A Cost-Effectiveness Analysis of Maternal Genotyping to Guide Treatment in Postnatal Patients
DISCLOSURE

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SickKids RestraComp
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Institute of Health Policy, Management and Evaluation
Canadian Federation of University Women
The Issues

- Treating a new mother with medications may present a dilemma due to concerns of unnecessary infant exposure through breastmilk
- Recent evidence of serious adverse events associated with codeine use in the neonatal period ⇒ labelling change by federal regulators and practice changes across the country
- Inconsistent practice guidelines across institutions
- Increased risk may be associated with maternal ultrarapid metabolizer (UM) phenotype (CYP2D6)
- Pharmacogenetic testing increasingly used to guide treatment and improve care
Rationale

- Genotyping may be able to identify at risk mother-infant pairs
- Analgesic medications are relatively inexpensive
- Adverse events (AEs) can be costly and place significant burdens on the health care system
- Genotyping can be expensive – *the promise of personalized medicine*
- HTA evidence is required to better inform clinical, institutional and policy decision makers
Objective

• To determine the incremental costs of CYP2D6 pharmacogenetic testing compared to standard of care in averting neonatal CNS depressive adverse events
Methods – Cost Effectiveness Analysis

- A cost-effectiveness analysis was conducted using a decision model, to determine the expected values of costs and effectiveness of the proposed intervention (CYP2D6 screening to guide treatment)
- Perspective: Societal (public payer, private payers, out-of-pocket)
- Time horizon: time of screening procedure to completion of drug therapy
- Outcome: CNS depressive adverse events
  - sedation, poor latch or feeding, difficulty breathing or limpness
- Extensive sensitivity analysis (including PSA) was performed
- Additional scenarios of a modified base case also evaluated
The Base Case and the Decision

Prenatal patient who may require analgesia after delivery

Pharmacogenetic screening prior to delivery. Non-opioid analgesics to women who test positive for UM phenotype and codeine administration (as required) if patient tests negative for UM

Standard care. No pharmacogenetic testing and codeine as required.
# Base Case Inputs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case Estimate</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Distribution for PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability UM</td>
<td>0.0800</td>
<td>0.0100</td>
<td>0.4000</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability test positive, given UM (True Positive)</td>
<td>0.9900</td>
<td>0.7000</td>
<td>1.0000</td>
<td>Fixed</td>
</tr>
<tr>
<td>Probability codeine used</td>
<td>0.6584</td>
<td>0.4155</td>
<td>0.8250</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability AE, among UM</td>
<td>0.6667</td>
<td>0.2174</td>
<td>1.0000</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability AE, non-UM</td>
<td>0.2174</td>
<td>0.0210</td>
<td>0.3077</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability of emergency room with AE</td>
<td>0.1143</td>
<td>0</td>
<td>0.2343</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability of hospital admission</td>
<td>0.9000</td>
<td>0.7500</td>
<td>1.0000</td>
<td>Beta</td>
</tr>
<tr>
<td>Test cost (genotyping analysis)</td>
<td>$150.00</td>
<td>$90.00</td>
<td>$1300.00</td>
<td>Gamma</td>
</tr>
<tr>
<td>Emergency room visit</td>
<td>$278.38</td>
<td>$6.50</td>
<td>$1769.95</td>
<td>Gamma</td>
</tr>
<tr>
<td>Parent lost productivity day</td>
<td>$250.23</td>
<td>$194.83</td>
<td>$525.26</td>
<td>Gamma</td>
</tr>
<tr>
<td>Hospital admission Cost</td>
<td>$6,865.32</td>
<td>$6.50</td>
<td>$387,058.59</td>
<td>Gamma</td>
</tr>
<tr>
<td>Hospital admission Quantity (days)</td>
<td>5.1</td>
<td>1</td>
<td>169</td>
<td>Gamma</td>
</tr>
</tbody>
</table>

AE=adverse event  
UM=ultrarapid metabolizer
Folding back the tree

- Incremental cost-effectiveness ratio (ICER)

\[
ICER = \frac{\text{costs per mother} \cdot \text{infant pair intervention group} - \text{cost per pair comparator group}}{\text{AEs per infant intervention group} - \text{AEs per infant comparator group}}
\]

\[
= \frac{\Delta C}{\Delta E}
\]
Assumptions

- Assume 0% codeine (or any other opioid) use if UM positive
- Only first incident of codeine use evaluated, subsequent exposure to opioid analgesics not accounted for
- Infants are exclusively breastfed during the interval of drug use
- Rates of opioid-related adverse events do not differ for male and female offspring
- Infants are born at term, and were healthy at birth
- CNS depressive events assumed to be due to exposure, unless alternate diagnosis is made by a clinician
- No maternal adverse events included in the model
Methods

- Sensitivity analysis was conducted to evaluate robustness of the model
  - 1-way sensitivity analysis
  - Probabilistic sensitivity analysis (PSA)

- Scenario analyses of selected populations
  - High UM rate (pUM=0.4, range: 0.12-0.45)
  - Caesarean Sections only (pCodeine=0.93, range: 0.78-1.0)
Results: Probabilistic Sensitivity Analysis

- ICER
  - genotyping strategy cost $10,433 per adverse event averted

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean Cost per Case (95% CI) $</th>
<th>Mean Adverse Events per Case (95% CI)</th>
<th>Incremental Cost-Effectiveness Ratio (95% CI) $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>537.09 (241.78, 1670.63)</td>
<td>0.1339 (0.0543, 0.2518)</td>
<td></td>
</tr>
<tr>
<td>No Screen</td>
<td>183.73 (12.15, 1137.30)</td>
<td>0.1687 (0.0691, 0.3095)</td>
<td></td>
</tr>
<tr>
<td>Incremental</td>
<td>353.36 (-55.14, 1235.91)</td>
<td>-0.0339 (-0.1785, 0.0566)</td>
<td>10,432.73</td>
</tr>
</tbody>
</table>
ICER Scatter
Result: One-Way Sensitivity Analysis

- The ICER was sensitive to:
  - costs of hospital admission as a result of an adverse event
  - when costs >$104,000 per event, screening was the preferred strategy

- Dominance of screening strategy sensitive to:
  - prevalence of codeine use
  - when \( p_{\text{codeine}} < 0.53 \), screening was dominated by standard care
## Results: Scenario - High UM rate

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean Cost per Case (95% CI)</th>
<th>Mean Adverse Events per Case (95% CI)</th>
<th>Incremental Cost-Effectiveness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>479.46 (235.70, 1524.12)</td>
<td>0.0877 (0.0345, 0.1603)</td>
<td></td>
</tr>
<tr>
<td>No Screen</td>
<td>287.11 (22.53, 1572.36)</td>
<td>0.2619 (0.1196, 0.4323)</td>
<td></td>
</tr>
<tr>
<td>Incremental</td>
<td>192.35 (-664.15, 1142.56)</td>
<td>-0.1743 (-0.3455, -0.0353)</td>
<td>1,137.56</td>
</tr>
</tbody>
</table>

![Graph showing incremental cost vs. incremental effectiveness](image)
## Results: Scenario – Caesarean Section

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean Cost per Case (95% CI)</th>
<th>Mean Adverse Events per Case (95% CI)</th>
<th>Incremental Cost-Effectiveness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>613.57 (234.70, 2268.88)</td>
<td>0.1885 (0.0152, 0.5371)</td>
<td></td>
</tr>
<tr>
<td>No Screen</td>
<td>267.73 (8.19, 1610.98)</td>
<td>0.2407 (0.0283, 0.5982)</td>
<td></td>
</tr>
<tr>
<td>Incremental</td>
<td>345.82 (-95.27, 1329.49)</td>
<td>-0.0522 (-0.2494, 0.0266)</td>
<td>6,626.50</td>
</tr>
</tbody>
</table>

![Scatter plot showing incremental cost vs. incremental effectiveness]
Discussion

- Pharmacogenetic testing resulted in increased costs over standard care but decreased AE rates, a value of $10,433
- Model was not sensitive to variation in most variables suggesting it is robust.
Strengths

• First example of a CEA to evaluate genotyping to guide treatment for a new mother and avert AEs in her child
• Unique example of CEA in maternal-child health
• Utilization rates similar to those previously published
• Inform policy decisions
Limitations

- Small amount of published data from which to ascertain rates and ranges
  - Decision model may mitigate this
- Clinical practice changes over time and across settings
- No measure of future benefits of knowledge of metabolizer status or maternal adverse events
- Loss of lifetime productivity due to death not captured in short time horizon
- Death rates too unstable to include life years in the model
Implications

- Findings are relevant to patients, clinicians, and decision makers
- For the clinician, screening may not be cost-effective for all populations
  - sound clinical management and observation is critical
- For decision makers, this strategy would reduce AEs but at a cost
  - benefits of pharmacogenetic screening strategies should be evaluated for specific screens and specific outcomes
- Will have implications for vast numbers of mothers and children each year in Canada and internationally, and will inform decision making regarding reimbursement for genetic testing
- This model may be adaptable to other pharmacogenetic health economic questions
- The field of pharmacogenetic testing and treatment is rapidly evolving