



**The Hospital for Sick Children
Technology Assessment at SickKids (TASK)**

**A COST-EFFECTIVENESS ANALYSIS OF MATERNAL
GENOTYPING TO GUIDE TREATMENT FOR
POSTPARTUM PAIN AND AVERT INFANT ADVERSE
EVENTS**

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REPORT HIGHLIGHTS

The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report and its appendices. Full documents are available for download

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Conflicts of interest

The authors declare no conflicts of interest.

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Introduction

In Ontario, a significant proportion of obstetrical deliveries are accompanied by surgical procedures or medical intervention. Most new mothers will therefore require some form of analgesia in the immediate postnatal period,¹ a time when establishment of breastfeeding is critical. Fortunately, most analgesics used post-natally are not contraindicated in lactating women,² and breastfeeding can proceed. Recently, long-standing recommendations regarding post-natal analgesia were called into question following a fatality of an infant whose mother had been taking acetaminophen with codeine for post delivery pain.³ Genotyping revealed that the mother was an ultra-rapid metabolizer (UM), causing her to produce higher amounts of morphine, the active metabolite of codeine. As a result, high amounts of morphine were excreted into her milk and ingested by the infant. The authors postulated that this was the reason for the child's intoxication and premature death.

Key Messages

- A majority of new mothers will require pain relief after the delivery of their child and while they are breastfeeding
- Some infants may experience adverse events when mothers are taking codeine containing analgesics
- Genotyping may be able to identify at risk mother-infant pairs, thereby averting adverse events in infants
- A cost-effectiveness analysis showed that implementing a genotyping program for all prenatal patients would result in an incremental cost effectiveness ratio of \$9,997 per infant adverse event averted
- This will have implications for many new mothers and their health care providers world-wide.

Consequently, the FDA⁴ and Health Canada⁵ issued public health advisories and label changes. This has led to modifications in clinical practice in maternity wards across Canada and North America.

Genotyping is used as a strategy to guide drug and dose selection in other areas of medicine where specific patient populations are more likely to benefit from a particular treatment. There is a test available to determine the activity of CYP2D6, the enzyme that metabolizes codeine, to determine if women are ultra-rapid metabolizers prior to drug administration. However, genetic testing is not without costs. Considering that the vast majority of women will require analgesia after delivery, any increases in health services use, owing to additional testing or adverse events experienced by infants would add costs to health care budgets. It is therefore important to ascertain the value for money of introducing CYP2D6 pharmacogenetic testing in post-partum women requiring analgesia.

Objectives

The primary objective was to conduct a cost-effectiveness analysis to determine the incremental costs of CYP2D6 pharmacogenetic testing compared to standard care in averting neonatal central nervous system (CNS) depressive adverse events during maternal treatment for postnatal pain.

Methods

Using a decision model, a cost-effectiveness analysis (CEA) was conducted from a societal perspective to compare two treatment options, namely, genotyping prior to delivery to guide treatment choice for postpartum analgesia as compared to standard care. Standard care consisted of no routine genotype testing and pharmacologic management of analgesia at the discretion of clinicians. This analysis was performed on a hypothetical cohort of prenatal patients who had not yet delivered their child and were anticipated to require treatment for analgesia after delivery. The primary effectiveness measure evaluated was the CNS adverse

event rate in infants. The base case was a prenatal patient whose metabolizer status was unknown, but who may require codeine analgesia after delivery and planned to breast feed her child. Parameter estimates, costs and ranges for sensitivity analyses were ascertained from a concurrent clinical study, from the literature and expert opinion.

Cost-effectiveness was expressed in terms of the incremental cost per adverse event averted, and was expressed in an incremental-effectiveness ratio (ICER), calculated from expected values of the decision analysis. Using Monte Carlo simulation as part of a probabilistic sensitivity analysis, a point estimate and 95% confidence interval (CI) were generated for ΔC and ΔE and the ICER.

Results

The base case analysis for the primary outcome of adverse events is shown below. The findings indicate that the screening option costs approximately \$521 per case while the no screen choice was less costly at \$175. There were 0.0346 fewer adverse events per case in the screening arm, resulting in a cost per adverse event averted of \$9,997

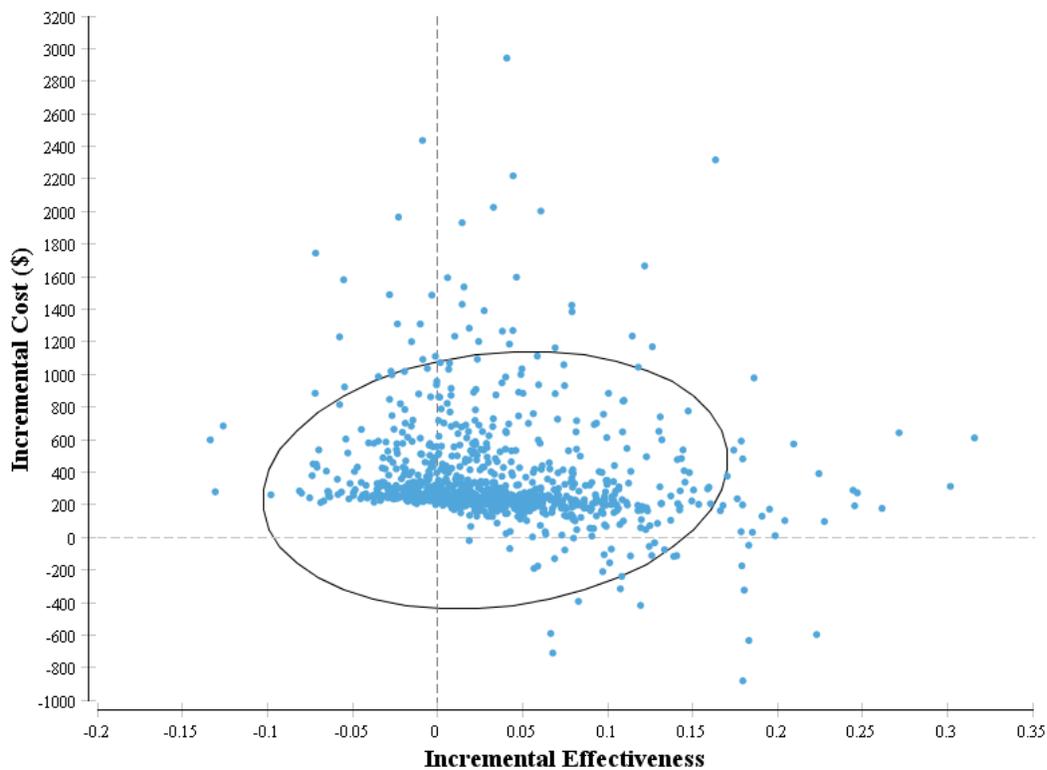
| Strategy | Cost Per Case | Adverse Events Per Case | Cost-Effectiveness Ratio |
|-----------|---------------|-------------------------|--------------------------|
| Screen | \$521 | 0.1339 | |
| No Screen | \$175 | 0.1656 | |
| Increment | \$346 | - 0.0346 | \$9,997 |

One-way sensitivity analysis indicated that the model was sensitive only to a single variable, the cost of a hospital admission. When hospital admission costs associated with a severe adverse event 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. That is, screening did not become cost saving.

Results of the probabilistic sensitivity analysis are shown below. After 1000 iterations of the model, the mean difference in costs was \$353 (95% CI -\$55 to \$1236) and the mean difference in adverse events was -0.0339 (95% CI (-0.0566 to 0.1785). The ICER was \$10,433.

| Strategy | Mean Cost per Case (95% CI) | Mean Adverse Events per Case (95% CI) | Cost-Effectiveness Ratio |
|--------------------|--------------------------------|--|--------------------------|
| Screen | \$537 (\$242, \$1671) | 0.1339 (0.0543, 0.2518) | |
| No Screen | \$184 (\$12, \$1137) | 0.1687 (0.0691, 0.3095) | |
| Incremental | \$353 (-\$55, \$1236) | - 0.0339 (-0.0566, 0.1785) | \$10,433 |

As seen in the scatterplot below, the incremental costs are nearly always positive, i.e. screening costs more than standard care, but that the incremental effects are also often positive, more adverse events are averted, with 75% of the points in the quadrant where both costs and adverse events averted are positive.



Conclusions

As genetic testing technologies improve and the demand for these services increases, it has become increasingly critical to evaluate their clinical merit and cost-effectiveness for allocation decision-making under constrained budgets. In this analysis, although genotyping to guide pharmacotherapy was not cost saving, the cost to avert an infant adverse event may represent good value for money. It is not yet known whether implementation would be clinically viable, however since analgesia is among the most common treatments used by lactating women these findings will have implications for many new mothers and their health care providers world-wide.

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