The Pharmacogenomics Journal (2018) 18, 391–397

www.nature.com/tpj

ORIGINAL ARTICLE

A cost-effectiveness analysis of maternal *CYP2D6* genetic testing to guide treatment for postpartum pain and avert infant adverse events

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Mothers with a *CYP2D6* ultrarapid metabolizer phenotype may expose their infants to risk of adverse events when taking codeine while breastfeeding, by producing more of the active metabolite, morphine. Pharmacogenetic testing may be a valuable tool to identify such mothers, but testing can be costly. The objective of the study was to determine the incremental costs of genotyping to avert neonatal adverse events during maternal pharmacotherapy. A cost-effectiveness analysis, using a decision model, was performed with a hypothetical cohort of prenatal subjects. Parameter estimates, costs and ranges for sensitivity analyses were ascertained from the literature and expert opinion. Sensitivity analyses were conducted to assess the robustness of the results. Probabilistic sensitivity analysis revealed an incremental cost-effectiveness (ICER) of $10 433 (Canadian dollars) for genotyping compared to no genotyping per adverse event averted. Results were sensitive to hospital admission costs. The ICER was lower when evaluating only subjects having caesarean deliveries or those from ethnic populations known to have a high prevalence of ultra-rapid metabolizers. Although genotyping to guide pharmacotherapy was not cost saving, the cost to avert an infant adverse event may represent good value for money in specific populations. With a growing demand for personalized medicine, these findings are relevant for decision makers, clinicians and patients.

The Pharmacogenomics Journal (2018) **18,** 391–397; doi:10.1038/tpj.2017.33; published online 11 July 2017

INTRODUCTION

The World Health Organization,[1] Health Canada, the Canadian Paediatric Society[2] and the American Academy of Pediatrics[3] recommend exclusive breastfeeding for all healthy infants for at least the first 6 months of life and continued breastfeeding for the first 2 years. The choice to breastfeed is complicated when maternal medication is required since, to some degree, most drugs will reach human milk.[4] Since success of breastfeeding is strongly related to initiation in the early hours of life,[3] this issue is particularly critical for medications used to treat pain in the immediate postnatal period.

In 2006, a case of a neonatal fatality in an infant whose mother had been taking acetaminophen with codeine for postnatal pain was reported.[5] Genotyping revealed that the mother was a Cytochrome P450 2D6 (*CYP2D6*) ultrarapid metabolizer (UM), producing higher concentrations of morphine from codeine. High concentrations of morphine were also found in infant blood. Subsequently, the FDA[6] and Health Canada[7] issued advisories and label changes for codeine-containing prescription products. A similar report was also issued by the European Medicines Agency (EMA).[8]

Following the infant fatality, an observational study of 72 mother-infant pairs[9] found that 24% of mothers who consumed codeine while breastfeeding reported infant symptoms with more emergency room visits among the symptomatic group compared to the asymptomatic group (24% vs 0%, $P = 0.002$). One case of respiratory depression was found in an infant whose mother was an UM. Together with the currently available literature,[9,10] the evidence suggests that there may be selected subgroups of infants who are more susceptible to the adverse effects of codeine though maternal milk. Moreover, infants may be uniquely susceptible to the effects of drugs because of their immature drug metabolizing capacity and because there is an upregulation of maternal drug metabolizing enzymes in the latter part of pregnancy.[11]

It is well known that humans display variability in drug response that can be partly attributed to differences in drug metabolism. In the case of codeine, pharmacogenetics plays a critical role, as this prodrug is metabolized to its active metabolite, morphine by the highly polymorphic *CYP2D6*. As a result of this polymorphism, individuals produce different amounts of morphine, depending on the presence and quantity-of-specific alleles, which may encode for both active and inactive enzyme.[12] Defining the phenotype is complicated because the presence of CYP2D6 allele multiplication alone does not guarantee an individual will have a UM phenotype. While some alleles will produce an active enzyme, others mutations result in dysfunctional enzyme activity, therefore, only the presence of multiple active alleles is predictive of UM status.[13,14]

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Received 6 December 2016; revised 8 May 2017; accepted 10 May 2017; published online 11 July 2017

Over 100 allelic variants coding for the *CYP2D6* enzyme have been identified in humans[15] with significant worldwide variability in their prevalence.[13,16,17] The worldwide prevalence of the UM phenotype ranges from 2 to 40%.[16,17]

Genotyping to identify the most common *CYP2D6* alleles is now possible, allowing one to partially predict a metabolic phenotype, and subsequently use this information to determine whether an individual receiving codeine is likely to produce high or low serum concentrations of morphine. A higher serum concentration of morphine corresponds with a higher incidence of adverse effects, notably, central nervous system (CNS) depression. A recent upsurge in genomics research, with scientists having now sequenced the full human genome[18] is bringing an increased understanding of specific gene functions. This increased understanding may allow clinicians to tailor pharmacotherapy for individuals, thus leading to overall improvements in health outcomes. The improved health outcomes and fewer adverse effects may lead to reduced health services use and emergency room visits, which may translate into potential savings to payers. However, pharmacogenetic testing is not without costs. To date, economic evaluations of particular pharmacogenetic tests to guide treatment are limited,[19–21] with only selected drug/enzyme combinations that have published cost-effectiveness analyses. Moreover, there have been no pharmacogenomic economic evaluations in maternal-child outcomes. The optimal use and clinical utility of alternative pharmacogenetic testing approaches as single gene tests, panels or more complex whole-exome- or genome-sequencing is currently an active field of enquiry. Before pharmacogenetic testing is incorporated into routine medical care it is critical that its cost-effectiveness be examined. The objective of this study was to determine the incremental costs of *CYP2D6* pharmacogenetic testing compared to standard care in averting neonatal CNS depressive adverse events during maternal treatment for postnatal pain. In the case of a newborn, maternal CYP2D6 metabolic activity is the most relevant, as it will dictate how much morphine is produced and potentially transferred to the infant.

MATERIALS AND METHODS

The study was approved by the Research Ethics Board of St Michael's hospital in Toronto, Ontario, Canada and was conducted in accordance with the Canadian Agency for Drugs and Technologies in Health guidelines for the economic evaluation of health technologies.[22]

Study design

A cost-effectiveness analysis (CEA) was conducted from societal and health care system perspective to compare standard care with genotyping prior to delivery to guide pharmacotherapy for postnatal analgesia. Standard care consisted of no routine genotyping and pharmacologic management of pain at the discretion of clinicians. The analysis was performed on a hypothetical cohort of prenatal patients who had not yet delivered their child and were anticipated to require analgesia after delivery. The CEA had a time horizon extending from prenatal genotype screening prior to delivery to the resolution of any postpartum adverse events, typically < 1 month after delivery. This time horizon was chosen to reflect the expectation that the adverse events associated with drug treatment will occur during treatment or shortly thereafter and will be relatively short-lived.

Decision analysis

A decision model was created using TreeAge Pro Software (version 2016),[23] to determine the expected values of costs and effectiveness of the proposed intervention as compared to standard care, in averting infant adverse events. The model was populated with inputs from published literature. All inputs were vetted by clinical experts in terms of current face validity and plausibility.

Local practice patterns depend on the prescribing habits and discretion of the attending physician, but generally, all patients who require analgesia are prescribed acetaminophen and non-steroidal anti-inflammatory drugs followed by acetaminophen/opiate combination as needed in a stepwise sequence. The decision model (Figure 1) begins with the clinical decision followed by a series of pathways that could occur in the course of the intervention or standard care. The base case was a prenatal patient whose *CYP2D6* status was unknown but who may have needed codeine-containing analgesics for pain relief after delivery and planned to breastfeed. The patient was not taking any other medications which may have similar adverse effects on the breastfed infant. The tree follows an episode of care and terminates upon completion of pharmacotherapy for postnatal pain relief and resolution of any adverse events.

The strategies evaluated were as follows:

1. Pharmacogenetic screening prior to the anticipated birth with the results of the screening available prior to delivery and used to guide analgesia prescriptions. Women who test positive for the UM phenotype are given only non-codeine analgesics while breastfeeding.
2. Standard care, no pharmacogenetic screening and analgesia administration after delivery as per local practice patterns.

Each tree pathway ends in a terminal node, which was populated by two values: the average costs for an individual following that particular pathway expressed in 2014 dollars, and the effectiveness for an individual following that pathway, either the presence or absence of an adverse event. A pathway is described in terms of the subject UM status, analgesic use, test sensitivity and specificity, and the probabilities of adverse events,

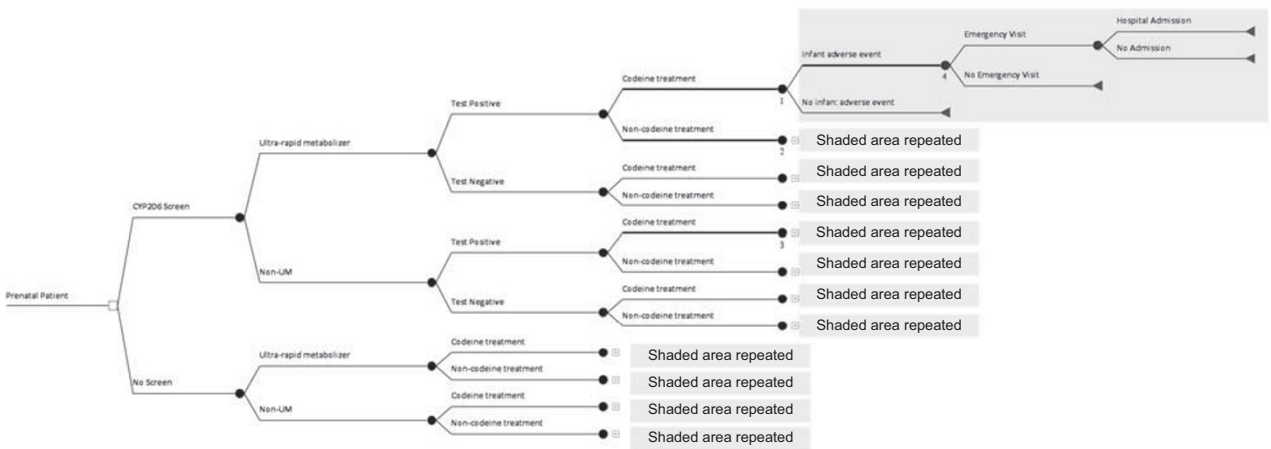

Figure 1. Decision model schematic for*CYP2D6* screening to guide pharmacotherapy. The model begins with a prenatal patient and the decision node is represented by a square. Circles indicate a chance node and triangles the terminal nodes. UM, ultra-rapid metabolizer.

Table 1. Model probability inputs

Parameter	*Base case estimate*	*Source*	*Minimum*	*Maximum*	*Distribution for PSA*
Probability of being UM	0.08	[16,17,37,38]	0.01	0.4	Beta
Probability of testing positive for UM, given UM (true positive)	0.99	Laboratory measures;[39–41]	0.70	1	Fixed
Probability of testing non-UM, given non-UM (true negative)	0.999	Laboratory measures;[39–41]	0.7	1	Fixed
Probability of receiving codeine given subject is screened and tests positive UM	0	Expert opinion	0	0.01	Fixed
Probability of codeine, given subject tests negative UM	0.6584	[42]	0.4155	0.825	Beta
Probability of codeine (not tested)	0.6584	[42]medical record extraction[25]	0.4155	0.825	Beta
Probability of an adverse event, given non-codeine (metabolizer status unknown)	0	[32,43]	0	0.03	Beta
Probability of an adverse event, given codeine use and UM	0.6667	[9]	0.2174	1	Beta
Probability of an adverse event, given codeine use and non-UM	0.2174	[9]	0.021	0.3077	Beta
Probability of emergency room visit with AE	0.1143	[9,43]	0	0.2343	Beta
Probability of hospital admission with Emerg visit, given AE	0.9	Expert opinion (Dr Shinya Ito)	0.75	1	Beta

hospital visits and hospital admission. Post hospital discharge costs were not captured in this model as it was assumed for the purpose of this study that there were no long-term sequelae experienced by infants following resolution of an adverse event.

Several assumptions were made to guide model development and better define the population to which this analysis is relevant. It was assumed that women exclusively breastfed their infants during the interval of drug use and that patients who tested positive for the UM phenotype did not take any codeine or other opioid-containing analgesic. Rates of adverse events were assumed to be the same for male and female offspring. All CNS depressive events in the infant were assumed to be due to exposure to codeine in maternal milk. The opioid analgesic tablet used was assumed to contain 30 mg of codeine and 325 mg acetaminophen, two tablets were prescribed every 4 h as needed. It was assumed that a range of doses would be used by patients. Only the first postnatal adverse event in the infant was included and was limited to CNS depressive events such as sedation, lethargy, irregular breathing, decreased alertness and poor feeding. Subsequent exposure to opioid analgesics and maternal adverse events were not included.

Cost-effectiveness was expressed in terms of the incremental cost-effectiveness ratio (ICER), calculated from dividing expected incremental costs (ΔC) between the two strategies by the expected incremental adverse events (ΔE) and represents the additional cost per adverse event averted. Probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulation modeling, computing a point estimate and 95% confidence interval for ΔC and ΔE and the ICER. The model was run 1000 times, with each iteration randomly selecting a parameter estimate from a specified distribution (Table 1).

Cost identification, measurement, and evaluation

Costs were calculated along each pathway of the model and are presented in 2014 Canadian dollars. The data sources for the items considered are shown in Table 2 and included intervention costs, direct health care costs and direct patient costs. The societal perspective included all direct health care costs, including costs to the publicly funded health care system, and to private payers, as well as out-of-pocket costs to the subjects (direct health care costs) and loss of productivity to the mothers and their family or caregivers (indirect costs), resulting from an adverse event. The health care system perspective included only costs to the publicly funded health care system. The intervention costs included testing costs, shipping to a laboratory licensed to perform genotyping as well as a post-test pharmacology specialist consultation with the patient.

Parameter estimates

The branch probability estimates and the ranges of estimates are shown in Table 1. Most parameter estimates were obtained from existing literature reports and from a database of an observational cohort study.[24] A medical chart review of all patients delivering a child at the same institution was conducted to provide additional model inputs.[25] Expert clinical judgment was used where the literature and the clinical study were unable to provide appropriate estimates. The primary outcome measured in the model was CNS depressive adverse events in the infant.

Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the model by assessing the effect of changes in uncertain parameter estimates on the results. A series of one-way and two-way sensitivity analyses was performed for most variables using ranges specified in Table 2. The variables evaluated in the sensitivity analysis included the costs of the genotyping procedure, the costs of hospitalization for an adverse event, the prevalence of UM status, the prevalence of codeine use and the rate of adverse events among UM.

Scenario analysis

In order to determine if the model would change when evaluating specific populations of interest, two selected scenario analyses were performed. In these analyses, base case parameter estimates were altered to reflect distinct population subgroups. The first scenario examined a population representing an ethnic group with a high prevalence of UM phenotype. In this scenario the probability of UM phenotype was estimated at 0.4, with a range of 0.12–0.45, approximating a North African population, which is among the groups with the highest incidence of the UM phenotype.[16] The second scenario analysis evaluated women with caesarean section deliveries only. As patients with surgical deliveries are more likely to experience pain and therefore more likely to use opioids, the rate of opioid use was increased to 93% for this scenario, with a range of 0.78 to 1.0. Moreover, because infants born by caesarean section may be more prone to adverse events in the days after birth, the probability of an adverse event was increased to 0.2174 (range: 0.0210, 0.6670).

RESULTS

Probabilistic sensitivity analysis

The PSA analysis evaluated all uncertainties simultaneously in a stochastic manner. The mean incremental costs were $353 (95% CI −$55, $1236) and the mean incremental adverse events was −0.0339 (95% CI −0.0566, 0.1785), resulting in a mean ICER of $10 433, when evaluated from the societal perspective (Table 3). The findings were similar when the model was run from the health care system perspective. The mean incremental costs per case were $352 (95% CI: −$10, $1,186), mean incremental effects

Table 2. Cost items, sources and unit prices

Cost Item	*Volume source*	*Base case volume*	*Unit price source*	*Base case unit price*	*Base case cost*	*Minimum*	*Maximum*	*Distribution for PSA*
Intervention								
Test cost (genotyping analysis)	1 for each subject in intervention strategy	1	Personal communication (C. Ross)	$150.00	$150.00	$90.00	$1300.00	Gamma
Post-test consult with Physician Specialist	1 for each subject in intervention strategy	1	Physician Schedule of Benefits[44]	$167.00	$167.00	N/A	N/A	Fixed
Sample Shipping costs	1 for each subject in intervention strategy	1	Courier published rates	$64.89	$64.89	$17.64	$72.93	Uniform
Codeine Tablet			Ontario Drug benefit formulary[45]	$0.0524	$0.3980	N/A	N/A	Fixed
	Drug use study	7.5954				0.5	18	Gamma
Additional Analgesics Used (as polytherapy with opioids)			Ontario drug benefit formulary[45]	$0.2244	$1.1500	N/A	N/A	Fixed
	Drug use study	5.1284				0.5	18	Gamma
Other Analgesics Used (non opioid only users)			Ontario drug benefit Formulary[45]	$0.2244	$0.9615	N/A	N/A	Fixed
	Drug use study	4.2847				0.5	17	Gamma
Adverse Event								
Call by parent for help or consultation to TIS	1 for each adverse event case	1	Hancock *et al.*[46]	$42.00	$42.00	$10.00	$78.00	Gamma
Ambulance	1 for each case going to ER	1	Ontario MOHLTC[47]	$240.00	$240.00	N/A	N/A	Fixed
Emergency Room Visit	1 for each case going to ER	1	Ontario case costing initiative[48]	$278.38	$278.38	$6.50	$1769.95	Gamma
Cost of Emergency Physician in the ER	1 for each case going to emergency room	1	Physician schedule of benefits[44]	$97.60	$97.60	N/A	N/A	Fixed
Parent lost productivity costs for Day missed from work/usual activities to be in ER with child	1 day of wages for each case going to ER	1	Statistics Canada-Labour force survey estimates[49,50]	$250.23	$250.23	$194.83	$525.26	Gamma
Hospital Admission			Ontario case costing initiative[48]	$6,865.32	$6,865.32	$6.50	$387,058.59	Gamma
	1 for each case admitted	5.1				1	169	Gamma
Cost of in-patient physician visit for day one	1 for each case admitted	1	Physician schedule of benefits[44]	$196.28	$196.28	N/A	N/A	Fixed
Cost of in-patient physician visit for subsequent days			Physician schedule of benefits[44]	$58.80	$58.80	N/A	N/A	Fixed
	Average days of admission less one	4.1				N/A	N/A	
Parent lost productivity costs for Day missed from work/usual activities to be in hospital with child	Average days of admission		Statistics Canada-Labour force survey estimates[49,50]	$250.23	$250.23	$194.83	$525.26	Gamma

Abbreviations: ER, emergency Room; N/A, not applicable

Table 3. Results of probabilistic sensitivity analysis for base case, societal and health care system perspectives

Strategy	*Perspective*	*Mean Cost per case (95% CI)*	*Mean adverse events per case (95% CI)*	*Cost-effectiveness ratio*
Screen	Societal	$537 ($242, $1671)	0.1339 (0.0543, 0.2518)	
	Health care system	$498 ($236, $1513)	0.1309 (0.0512, 0.2400)	
No Screen	Societal	$184 ($12, $1137)	0.1687 (0.0691, 0.3095)	
	Health care system	$146 ($10, $908)	0.1656 (0.0683, 0.3017)	
Increment	Societal	$353 (− $55, $1236)	−0.0339 (−0.0566, 0.1785)	$10 433
	Health care system	$352 (− $10, $1186)	−0.0346 (−0.1682, 0.0440)	$10 174

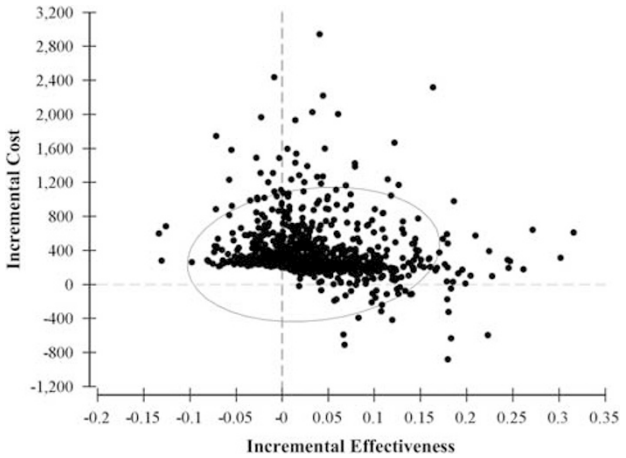

Figure 2. Scatter plot of incremental cost-effectiveness ratios (ICERS) for adverse events averted. Incremental effects are shown on the *y* axis and incremental costs on the *x* axis.

were − 0.0346 (95% CI − 0.1682, 0.0440), and the mean ICER, $10 174.

The results of the Monte Carlo simulations are depicted in the scatter plot (Figure 2). Incremental costs were positive for 97% of simulations, that is, screening costs more than standard care. The scatter is not uniform with incremental costs mostly between $150 and $350, and incremental effects between − 0.04 and 0.1 adverse events averted. Incremental effects were positive for 72.8% of simulations, that is, more adverse events are averted, with 69.8% of the scatter in the quadrant where both costs and adverse events averted are positive.

Uncertainty analysis

The one-way sensitivity analysis indicated that the model was sensitive only to a single variable: costs of hospital admission. When hospital admission costs associated with a severe AE were greater than $104 000 per stay, the screening strategy became cost saving. The model decision did not change upon varying any of the other variables within the specified ranges, including a relatively wide range for test cost. That is, screening did not become cost saving. When the probability of codeine use was varied to lower than 0.53 the screening strategy became dominated, it cost more money and had lower effectiveness.

In a two-way sensitivity analysis of cost of hospital admission varied with the probability of codeine use, the screening strategy became preferred as costs of hospital admission rose and probability of codeine use increased. Similarly, in a two-way analysis of cost of hospital admission and the probability of an adverse event the screening strategy became preferred as the probability of an adverse event and costs of hospital admission increased. However, when costs of hospital admission were less than $80 000 the no screen strategy was preferred, even when the probability of an adverse event was extremely high.

Scenario analysis

When the model PSA was run for a group of patients with a high UM prevalence the incremental costs were $192 (95% CI − $664, $1143), the incremental effects were − 0.1743 (95% CI − 0.3455, -0.0353) and the mean ICER, $1104. In the second scenario, that of a group of patients delivering by caesarean section only, the PSA revealed mean incremental costs of $346 (95% CI − $95, $1329), mean incremental effects of − 0.0522 (95% CI − 0.0266, 0.2494) and a mean ICER of $6627.

DISCUSSION

As genetic testing strategies improve and the demand for these services increases it is critical to evaluate their clinical utility and cost-effectiveness for allocation decision-making under constrained budgets. This study demonstrated that pharmacogenetic testing had an ICER of $10 433 per adverse event averted from a societal perspective and $10 174 from a health care system perspective. These differences are small as there were minimal differences in cost variables between the two perspectives.

Although the screening strategy did not save money it was not dominated by standard care. That is, it cost more but also produced, on average, a more favorable outcome, a reduction in infant adverse events. The ICER was sensitive only to the costs of a hospital admission for an adverse event. When hospital admission costs were extremely high, the testing strategy was dominant. This price for a hospital stay is unlikely, suggestive of a lengthy admission with extensive procedures or interventions. Though the parameter estimate had a range that included this value, the mean costs of hospitalization was significantly lower, at $6850. The second variable of note in the one-way sensitivity analysis was the probability of codeine use in the population. When codeine use was $< 53\%$ the screening strategy was dominated by standard care. This is an important value; the rate of codeine use varies across institutions and settings, resulting from the fact that alternative, effective analgesics exist, and treatment preferences vary across jurisdictions.[26,27] Analgesic use is driven by local institutional practice patterns, which may or may not be protocolized, as well as by individual clinician and patient preferences. It is quite likely that a rate of codeine use could be lower than this value, leaving genetic screening as a non-viable option. The data on the rates of codeine use in postnatal populations around the world is limited and more research is required to better understand which populations may benefit most from this type of screening strategy. Despite this, the findings are relevant for jurisdictions with public or private payer health care systems that need such evidence to make informed choices regarding genotype screening strategies.

The scatter plot of the PSA indicated that 70% of iterations were in the upper right quadrant, more costly but more effective, and 27% were in the lower right, less costly and more effective, quadrant. Thus, decision makers are faced with the challenge of determining their willingness to pay for *CYP2D6* testing and balance the cost of testing against other interventions competing for the same resources.

This CEA found that screening reduced adverse events. This reduction was not large, as the overall rate of susceptible cases resulting from UM status is relatively small in the base case population. The costs to avert an adverse event were lower than the costs of some hospital stays. Despite this, there may be other strategies to avert adverse events in this particular setting, that is, a postnatal ward at an academic hospital. Kelly *et al.*[24] observed fewer adverse events when a more judicious and cautious approach to dosing and a more careful adherence to a follow-up protocol were used. Direct administration of morphine may be an alternative as it confers pain relief mediated by the opioid receptors but is not complicated by genetic polymorphisms in metabolic conversion to active agent. Alternatively, a number of other analgesics, including non-steroidal anti-inflammatory agents may be administered that could offer equivalent pain relief and fewer risks to the infant, or could be used as adjunctive therapy.

This study was limited by the availability of the published data. There were few studies from which parameter estimates could be derived since the literature addressing the safety of codeine use by breastfeeding mothers is scant.[28–33] For some parameters, such as rates of hospital admission following an adverse event, expert opinion was used due to a lack of published evidence. Moreover, when only a single estimate was available in the literature, expert opinion was required to estimate plausible ranges. As this study was a model of a hypothetical cohort of patients, we were not able to collect the primary data in the real world setting to determine the number of patients who may have been adequately treated on other analgesics. A medical chart review at a local institution was performed in 2014 to estimate the number of patients using opioids in the postnatal ward.[25] Those findings confirmed the validity of the base case rate and informed the current ranges used in the sensitivity analysis (Table 1).

Although there was an assumption that infants were solely breastfed during maternal therapy there is the possibility that, in a real world setting, some supplementary feeding would occur, thereby reducing exposure to codeine. Our parameters were derived from the literature that likely included some cases where the infant would have received supplementary feeding. Determining whether the adverse event rate has changed due to changes in prescribing as a result of medical advisories remains an area for future research. Further data would be helpful in ascertaining the current adverse event rate. For this reason, to accommodate parameter uncertainty, relatively wide ranges were used in the sensitivity analysis.

Since few studies following infants exposed to codeine through breastmilk exist, and the total number of adverse events was small, no clinical assessment of adverse event severity could be incorporated into the model. The analysis did account for the effect of severity of the adverse event on health resource use by distinguishing between infants who did not require emergency services, who did make emergency room visits and who required hospital admission. As large ranges for the point estimates did not change the model decision in sensitivity analysis, it is not expected that more severe or less severe events would have altered the findings appreciably.

The model did not include any patient/parent out-of-pocket expenses as a result of an adverse event. This data could only be derived from the clinical study.[24] as no previously published work collected this data. None of the parents whose infants experienced an adverse event in this study reported any out-of-pocket expenses associated with the event. These expenses would have likely been limited to transportation expenses to the hospital and were expected to be negligible in comparison to hospital admission costs, therefore having little impact on the overall ICER. The model also did not capture any long-term sequelae in the child resulting from an adverse event. Long-term effects in infants experiencing opiate-related CNS depression remain unknown and therefore a longer time horizon could not be incorporated in the analysis. The model investigated only screening for *CYP2D6* metabolizer status; however, other genetic variants are known to play a role in the metabolic pathway of codeine and genotyping alone does not determine ultimate phenotype patients will display.[34,35] This analysis did not evaluate the potential cost-effectiveness of testing for genetic variants of other enzymes or for testing an infant directly. Finally, it is currently not possible to estimate health state utilities for infants to calculate quality-adjusted life-years (QALY)[36] and a cost-utility analysis could therefore not be conducted. This remains a limitation of the study and the field and may limit comparability across other interventions. The outcome of interest, adverse events averted, is nevertheless of clinical importance and relevant to decision makers.

The pharmacogenetic screen evaluated here would reveal information to a patient about her metabolism of codeine to its active metabolite morphine, and would also provide information about her metabolic capacity for a number of other medications that are metabolized by *CYP2D6*. The benefits of knowledge of metabolizer status on any future exposure to opioids, or other drugs metabolized by *CYP2D6*, were not incorporated into the analysis. Should this knowledge remain with the patient, it would allow clinicians to tailor prescribing to better suit the patient. This would be expected to translate into a better clinical effectiveness and safety profile for the patient, resulting in a more efficient allocation of health resources in the future.

As researchers learn more about the role of genetics in the susceptibility to both beneficial and harmful effects of medications, genetic testing will become more valuable in guiding patient care. Cost-effectiveness analysis has been used to evaluate the benefits of pharmacogenetic testing to guide treatment and improve outcomes in patients exposed to warfarin or drugs that metabolized by thiopurine methyl-transferase.[19,20] However, to date, there have been no studies evaluating the cost-effectiveness of pharmacogenetic testing to guide pharmacotherapy in lactating patients. Nor have there been evaluations that look at pharmacogenetic screening in a mother to avert outcomes in her infant. As analgesics are among the most common medications used by lactating women, particularly in the perinatal period, this type of evaluation is relevant to a majority of patients. For the decision maker, this provides a step towards understanding the value of novel interventions. New pharmacogenetic technologies are emerging at a rapid pace but the benefits to the patient, and to society, must be evaluated systematically before such strategies are implemented. Choosing the technologies that represent the best value for the health care dollar invested are critical to improving health policy decision-making.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by scholarships from the Ontario Student Opportunity Trust Fund – Hospital for Sick Children Foundation Student Scholarship Program, the Ontario Graduate Scholarship Program, the Institute of Health Policy, Management and Evaluation and the Canadian Federation of University Women.

AUTHOR CONTRIBUTIONS

MEM, HB, GK, SI, WJU designed the research. MEM, DFL performed the research and analyzed the data. MEM, WJU wrote the paper. MEM, DFL performed the research and analyzed the data. MEM, WJU wrote the paper.

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