatically with the use of drug therapy. Conversely, adverse drug reactions (ADRs) can occur with any drug; it is estimated that ADRs are the reasons for up to 30% of hospital admissions and are responsible for the healthcare cost of $14–18 billion each year in the United States.[2] ADRs are the fourth-highest cause of death in the United States.[2] Approximately 100,600–218,000 children die from ADRs every year in the United States, with 3600–10,000 deaths occurring in the same population per year in Canada.[3,4] Pharmacogenomics aims to identify genetic variations that impact drug response or ADRs and is a promising approach to mitigate ADRs by enabling the identification of at-risk patients before therapy initiation. Significant pharmacogenomic discoveries have already impacted clinical practice, such as HLA-B *15:02 for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.[5] Pretreatment screening of these gene variants decreases the risk of ADRs, and this testing is a standard part of clinical practice in some countries.[6]

To address these clinical needs, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)[7] was initially founded as the Genotype-specific Approaches to Therapy in Childhood (GATC) in 2005 to identify predictive genomic biomarkers of ADRs in children. GATC was first established at the British Columbia Children's Hospital in Vancouver, Canada, and subsequently extended to include a network of active surveillance sites at 13 major pediatric hospitals across Canada, covering the population of more than 75% of Canadian children (Figure 1). Surveillance clinicians (surveillors) are employed by CPNDS at each site, and they actively seek to identify and document ADRs, recruit patients into drug safety studies, and collect relevant biological samples and clinical information. GATC developed its first focused pharmacogenomic panel of single-nucleotide variants to study the genetics of ADRs, and the scope of these genomic analyzes has expanded to include genome-wide genotyping and exome sequencing. In 2009 GATC was renamed CPNDS to reflect an expansion that included 13 adult active surveillance sites (Figure 1). CPNDS is an active surveillance model and has enabled researchers to complete and publish pharmacogenomics research on specific ADRs, such as cisplatin-induced ototoxicity,[8–12] codeine-induced mortality,[13–16] and anthracycline-induced cardiotoxicity.[17–20] The objective of this article is to provide an overview of

the drugs, ADRs, and other clinical information in the CPNDS database as a resource for drug safety research.

Methods

Enrollment and Data Collection

All CPNDS studies are approved by research ethical boards at all institutions. Written informed consent is obtained from each patient or the parent/legal guardian when the patient is 14 years old or older, and the assent is obtained from the patient aged between 7 and 13 years old with the consent of the parent/legal guardian. When the patient is 6 years old or younger, we only obtain the consent of the parent/legal guardian. Each recruited patient is issued a unique nonidentifiable patient number.

The details of CPNDS recruitment and data entry methods were previously described[21] (Supplemental Figure S1). In brief, health care professionals at each active surveillance site identify patients with ADRs and refer them to CPNDS surveillors. CPNDS surveillors identify and enroll patients who have experienced ADRs as well as patients who received the same medications without having experienced an ADR (drug-matched controls) and subsequently collect their clinical data and biological samples for genomic analyzes. We recruit the patients with our focused ADRs, but we also collect any ADRs that the clinicians or the surveillors come across, and the ADRs are characterized by established criteria such as Common Terminology Criteria for Adverse Events for each research project.[22]

Genomic DNA is extracted from biological samples (saliva or blood) and stored at the CPNDS laboratory, part of the University of British Columbia, Vancouver, Canada. Deidentified clinical information is uploaded from a remote database at surveillance sites via a secure virtual private network to the host clinical FileMaker Pro database (Apple, Inc, Cupertino, California). The database includes detailed clinical information of demographic characteristics, medical history, medication history, medical diagnostic tests, laboratory radiological tests with results, and ADR descriptions. In order to enhance communication and maintain quality of the network, we hold regular teleconferences and site visits.

In this report, we analyzed the information collected and uploaded on the database between May 15, 2005 and May 9, 2017. The information collected for this report included the numbers of ADR and non-ADR reports, date of enrollment, sex, date of birth, date of reaction, self-reported ancestry, reactions, ADR probability scale (Naranjo scale),[23] number of reactions per patient, suspected and concomitant drugs, and details of fatal cases. The ADR Probability Scale, known as the Naranjo scale, was used to standardize the assessment of causality for all adverse drug reaction reports.[23] The Naranjo scale consists of 10 questions with high interrater reliability[23] to evaluate the probability that a specific drug caused a specific adverse drug reaction (Supplemental Table S1). The output of the Naranjo scale can range between –4 and 13. The higher the output, the more likely the reaction is related to the drug.[23] The ADR is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or lower.[23]

Patient Demographics

All data were collected from the host database based on the information uploaded by surveillors. "Pediatric" and "adult" were defined based on the patients' age at the time of reaction ($\leq$21 years old for pediatric cases, and $>$21 years old for adult cases), in line with the recent policy statement by American Academy of Pediatrics.[24] Ancestry was identified based on the self-reported geographical origin of the patients, parents, and grandparents. This self-reported approach has been proven to be consistent with genetic ancestry as determined by principal component analysis.[25] Ancestry was divided into the categories below: Canada, Caribbean, East Asia, Europe, First Nations, Latin-America, Mexico, Mexico/Latin-America, Middle East, North Africa, Oceania, South Asia, Southeast Asia, sub-Saharan Africa, United States of America, admixtures of Canada/United States/Europe, and other admixtures.

ADR Characterization

An ADR report (ie, ADR case) refers to the detailed description of an ADR. A non-ADR report (ie, drug-matched control) refers to the detailed description of medication use that was not associated with an ADR. The reactions were categorized into 38 common and/or clinically relevant categories (Supplemental Table S2).

Statistical Analyses

The data were imported into Excel for Mac (version 15.34, Microsoft, Redmond, Washington), analyzed, and summarized with Excel and Statistical Package for the Social Sciences (SPSS, version 24.0.0.0 and version 24.0.0.2; IBM, Armonk, New York).

Results

At the time of analysis, the CPNDS database consisted of 93,974 reports of medication use. It consisted of 10,475 ADR cases and 83,499 non-ADR reports. ADR cases consisted of similar numbers of female and male cohorts (51.3% and 48.7%, respectively).

Overall, 72.6% of the cases were pediatric cases, and 27.4% were adult cases, partly reflecting predominance

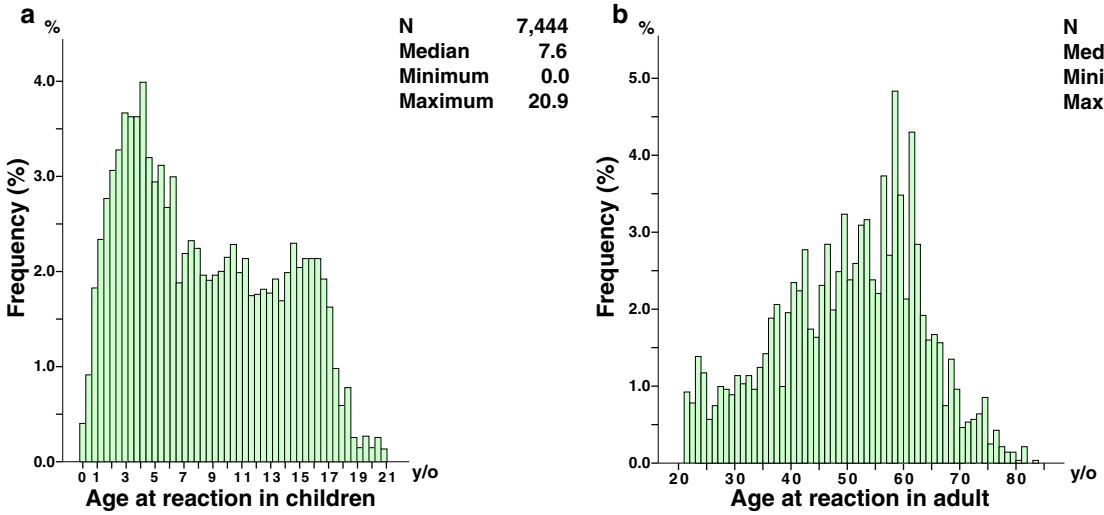

Figure 2. Distributions of the age at time of reactions of ADR cases in the Canadian Pharmacogenomics Network for Drug Safety database in the pediatric (a) and adult populations (b). The median ages at reaction were 7.6 years for pediatric and 51.7 years for adult cases.

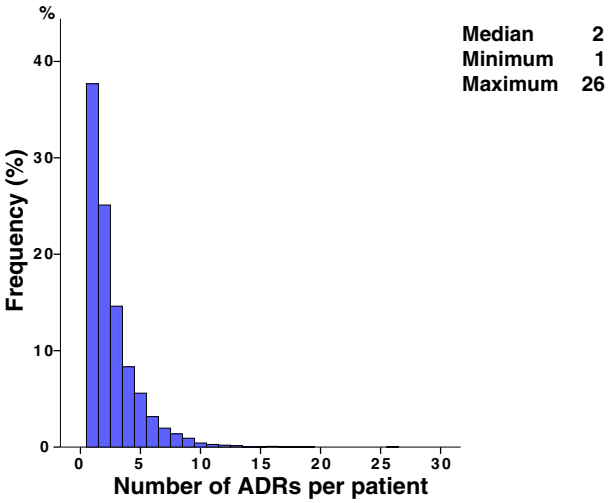

Figure 3. The numbers of reactions per patient in the Canadian Pharmacogenomics Network for Drug Safety database of the total population. ADR indicates adverse drug reactions.

Table 1. Self-reported Ancestry Distribution of CPNDS Database

Ancestry	Proportion (%)
Europe	38.2
Canada	9.6
Mixture of Canada/United States/Europe	5.3
East Asia	4.9
Southeast Asia	3.8
South Asia	3.7
Middle East	1.5
First Nations	1.0
Latin-America	0.9
Sub-Saharan Africa	0.6
Caribbean	0.6
North Africa	0.5
Oceania	0.2
Mexico	<0.1
Mexico/Latin America	<0.1
United States	<0.1
Unknown	18.0
Admixture	11.0

CPNDS indicates Canadian Pharmacogenomics Network for Drug Safety.

of pediatric institutions/programs in the CPNDS. Despite the effort to obtain the information, the age at time of the ADR was not identified in 217 cases because the specific date was not indicated in the medical record, or the patient/parent was unable to recall the date of ADR. The median age of pediatric ADR cases was 7.6 years old (range 0.0-20.9) (Figure 2a), and the median age of adult ADR cases was 51.7 years old (range 21.1–83.1) (Figure 2b).

The median number of ADRs per patient was 2 and ranged from 1 reaction to as many as 26 ADRs (Figure 3). Although the median number of reported ADRs was 2 in both adults and children, adult patients tended to have higher numbers of ADRs compared to children overall (Supplemental Figure S2a and S2b). The patient with 26 ADRs was a 56-year old man with hepatitis C on multiple courses of antiviral medications including interferon and ribavirin. The ADRs reported for this patient included cutaneous reactions, mood irritability, hematological disorders (anemia, neutropenia), and hepatic toxicity as well as others.

Although our enrollment target is Canadian residents, their self-reported ancestry originated from all over the world. Self-reported ancestry showed that the highest percentage of study participants were from Europe (38.2%), followed by Canada (9.6%), and East Asia (4.9%) (Table 1). In addition, a considerable number of cases reported admixtures of 2 or more ancestries (11.0%) or unknown ancestry (18.0%).

Table 2. Summary of the 20 Most Frequent Adverse Drug Reactions in the CPNDS Database

	ADR	Number
1	Cutaneous adverse reactions	1283
2	Peripheral neuropathy	1212
3	Cardiotoxicity	750
4	CNS toxicity	668
5	Ototoxicity	560
6	Mucositis	521
7	Neutropenia	408
8	Anaphylaxis	224
9	Nephrotoxicity	208
10	Hepatotoxicity	194
11	Nausea/vomiting	184
12	Febrile neutropenia	161
13	Diabetes mellitus/hyperglycemia/glucosuria	159
14	Abdominal pain/constipation/ileus	151
15	Bleeding	116
16	Mood swing/depression	115
17	Thrombosis	111
18	Osteonecrosis	106
19	Hypertension	105
20	Respiratory toxicity	105

CNS indicates central nervous system; CPNDS, Canadian Pharmacogenomics Network for Drug Safety.

Table 3. The Top 20 Suspected Drugs With Regard to Adverse Drug Reactions in the CPNDS Database

	Suspected Drugs	Number
1	Methotrexate	1356
2	Vincristine	1072
3	Doxorubicin	960
4	Cisplatin	702
5	L-Asparaginase	651
6	Cyclophosphamide	618
7	Dexamethasone	535
8	Cytarabine	509
9	Etoposide	381
10	6-Mercaptopurine	378
11	Prednisone	369
12	Sulfamethoxazole	367
13	Trimethoprim	363
14	Daunorubicin	253
15	Bleomycin	211
16	Ribavirin	200
17	Paclitaxel	182
18	Carboplatin	167
19	Amoxicillin	155
20	6-Thioguanine	145

CPNDS indicates Canadian Pharmacogenomics Network for Drug Safety.

The most frequently described ADRs in the entire cohort were cutaneous ADRs induced by various drugs such as chemotherapeutic drugs and antibiotics. Other ADRs which occurred in the database at a high frequency in both adult and pediatric cohorts included cancer chemotherapy-related ADRs (eg, peripheral neuropathy, cardiotoxicity, ototoxicity, mucositis, and neutropenia) and other ADRs such as those of the central nervous system (Table 2). ADRs that were frequently observed only in adult patients of the CPNDS database included anemia, mood swing/depression, and pruritus (Supplemental Table S3a and S3b). All 38 ADR categories organized by organ system are shown in Supplemental Table S2. Probability scales of ADR causality by Naranjo score showed that in the majority of cases, the causality was possible (49.5%) or probable (43.4%).

There were 406 different drugs classified as suspected ADR-causal drugs. The 20 most commonly suspected ADR-causal drugs were largely comprised of cancer chemotherapeutic drugs, with 11 of the most frequent drugs primarily used for the treatment of acute lymphoblastic leukemia, the most frequent childhood cancer (Table 3).[26]

The CPNDS database also contains reports of cases in whom ADRs resulted in fatalities (Supplemental Table S4). Of the 6 fatal cases, 4 cases were children, and 2 were adults. The pediatric patients died due to cancer chemotherapeutic–related ADRs, whereas the adult patients died of severe toxic epidermal necrolysis skin reactions.

Discussion

The CPNDS database contains in-depth clinical information about many different ADRs and the drugs suspected to cause them. The ancestry distribution in the database reflects the diversity of the Canadian population. In line with the initial targeted focus of CPNDS on ADRs in pediatric health centers across Canada, the majority of the database consists of pediatric cases. The high frequencies of ADRs and suspected drugs related to cancer chemotherapy reflect the strong initial focus of CPNDS on ADRs in the treatment of childhood cancer, but are also in line with the higher incidence of severe ADRs and the ease of identifying the ADRs associated with cancer treatment. The higher number of the ADRs per patient in the adult population may be due to the difficulty of communicating symptoms in children, especially those of young age. It may also reflect a high incidence of ADRs in specific patient populations targeted by the CPNDS in the adult patients, who include cancer patients and patients with hepatitis C. This study also showed that the CPNDS can capture rare but severe reactions such as severe skin reactions as in Stevens-Johnson syndrome and toxic epidermal necrolysis. The high number of "other" ADRs is reflective of the diversity of ADRs in the database.

The success of this network can largely be attributed to active ADR surveillance, enabling the focused targeting of drugs and ADRs of interest and a reliable network of collaborators across the country (Supplementary Figure S1). Active ADR surveillance is critical

Table 4. Selected Findings From the Pharmacogenomic Project by the Canadian Pharmacogenomics Network for Drug Safety

Drug	ADR	Pharmacogenomic Biomarkers	References
Anthracycline	Cardiotoxicity	*RARG* *SLC22A17* *SLC28A3* *UGT1A6*	17–20
Anticonvulsant	Severe skin reactions	*HLA-A*31:01* *HLA-B*15:02*	27
Cisplatin	Ototoxicity	*ABCC3* *ACYP2* *COMT* *SLC16A5* *TPMT* *WFS1*	8–12
Codeine	Mortality	*ABCB1* *CYP2D6*	13–16
Interferon	Hepatic toxicity	*rs2205986 (variant near IRF6)*	28
Vincristine	Peripheral neuropathy	*ABCC1* *CEP72* *SLC5A7* *TTPA*	29
Warfarin	Therapeutic INR	*CYP2C9* *VKORC1*	30

ADR indicates adverse drug reactions; INR, international normalized ratio.

to recruiting new patients as well as to following up on long-term clinical outcomes of ADRs. Regular communication between the CPNDS headquarters in Vancouver and other centers across the country via teleconferences and site visits allows for enhanced communication and provides opportunities for additional training and education. The collection of these data has been made possible through collaboration among clinicians, researchers, regulators, and policymakers. The CPNDS is composed of clinicians in many disciplines, including clinicians with expertise in areas such as clinical pharmacology, pediatric oncology, audiology, and medical genetics and researchers with expertise in several disciplines including genomics, computer science, molecular biology, statistics, economics, and pharmacology. The multidisciplinary nature of the team has led to clinically prioritized questions and achievable research projects,[8–20,27–30] including recently published studies on pharmacogenomics biomarkers of interferon-β–induced hepatic toxicity[28] and vincristine-induced peripheral neuropathy[29] (Table 4).

Looking toward the future, the CPNDS aims to expand the number of ADRs targeted for pharmacogenomic analyses and to work together with researchers worldwide for the replication of pharmacogenomic findings in independent patient cohorts. It is increasingly evident that genetic differences can affect individual susceptibility to ADRs through variation in genes that impact drug response. For example, 1 case report from the Hospital for Sick Children, Toronto, Canada, described an infant who died after ingesting breast milk from the mother who had received codeine.[31] Follow-up analyses revealed that the CYP2D6 ultrarapid metabolizer status (*CYP2D6* gene duplication) of the mother likely increased the metabolism of codeine into morphine, which was delivered into the infant via breast milk, resulting in a fatal morphine overdose.[31] This case report was followed by a case-control study supported by CPNDS that confirmed the increased risk of codeine intake for breastfeeding mothers with a *CYP2D6* gene duplication.[13,14] These findings resulted in public health warnings by US Food and Drug Administration,[32] Health Canada,[33] and the European Medicines Agency.[34] To facilitate the implementation of new pharmacogenomic findings into clinical practice, the CPNDS established a Clinical Recommendations Group to develop clinical practice guidelines to help guide the implementation of clinical pharmacogenomics. The Clinical Recommendations Group has published clinical practice recommendations regarding anthracycline-induced cardiotoxicity,[35] carbamazepine-induced hypersensitivity reactions,[36] cisplatin-induced ototoxicity,[37] the safety and effectiveness of codeine,[38] and warfarin therapy.[39] The CPNDS is 1 of 3 pharmacogenomic clinical practice guideline groups cited by The Pharmacogenomics Knowledgebase (PharmGKB)[40] along with the Dutch Pharmacogenomic Working Group and the Clinical Pharmacogenetics Implementation Consortium in the United States. The clinical recommendations aid incorporation of pharmacogenomic biomarkers into clinical practice. CPNDS also conducts pharmacogenetic testing for anthracycline-induced cardiotoxicity, cisplatin-induced ototoxicity, and thiopurine-induced myelosuppression to preemptively identify the risk of those ADRs before the start of oncologic treatment. This project is ongoing at British Columbia Children's Hospital and is now expanding to other large pediatric academic health centers across Canada.

There are challenges in developing and maintaining the CPNDS database. Considerable time, effort, and resources are required to maintain the network.[21] Grant-funding programs to support national and longitudinal efforts such as this are infrequent and highly competitive. Quality control and quality assurance are major challenges for active surveillance. A limitation of the CPNDS database is that it does not reflect the epidemiology of all ADRs in Canada because the network does not capture all the ADRs occurring in the participating institutions. Given the targeted nature of the surveillance, the large number of pediatric cases in the CPNDS database does not mean that children are more susceptible to ADRs. The database predominately

contains ADRs and suspected drugs related to cancer therapy because we initially focused on a cancer cohort of children due to the severity and frequency of ADRs in this population. Similarly, housing only 6 fatal ADRs out of 10,475 cannot be interpreted as the mortality rate of ADRs because the focus of surveillance has not been specifically on fatal cases and because of the difficulty of obtaining consent and biological material from deceased patients and families. The dominance of European genetic ancestry in the CPNDS database makes it challenging to validate genetic biomarkers in other ancestral populations. To overcome this, we use non-European ancestries as a replication cohort to validate the discovered genes[20] and promote international collaboration.

Conclusion

In conclusion, this report shows that the CPNDS database holds a vast amount of valuable information focusing on ADRs to study the pharmacogenomics of ADRs. The CPNDS/GATC was started to respond to the unmet need of mitigating ADRs and identifying important pharmacogenomic biomarkers. The database reflects the ADRs targeted by the network for study so far to identify novel pharmacogenomics biomarkers. The CPNDS also raises awareness of ADRs among Canadian healthcare professionals and organizes the knowledge translation and clinical implementation of pharmacogenomic biomarkers in order to bring research findings resulting from this resource into the clinic for the benefit of patients.

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Contributions

R.T., B.I.D., G.E.B.W., J.S.H., G.S.S.G., C.J.D.R., and B.C.C. contributed to the design of the study. R.T., A.K., A.K.B., and J.N.T. collected the data. R.T. analyzed the data and drafted the manuscript. R.T. and J.S.H. created the tables and figures. All authors critically revised the manuscript and approved the final version to be published.

Conflict of Interests

Pfizer Canada provided unrestricted matching funds to a Genome Canada grant awarded in 2005.

Data Sharing

We cannot share the data of this report because the data contain information that relates to our current and future pharmacogenomics projects.

References

1. Rotermann M, Sanmartin C, Hennessy D, Arthur M. Prescription medication use by Canadians aged 6 to 79. *Health Rep.*. 2014;25(6)3–9.
2. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc*. 2001;41(2):192–199.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200–1205.
4. Rawson, N. Adverse drug reactions in Canada: facts v. urban myths. *Canadian Health Policy*. 2013. https://www.canadianhealthpolicy.com/products/adverse-drug-reactions-in-canada-facts-v-urban-myths.html. Accessed October 15, 2018.
5. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428(6982):486.
6. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med*. 2011;364(12):1126–1133.
7. Canadian Pharmacogenomics Network for Drug Safety. 2018. http://cpnds.ubc.ca/. Accessed October 15, 2018.
8. Ross CJ, Katzov-Eckert H, Dube MP, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. *Nat Genet*. 2009;41(12):1345–1349.
9. Pussegoda K, Ross CJ, Visscher H, et al. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clin Pharmacol Ther*. 2013;94(2):243–251.
10. Bhavsar AP, Gunaretnam EP, Li Y, Hasbullah JS, Carleton BC, Ross CJ. Pharmacogenetic variants in TPMT alter

cellular responses to cisplatin in inner ear cell lines. *PloS One*. 2017;12(4):e0175711.
11. Drögemöller BI, Monzon JG, Bhavsar AP, et al. Association between SLC16A5 genetic variation and cisplatin-induced ototoxic effects in adult patients with testicular cancer. *JAMA Oncol*. 2017;3(11):1558–1562.
12. Drögemöller BI, Brooks B, Critchley C, et al. Further investigation of the role of ACYP2 and WFS1 pharmacogenomic variants in the development of cisplatin-induced ototoxicity in testicular cancer patients. *Clin Cancer Res*. 2018;24(8):1866–1871.
13. Madadi P, Ross CJ, Hayden MR, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther*. 2009;85(1):31–35.
14. Sistonen J, Madadi P, Ross CJ, et al. Prediction of codeine toxicity in infants and their mothers using a novel combination of maternal genetic markers. *Clin Pharmacol Ther*. 2012;91(4):692–699.
15. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012;129(5):e1343–e1347.
16. Lam J, Woodall KL, Solbeck P, et al. Codeine-related deaths: the role of pharmacogenetics and drug interactions. *Forensic Sci Int*. 2014;239:50–56.
17. Visscher H, Ross CJ, Rassekh SR, et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol*. 2012;30(13):1422–1428.
18. Visscher H, Ross CJ, Rassekh SR, et al. Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. *Pediatr Blood Cancer*. 2013;60(8):1375–1381.
19. Visscher H, Rassekh SR, Sandor GS, et al. Genetic variants in SLC22A17 and SLC22A7 are associated with anthracycline-induced cardiotoxicity in children. *Pharmacogenomics*. 2015;16(10):1065–1076.
20. Aminkeng F, Bhavsar AP, Visscher H, et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet*. 2015;47(9):1079–1084.
21. Carleton B, Poole R, Smith M, et al. Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. *Pharmacoepidemiol Drug Saf*. 2009;18(8):713–721.
22. National Cancer Institute. 2018. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed October 15, 2018.
23. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
24. Hardin AP, Hackell JM. Age limit of pediatrics. *Pediatrics*. 2017;140(3). https://doi.org/10.1542/peds.2017-2151
25. Visscher H, Ross CJ, Dube MP, et al. Application of principal component analysis to pharmacogenomic studies in Canada. *Pharmacogenomics J*. 2009;9(6):362–372.
26. Kato M, Manabe A. Treatment and biology of pediatric acute lymphoblastic leukemia. *Pediatr Int*. 2018;60(1):4–12.
27. Amstutz U, Ross CJ, Castro-Pastrana LI, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther*. 2013;94(1):142–149.
28. Kowalec K, Wright GEB, Drögemöller BI, et al. Common variation near IRF6 is associated with IFN-β-induced liver injury in multiple sclerosis. *Nat Genet*. 2018;50(8):1081–1085.
29. Wright GEB, Amstutz U, Drögemöller BI, et al. Pharmacogenomics of vincristine-induced peripheral neuropathy implicates pharmacokinetic and inherited neuropathy genes [published online ahead of print July 12, 2018]. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.1179.
30. Shaw K, Amstutz U, Hildebrand C, et al. VKORC1 and CYP2C9 genotypes are predictors of warfarin-related outcomes in children. *Pediatr Blood Cancer*. 2014;61(6):1055–1062.
31. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368(9536):704.
32. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. US Food and Drug Administration. Published 2017. https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm Accessed October 15, 2018.
33. Important Safety Information on Tylenol with Codeine in Nursing Mothers and Ultra-Rapid Metabolizers of Codeine - For Health Professionals. Government of Canada. Published 2013. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14526a-eng.php Accessed October 15, 2018.
34. European Medicines Agency. Codeine-containing medicines. 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f. Accessed October 15, 2018.
35. Aminkeng F, Ross CJ, Rassekh SR, et al. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br J Clin Pharmacol*. 2016;82(3):683–695.
36. Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia*. 2014;55(4):496–506.
37. Lee JW, Pussegoda K, Rassekh SR, et al. Clinical practice recommendations for the management and prevention of cisplatin-induced hearing loss using pharmacogenetic markers. *Ther Drug Monit*. 2016;38(4):423–431.
38. Madadi P, Amstutz U, Rieder M, et al. Clinical practice guideline: CYP2D6 genotyping for safe and efficacious codeine therapy. *J Popul Ther Clin Pharmacol*. 2013;20(3):e369–e396.
39. Shaw K, Amstutz U, Kim RB, et al. Clinical practice recommendations on genetic testing of CYP2C9 and VKORC1 variants in warfarin therapy. *Ther Drug Monit*. 2015;37(4):428–436.
40. The Pharmacogenomics Knowledgebase (PharmGKB). 2018. https://www.pharmgkb.org/page/cpnds. Accessed October 15, 2018.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.