From 57 to 6 strategies: Use of economic evaluation methods to identify efficient diagnostic strategies

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Disclosure

I have no actual or potential conflict of interest in relation to this topic or presentation.
**Pulmonary Embolism**

- Manifestation of venous thromboembolism
- Blockage of pulmonary artery and its branches
  - Obstructs blood flow = right ventricular strain, cardiovascular compromise and low blood oxygen levels
  - Clinical presentation: asymptomatic ↔ sudden death
Challenges in reaching a diagnosis

- Non-specific symptoms
  - Low diagnostic yield

- **Radiation exposure:** Highest in CT; lower radiation dose in VQ-based nuclear technologies.

- **Accessibility:** Canadian Medical Imaging Inventory (CMII) suggests that CT is most commonly available

Multi-component approach for diagnosis:
- clinical risk assessment
- rule-out tests
- diagnostic imaging
Possible Diagnostic Pathways for PE

Adults with suspected acute PE

Clinical decision rules
Wells or Geneva Rules

PERC

D-dimer

Imaging Leg US

Diagnostic Imaging Study
- CT-based studies (multi-detector)
- MRI
- VQ-based studies
  - Planar scintigraphy
  - VQ SPECT
  - VQ SPECT-CT
- Thoracic US

Discharge with or without monitoring

Detection

Treatment
Decision Problem

What is the cost-effectiveness of diagnostic pathways* to test adult patients suspected of acute pulmonary embolism?

*NOTE: Diagnostic pathway would represent all permutations possible involving risk stratification and the diagnostic imaging technology that are identified in the clinical review.
METHODS
Overview of Methods

• Type of Analysis: Cost-utility analysis
• Model structure:
  • Decision tree= immediate outcome from diagnostic strategies
  • Markov model= captures long-term implications of diagnosis results in initiating and continuing medical treatment
• Population: hemodynamically stable adults (55 years) suspected of a new-onset PE (i.e., 41.4% males; prevalence of PE =15.2%)
• Perspective: Canadian healthcare payer
• Time horizon: Lifetime, 1.5% discounting
Diagnostic Strategies

- 56 diagnostic strategies evaluated:
  - 47 based on the diagnostic pathways

<table>
<thead>
<tr>
<th>Clinical prediction rule</th>
<th>‘Rule out’ tests</th>
<th>Diagnostic Imaging</th>
<th>Non-Dx Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells (i.e, 3-level, 2-level)</td>
<td>d-Dimer</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>Revised Geneva</td>
<td>PERC ➔ d-Dimer</td>
<td>MRI</td>
<td>Leg US</td>
</tr>
</tbody>
</table>

- 9 controls:
  - Negative control: No screening – no treatment [n=1]
  - Positive controls: All proceed with diagnostic imaging [n=8]
Decision Tree (i.e., Diagnostic Accuracy)
## Linking Diagnosis to Clinical Management

<table>
<thead>
<tr>
<th>Outcome from Decision Tree</th>
<th>Clinical Management</th>
<th>Changes to Markov model</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positive</td>
<td>Receive treatment (3 mo)</td>
<td>↓ risk of recurrent PE ↑ risk of on-treatment bleeding AE</td>
</tr>
<tr>
<td>False Positive</td>
<td>Receive treatment (3 mo)</td>
<td>↑ risk of on-treatment bleeding AE</td>
</tr>
<tr>
<td>True Negative</td>
<td>No treatment</td>
<td>None: general population model</td>
</tr>
<tr>
<td>False Negative</td>
<td>No treatment</td>
<td>Treatment withheld until recurrent PE: ↑ risk of recurrent PE and PE-related mortality</td>
</tr>
</tbody>
</table>
Markov Model (i.e., Diagnostic Utility)

Diagram:

- On treatment:
  - PE (first or recurrent)
  - CRNM (off txt: 4d)
  - ICH (off txt: 2wk)
  - Extracranial bleed (off txt: 1wk)
  - CTEPH

- Off Treatment:
  - Off Treatment

Long-term Health States:
- Post ICH
- Death

True Positives (TP)
Markov Model (i.e., Diagnostic Utility)
Markov Model (i.e., Diagnostic Utility)
Markov Model (i.e., Diagnostic Utility)
Efficiency in Diagnostic Models

**Issue:** Conventional method of probabilistic analysis entails running the full hybrid model across the 56 diagnostic strategies.

→ Long run time on Excel (i.e., 5,000 replications)

**Alternative:** Five sub-models exist

- Decision Tree: Diagnostic test accuracy
- Markov model: Diagnostic utility/clinical management
- Diagnosis test accuracy is coupled unidirectionally to clinical management
- Outcome from test submodel impacts outcome of the diagnostic utility submodels, but not the other way
Steps for Alternative Approach

1. Run diagnostic test submodel probabilistically over ‘n’ replications to determine 2x2 table of test results for each diagnostic strategies.

<table>
<thead>
<tr>
<th>Replication</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.842</td>
<td>0.158</td>
<td>0.132</td>
<td>0.039</td>
<td>0.809</td>
<td>0.020</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.849</td>
<td>0.151</td>
<td>0.134</td>
<td>0.040</td>
<td>0.808</td>
<td>0.018</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>N</td>
<td>0.837</td>
<td>0.163</td>
<td>0.140</td>
<td>0.054</td>
<td>0.794</td>
<td>0.012</td>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Run probabilistically the four diagnostic utility submodels for ‘n’ replication to calculate expected costs and utilities associated with the four diagnostic outcomes.

<table>
<thead>
<tr>
<th>Replication</th>
<th>TP Costs</th>
<th>TP QALYs</th>
<th>FP Costs</th>
<th>FP QALYs</th>
<th>FN Costs</th>
<th>FN QALYs</th>
<th>TN QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22,195</td>
<td>15.426</td>
<td>8,253</td>
<td>18.070</td>
<td>22,232</td>
<td>9.904</td>
<td>18.131</td>
</tr>
<tr>
<td>2</td>
<td>13,190</td>
<td>15.490</td>
<td>5,228</td>
<td>17.880</td>
<td>14,752</td>
<td>10.957</td>
<td>17.937</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

3. Calculate expected costs and utilities for each strategy based on weighting the proportions of TP, FP, TN, FN in each replication.

\[
\text{Costs} = p_{TP} \times \text{Cost}_{TP} + p_{FP} \times \text{Cost}_{FP} + p_{FN} \times \text{Cost}_{FN}
\]

\[
\text{QALYs} = p_{TP} \times \text{QALYs}_{TP} + p_{FP} \times \text{QALYs}_{FP} + p_{TN} \times \text{QALYs}_{TN} + p_{FN} \times \text{QALYs}_{FN}
\]
RESULTS
**Reference Case (Conventional)**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Diagnostic Test Accuracy</th>
<th>Costs</th>
<th>QALYs</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>ICUR (cost/QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification</td>
<td>Dx Imaging Test for non-Dx</td>
<td>TP</td>
<td>FP</td>
<td>TN</td>
<td>FN</td>
<td>2,860</td>
</tr>
<tr>
<td>No Imaging</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0.848</td>
<td>0.152</td>
<td>2,860</td>
</tr>
<tr>
<td>Revised Geneva</td>
<td>PERC&gt;d-dimer CT CT</td>
<td>0.133</td>
<td>0.039</td>
<td>0.809</td>
<td>0.018</td>
<td>3,758</td>
</tr>
<tr>
<td>Wells: 3 tier</td>
<td>PERC&gt;d-dimer CT CT</td>
<td>0.134</td>
<td>0.040</td>
<td>0.808</td>
<td>0.018</td>
<td>3,767</td>
</tr>
<tr>
<td>Wells: 2 tier</td>
<td>PERC&gt;d-dimer CT CT</td>
<td>0.138</td>
<td>0.047</td>
<td>0.801</td>
<td>0.014</td>
<td>3,895</td>
</tr>
<tr>
<td>Wells: 2 tier</td>
<td>d-dimer CT CT</td>
<td>0.139</td>
<td>0.054</td>
<td>0.794</td>
<td>0.013</td>
<td>4,004</td>
</tr>
<tr>
<td>Gestalt</td>
<td>CT CT</td>
<td>0.141</td>
<td>0.079</td>
<td>0.769</td>
<td>0.011</td>
<td>4,397</td>
</tr>
</tbody>
</table>

*The remaining 51 strategies were found to be dominated or extendedly dominated by the six strategies on the efficiency frontier

- Run time on Excel ~ 7 days
## Reference Case (Alternative)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Dx Imaging</th>
<th>Test for non-Dx</th>
<th>Diagnostic Test Accuracy</th>
<th>Costs</th>
<th>QALYs</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>ICUR (cost/QALYs)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Imaging</td>
<td></td>
<td></td>
<td></td>
<td>2,997</td>
<td>16.828</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Revised Geneva</td>
<td>PERC&gt;d-dimer</td>
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<td>CT</td>
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<td>CT</td>
<td>0.140</td>
<td>0.054</td>
<td>0.794</td>
<td>0.012</td>
<td>4,183</td>
</tr>
<tr>
<td>Gestalt</td>
<td></td>
<td></td>
<td></td>
<td>4,571</td>
<td>17.497</td>
<td>388</td>
<td>0.006</td>
<td>57,097</td>
</tr>
</tbody>
</table>

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- Run time on Excel = 4 hours
Cost-Effectiveness Acceptability Curve (Alternative)
Sensitivity Analysis

- Range of sensitivity analyses conducted including scenarios (e.g., discount rate, different clinical DTA and utility inputs), subgroups (i.e., age, inpatient, pregnant) and exploratory analysis (i.e., inclusion of thoracic US)

- Model sensitive to:
  - Time horizon: Alters Risk/benefit
  - PE prevalence
  - Patients contra-indicated for CT imaging: Changes strategies evaluated
Discussion

• Increased complexity required to evaluate the cost-effectiveness of diagnostic strategies
  • Capture beyond diagnostic accuracy to diagnostic utility
  • Sequence of tests (each set of tests serves different diagnostic functions)
• CT present in all ‘cost-effective’ pathways
  • the key trade-offs lied with risk stratification and rule-out test
• Efficiency achieved by recognizing relationship between diagnosis outcome and management
Acknowledgement

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CADTH PE research team
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