NGS & Return of Secondary Findings for Colorectal Cancer Syndromes

A Cost-Effectiveness and Value-based Framework Analysis

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Univ. of Washington (Veenstra)
Reference case

Canada

- Maximize health status s/t budget constraints
- $\Delta C / \Delta QALY < \lambda$
- $\lambda$ is opportunity cost (shadow price)
- Healthcare system perspective
- QALY via EQ-5D, HUI
Value
(preference-based)

Personal utility = value patients ascribe to genomic information
  • Enhances sense of control, self-identity (Foster, 2009)
  • Resolves diagnostic uncertainty (Regier, 2009)

Decision-makers need a quantification and valuation of all health and non-health effects of interventions, and summarize those effects in a single quantitative measure (Second Panel on Cost-Effectiveness in Health and Medicine, 2016)
Secondary Findings

Next generation sequencing & SFs

• Information of risk of disease not related to the patient’s current diagnosis

American College of Medical Genetics and Genomics

• Return SFs with effective medical treatment (58 genes)

Canadian College of Medical Geneticists

• For monogenic diseases, don’t return b/c of high costs financial and emotional
Aim: What is the predicted uptake and willingness to pay of different strategies for returning secondary findings? (Regier et al, 2015)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Option A</th>
<th>Option B</th>
<th>No information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease risk</strong></td>
<td>Diseases with a 5% lifetime risk or higher</td>
<td>Diseases with a 90% lifetime risk or higher</td>
<td>No information</td>
</tr>
<tr>
<td>More diseases will be identified if the lifetime risk is lower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease treatability</strong></td>
<td>Recommended effective medical treatment only</td>
<td>Recommended effective lifestyle change only</td>
<td>No information</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td>Very severe health consequences</td>
<td>Severe health consequences</td>
<td>No information</td>
</tr>
<tr>
<td>Health consequences of the diseases you may develop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carrier status</strong></td>
<td>Does not provide information on carrier status</td>
<td>Information on whether your family members could be affected</td>
<td>No information</td>
</tr>
<tr>
<td>Disease risk not affecting you but could affect your family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost to you</strong></td>
<td>$1500</td>
<td>$750</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Your preference</strong></td>
<td><strong>Option A □</strong></td>
<td><strong>Option B □</strong></td>
<td>No information □</td>
</tr>
<tr>
<td>Scenario no.</td>
<td>New policy scenario</td>
<td>Prevailing policy scenario</td>
<td>Average incremental willingness to pay, $ (95% CI)*</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
</tbody>
</table>
| 1           | Return results only for disorders with:  
• Recommended effective medical treatment  
• Severe health consequences  
• ≥ 80% lifetime risk          | Information on incidental findings is not returned                                      | 445 (322–567)                                      | 66 (63–71)                                           |
| 2           | Return results only for disorders with:  
• Recommended effective medical treatment and lifestyle change  
• Severe health consequences  
• ≥ 80% lifetime risk          | Information on incidental findings is not returned                                      | 641 (520–762)                                      | 73 (69–77)                                           |
| 3           | Patient’s choice between 2 options —  
Return results only for disorders with:  
• Any treatability level  
• Severe health consequences  
• ≥ 80% lifetime risk  
Or return results only for disorders with:  
• Recommended effective medical treatment  
• Severe health consequences  
• ≥ 80% lifetime risk | Recommended effective medical treatment only; severe health consequences;  
≥ 80% lifetime risk | 280 (248–313)                                      | • Medical and nonmedical treatment  
27 (24–29)  
• Medical treatment only 49 (45–52)  
• Total uptake 76 (72–79) |

Note: CI = confidence interval.  
*Willingness to pay was derived from the estimates of the mixed logit statistical model using the compensating variation formula. All estimates are in 2013 Canadian dollars.
Value for Money

$\Delta$Cost/$\Delta$QALY for returning SFs (Bennette et al, 2015)

- $44,800$ (cardiomyopathy), $115,020$ (colorectal cancer), $133,400$ (population screening)

Decision uncertainty

- $85\%$ (cardiomyopathy), $28\%$ colorectal cancer, $10\%$ (population screening)

Limitations

- Upstream cost/consequences
- Personal utility
Research question

• $\Delta\text{Cost}/\Delta\text{QALY}$ of NGS for colorectal cancer and polyposis syndromes (CRCP) & return of secondary findings

  \[ \text{ICER} = \frac{\Delta\text{C}}{\Delta\text{QALYs}} < \lambda \]

• What is the net monetary benefit when allowance is made for personal utility?

  \[ \text{V-NMB} = \xi + \lambda \Delta\text{QALYs} - \Delta\text{C} \]
Table: Incremental costs and QALYs of adjusted cost-effectiveness model for a 50 year-old colorectal cancer patient tested for Lynch Syndrome, $\lambda = $100,000/QALY

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Number of findings detected in population</th>
<th>Incremental $</th>
<th>Incremental QALYs</th>
<th>ICER ($/QALY)</th>
<th>Net Monetary Benefit†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer Polyposis Syndromes</td>
<td>1540</td>
<td>$5,290</td>
<td>0.100</td>
<td>$53,063</td>
<td>$6,176</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>42</td>
<td>-$14,324</td>
<td>0.214</td>
<td>-$67,020</td>
<td>$37,193</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>67</td>
<td>$26,976</td>
<td>1.813</td>
<td>$14,880</td>
<td>$155,810</td>
</tr>
<tr>
<td>Hypertrophic and dilated cardiomyopathy</td>
<td>22</td>
<td>$188,010</td>
<td>0.692</td>
<td>$271,746</td>
<td>-$117,328</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>21</td>
<td>$542,154</td>
<td>0.198</td>
<td>$2,739,354</td>
<td>-$520,866</td>
</tr>
<tr>
<td>Malignant hyperthermia susceptibility</td>
<td>9</td>
<td>-$2,585</td>
<td>0.008</td>
<td>Dominated</td>
<td>$4,903</td>
</tr>
<tr>
<td>Long QT Syndromes</td>
<td>5</td>
<td>$286,004</td>
<td>0.114</td>
<td>$2,501,041</td>
<td>-$273,073</td>
</tr>
<tr>
<td>Other, rare conditions (combined)</td>
<td>11</td>
<td>$723,825</td>
<td>0.000</td>
<td>Dominated</td>
<td>-$722,328</td>
</tr>
<tr>
<td><strong>Total (SFs excluding CRCP)</strong></td>
<td><strong>176</strong></td>
<td><strong>$4,225</strong></td>
<td><strong>0.006</strong></td>
<td><strong>$769,928</strong></td>
<td><strong>-$5737</strong></td>
</tr>
<tr>
<td><strong>Total (all conditions)</strong></td>
<td><strong>1716</strong></td>
<td><strong>$5,961</strong></td>
<td><strong>0.105</strong></td>
<td><strong>$72,394</strong></td>
<td><strong>$4,587</strong></td>
</tr>
</tbody>
</table>
Figure: Cost-effectiveness acceptability curve with selected values of interest
Decision uncertainty

Reference case

- $\lambda=100,000 \text{ per QALY}$
- Probability of CRCP/SF cost-effectiveness was 79%

Incorporating preference-based personal utility

- $\lambda=$$100,000$ and $\xi=$ $445$
- V-NMB was $5,530$ (CR: -$3,013; $17,736$).
- The probability of CRCP/SF cost-effectiveness was 86%
Discussion

Methodological

• Preference-based utility for non-health outcomes not endorsed by CADTH
• Existing frameworks can be extended, not the reference case
• $\lambda = 100,000 \perp \xi = $445
• Need careful consideration of ethics implications

Applied

• Return of SF probably do not provide value for money
• Substantial decision uncertainty, inherent in precision medicine applications
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