Pharmacoeconomic Modeling

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Pharmacoeconomics

• Evaluates economic outcomes of pharmaceuticals and their impacts on people, organizations, and society
• Outcomes can include cost, mortality, morbidity, functional status, mental well-being, other aspects of health-related quality of life, etc.

Pharmacoeconomic Study Designs

• Clinical trials
• Observational studies
• Decision Analysis

Today’s talk will focus on the last of the 3 designs:
DECISION ANALYSIS
Decision Analysis

• Formal approach to “identifying, clearly representing, and formally assessing important features of a decision”
• Simplifications of complex systems that identify essential elements

Decision Analysis Approaches

• Most frequently used healthcare / pharmacoeconomic decision analytic approaches
  – Decision trees
  – Markov models
• Less frequently used approaches
  – Discrete event simulation
  – Dynamic transmission models
  – Partitioned survival models
  – Compartment models

Decision Trees

• “Models” that use a tree-like structure to organize thoughts and data about problems (e.g., treatment decisions) and their consequences
• Characterized by decisions, chances, and outcomes
• Results based on probabilities and “rewards” for outcomes
• Time usually not directly modeled in decision trees
Markov Models

- Repetitive decision trees used for modeling conditions that have events that may occur repeatedly over time or for modeling predictable events that occur over time (e.g., screening for disease at fixed intervals)
  - e.g., Cycling among heart failure classes or screening for colorectal cancer
- Use of Markov models simplifies presentation of tree structure
- Markov models explicitly account for timing of events

Outline

- Step-by-step (re)construction of rotavirus vaccination decision tree
- Bird’s-eye-view of diabetes prevention markov model
- 8 “competitive” diabetes Markov models
- Questions from audience

(Re)construction: Rotavirus Vaccination Decision Tree

The Rotavirus Problem

- "Rotavirus gastroenteritis is a major cause of mortality and morbidity among children 5 years of age.”
- "Worldwide, ∼500,000 childhood deaths are attributable to rotavirus disease each year, with the vast majority of these deaths occurring in developing countries.”
- "In Egypt, 33%–44% of all episodes of diarrhea in children <5 years of age are caused by rotavirus.”

Need for Vaccination

- "Because of the high burden of disease in both developed and developing countries, the need for an effective vaccine against the disease has been recognized by the Centers for Disease Control and Prevention, the World Health Organization (WHO), PATH, the Pan American Health Organization, and the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunizations)"
- [In 2010] "There are 2 newly licensed rotavirus vaccines and several vaccines still under development"

5 Steps in Developing a Decision Tree

1. Imagine the model, and draw the tree
2. Identify the probabilities
3. Identify the outcome values
4. Calculate expected values
5. Perform sensitivity analyses
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Types of Nodes

- Decision trees have a (horizontal) “trunk” and “branches”
- Main branch point is a decision, characterized by decision node (square)
- Succeeding branch points usually chances, characterized by chance nodes (circles)
- Terminal nodes (branch endings, commonly triangles)

Initial Decision *

* Tree construction demonstrated using TreeAge software
Rule 1
Node branches must be exhaustive and mutually exclusive.

Rule 2
At each chance node, the sum of the branch probabilities must equal 1.0
No Rotavirus / Rotavirus

No Rotavirus Program

Rotavirus vaccination?

Vaccination Program

Rotavirus

No Rotavirus

Rotavirus "Terminal Nodes"

No Rotavirus Program

Rotavirus

Vaccination Program

No Vaccination Program Tree

No Rotavirus

No med care

Phys visit

Hospital care

Death
ISPOR-SMDM Modeling Good Research Practices

- Consult with experts and stakeholders prior to, during, and after model development
- "Develop clear statement of decision problem, modeling objective, and scope of model"
- "Conceptual structure of a model should be driven by the decision problem or research question and not determined by data availability??"
- Model simplicity aids transparency, but model needs to be complex enough to answer question
5 Steps in Developing a Decision Tree

1. Imagine the model, and draw the tree
2. **Identify the probabilities**
3. Identify the outcome values
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Sources of Probabilities

- Observational data
  - Case/control studies
  - Cohort studies
  - Registries
- Clinical trials
- Literature
- "Expert" opinion / "best guess"
- Ideally all data come from a single study (allows maintenance of correlation structure within the data)
  - Rarely achieved
  - Most models resemble Chinese Menu
    - "One from column A and one from column B"

Estimation of Probabilities

- Can range from simple proportions to results of survival analysis and partitioned survival analysis, etc.
- To translate rates into probabilities:

\[ P(t) = 1 - e^{R(t)} \]

where \( P(t) \) equals the probability, \( R(t) \) equals the rate per period; and \( t \) equals the length of the period
No Vaccination Program Probabilities

- Rotavirus: 0.95
- Rotavirus Severity
  - No formal medical care required: 0.70
  - Physician visit: 0.27
  - Hospital visit: 0.03
  - Death | Hospital visit: 0.06

Vaccination Program Probabilities

- Vaccine uptake
  - No vaccination: 0.02
  - First vaccination: 0.98
  - Second vaccination | first: 0.9898
- Rotavirus Relative risk
  - Partial vaccination: 0.6775
  - Full vaccination: 0.355
- Medical care relative risk
  - Hospital visits: 0.209
  - Physician visits: 0.209
5 Steps in Developing a Decision Tree

1. Imagine the model, and draw the tree
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Outcomes

• # of cases of rotavirus
• # physician visits
• # hospital visits
• # deaths
• Costs
• DALYs
• Cost / case averted
• Cost / death averted
• Cost / DALY averted

Costs *

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost</th>
<th>Disc Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician visit</td>
<td>23.3</td>
<td>21.2</td>
</tr>
<tr>
<td>Hospital visit</td>
<td>102.5</td>
<td>96.7</td>
</tr>
<tr>
<td>Death</td>
<td>51.3</td>
<td>48.4</td>
</tr>
<tr>
<td>1 dose of vaccine</td>
<td>53.2</td>
<td>53.2</td>
</tr>
</tbody>
</table>

* Costs in 2005 Egyptian pounds (LE)
Discount rate: $1.03^{1.97067}$
5 Steps in Developing a Decision Tree

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Two Methods of Calculation

- Average out and fold back – Most common method
- Path probabilities
Average Out Formula

\[ \text{Expected Value} = \sum_{i=1}^{n} \text{Probability}_i \times \text{Outcome}_i \]

Roll Back of Cost: No Vaccination Strategy

\[
.05 \times 0 + .95 \times .07 \times 0 + .95 \times .27 \times 23.3 + .95 \times .028 \times 102.5 + .95 \times .002 \times 53.2 = 8.81
\]

* Assumes 1,909,000 birth cohort

<table>
<thead>
<tr>
<th>Service</th>
<th>Vaccination</th>
<th>No Vaccination</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>673,054</td>
<td>1,813,550</td>
<td>-1,140,496</td>
</tr>
<tr>
<td>Outpatient</td>
<td>44,917</td>
<td>483,311</td>
<td>-438,395</td>
</tr>
<tr>
<td>Hospital</td>
<td>5049</td>
<td>52,557</td>
<td>-47,508</td>
</tr>
<tr>
<td>Deaths</td>
<td>392</td>
<td>3264</td>
<td>-2873</td>
</tr>
<tr>
<td>Partial Vacc</td>
<td>56,125</td>
<td>0</td>
<td>56,125</td>
</tr>
<tr>
<td>Full Vacc</td>
<td>1,814,695</td>
<td>0</td>
<td>1,814,695</td>
</tr>
</tbody>
</table>

* Expected Events

* 8.31 discounted LE
Expected Costs *

<table>
<thead>
<tr>
<th>Service</th>
<th>Vaccination</th>
<th>No Vaccination</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>987,340</td>
<td>10,623,989</td>
<td>-9,636,648</td>
</tr>
<tr>
<td>Hospital</td>
<td>488,225</td>
<td>5,082,258</td>
<td>-4,594,033</td>
</tr>
<tr>
<td>Death</td>
<td>18,937</td>
<td>157,834</td>
<td>-138,897</td>
</tr>
<tr>
<td>Vaccine</td>
<td>198,037,951</td>
<td>0</td>
<td>198,037,951</td>
</tr>
<tr>
<td>Total</td>
<td>199,532,454</td>
<td>15,864,080</td>
<td>183,668,374</td>
</tr>
</tbody>
</table>

Assumes 1,909,000 birth cohort
Costs expressed in 2005 discounted Egyptian pounds (LE) (at the time, 5.79 LE = $1US)

Cost-Effectiveness Ratios *

<table>
<thead>
<tr>
<th>Service</th>
<th>ΔCost</th>
<th>ΔEffect</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/Case</td>
<td>183,668,374</td>
<td>1,140,496</td>
<td>161</td>
</tr>
<tr>
<td>Cost/Death</td>
<td>183,668,374</td>
<td>2873</td>
<td>63,929</td>
</tr>
<tr>
<td>Cost/DALY</td>
<td>183,668,374</td>
<td>94,993</td>
<td>1933</td>
</tr>
</tbody>
</table>

Assumes 1,909,000 birth cohort
Costs expressed in discounted Egyptian pounds (LE) (at the time, 5.79 LE = $1US)

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Sensitivity Analysis

- Demonstrates dependence/independence of a result on a particular assumption
- Identifies critical values of variables
- Identifies uncertainties requiring further research

Why Sensitivity Analysis?

- Even if data in model come from representative samples of target population, drawing different samples from target population would result in different point estimates
  - Can’t be certain that data in model represent correct estimates for population
- Often common for data to be:
  - Drawn from narrow samples that may not be representative of population for whom model is making predictions
  - Borrowed from related, but different diseases
  - E.g., second vaccination rates borrowed from different vaccines

Examples of Uncertainties

- Rotavirus incidence
  - 0 to 3-year incidence: 2 samples children under age 3 (N= 272 and 363) in 2 small geographic regions in Egypt
  - 4- and 5-year incidence: extrapolated from age-specific prevalence data from 3 hospital studies
  - Combined data used to define incidence for children under 5 for entire country
- Morbidity (% physician, %hospitalization)
  - 56 children plus 4 hospital-based surveillance studies from geographically and socioeconomically diverse populations
Results of Sensitivity Analysis

- Most influential parameters (in descending order)
  - Vaccine price
  - Rotavirus incidence
  - Rate of seeking outpatient care
  - Rate of seeking inpatient care
  - Outpatient care cost
  - Inpatient care cost
- If vaccine cost was 3.86 LE per dose (vs 53.2), the intervention becomes cost saving

Author’s Conclusions

- Inclusion of a rotavirus vaccine in Egypt’s Expanded Program on Immunization would have significant costs
- But should decrease costs associated with medical care and should increase health benefit of population and economic performance from resultant increases in a child’s life expectancy, quality of life, and parents’ productivity in the labor force
  - 7.3% decrease in vaccine costs; how important is that?
- Analysis should be seen as preliminary and should serve as a starting point for further refinement in parameter estimates and an expansion to consider a broader societal perspective including indirect costs.

Ratios Without Cost Offsets

<table>
<thead>
<tr>
<th>Service</th>
<th>Original ICER</th>
<th>Revised ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/Case</td>
<td>161</td>
<td>174</td>
</tr>
<tr>
<td>Cost/Death</td>
<td>63,929</td>
<td>68,931</td>
</tr>
<tr>
<td>Cost/DALY</td>
<td>1933</td>
<td>2085</td>
</tr>
</tbody>
</table>
(Repeat) Markov Models

- Repetitive decision trees used for modeling conditions that have events that may occur repeatedly over time or for modeling predictable events that occur over time (e.g., screening for disease at fixed intervals)
- Use of Markov models simplifies presentation of tree structure
- Markov models explicitly account for timing of events

"Bushiness" of Repetitive Trees

State Transition / Markov Models

- Develop a description of the disease by simplifying it into a series of states
- e.g., models of heart failure (HF) might be constructed with five health states
  - HF subdivided into New York Heart Association (NYHA) classes I through 4, and death (either from heart failure or other causes)
State Transition Model, NYHA Class and Death

Heart Failure Model

State Transition of Markov Models (II)

- Disease progression described probabilistically as a set of transitions among states in periods, often of fixed duration (e.g., months, years, etc.)
- Likelihood of making a transition defined as a set of transition probabilities
- Assess outcomes such as resource use, cost, and QALYs based on resource use, cost, and preference scores while making transitions among states
- e.g., average cost among patients who begin a period in NYHA class 1 and begin the next period in NYHA class 2

Mathematical Description of Effect of Intervention

- Develop mathematical description of effects of an intervention as a change in either (or both):
  - Transition probabilities among states (e.g., by reducing probability of death) or
  - Outcomes within states (e.g., after intervention, those in NYHA class 1 cost $500 less than do those without intervention)
“5” Steps in Developing Markov Model

1. Imagine the model, draw the “tree”
   1A. Enumerate the states
   1B. Define the allowable state transitions

2. Identify the probabilities
   2A. Associate probabilities with transitions
   2B. Identify a cycle length and number of cycles
   2C. Identify an initial distribution of patients within states

3. Identify the outcome values

4. Calculate the expected values

5. Perform sensitivity analysis

Steps 1-1b: Imagine the model, draw the “tree”

Diabetes Prevention Model

Steps 2-2c: Identify the Probabilities

"Key" Transition Probabilities

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of progression from IGT to T2D/100 patient years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years 1-3</td>
<td>11.0</td>
<td>7.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Years 4+</td>
<td>5.6</td>
<td>4.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Transition probabilities of regression from IGT to NGR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>10.0</td>
<td>12.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>5.6</td>
<td>6.8</td>
<td>13.3</td>
</tr>
<tr>
<td>Year 3</td>
<td>3.5</td>
<td>8.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Year 4+</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Rates of progression from NGT to T2D/100 patient years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All years</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Step 3: Identify the Outcome Values
### “Key” Cost Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual costs of intervention ($A)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>154</td>
<td>998</td>
<td>1487</td>
</tr>
<tr>
<td>Year 2</td>
<td>75</td>
<td>898</td>
<td>915</td>
</tr>
<tr>
<td>Year 3</td>
<td>75</td>
<td>899</td>
<td>940</td>
</tr>
<tr>
<td>Year 4</td>
<td>172</td>
<td>292</td>
<td>120</td>
</tr>
<tr>
<td>Year 5+</td>
<td>15</td>
<td>128</td>
<td>39</td>
</tr>
<tr>
<td><strong>Cost of states ($A)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGR</td>
<td>1907</td>
<td>1907</td>
<td>1907</td>
</tr>
<tr>
<td>IGT</td>
<td>2158</td>
<td>2158</td>
<td>2158</td>
</tr>
<tr>
<td>T2D</td>
<td>5018</td>
<td>5018</td>
<td>5018</td>
</tr>
</tbody>
</table>

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### Step 4: Calculate the Expected Values

**Results**

- Intensive lifestyle change ($A 62,091) cost less than control ($A 62,380) or metformin ($A 63,597)
- Intensive lifestyle change (11.21 QALYs) led to a greater number of QALYs than control (10.82) or metformin (10.94)
- Intensive lifestyle change dominates control or metformin (costs less and does more)
Diabetes Modeling

- One of the most modeled diseases in the world
- 8 “major” models that compete with one another, plus many additional models
  - IMS CORE Diabetes Model
  - University of Michigan Model for Diabetes
  - Economics and Health Outcomes in Type 2 Diabetes Mellitus Model
  - United Kingdom Prospective Diabetes Study (UKPDS) Outcomes model
  - The UKPDS Risk Engine
  - Centers for Disease Control (CDC)-RTI Diabetes Cost-effectiveness Model
  - Cardiff Research Consortium Model
  - Evidence-Based Medicine Integrator Simulator

Competitions

- Mount Hood Challenge
  - Sporadically held (#4, 2004; #5, 2010)
- Focal point: comparison of health economic diabetes models both in terms of structure and performance
- At the 5th Challenge the 8 models were used to simulate results of 4 diabetes randomized controlled trials: ASPEN, ADVANCE, ACCORD (blood pressure) and ACCORD (glucose)


Mount Hood Results, ASPEN / ADVANCE Trials

<table>
<thead>
<tr>
<th></th>
<th>ASPEN</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interv</td>
<td>Cont</td>
</tr>
<tr>
<td>TRIAL</td>
<td>13.7</td>
<td>15.0</td>
</tr>
<tr>
<td>ECHO</td>
<td>12.3</td>
<td>14.8</td>
</tr>
<tr>
<td>UKPDS-OM</td>
<td>9.6</td>
<td>11.1</td>
</tr>
<tr>
<td>UKPDS-RE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IMS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Michigan</td>
<td>2.7</td>
<td>3.3</td>
</tr>
<tr>
<td>CDC-RTI</td>
<td>12.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Cardiff</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ASPEN: composite endpoint; ADVANCE: CVD mortality
Mount Hood Results, ACCORD Trials

<table>
<thead>
<tr>
<th></th>
<th>ACCORD BP</th>
<th></th>
<th>ACCORD GL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interv</td>
<td>Cont</td>
<td>Diff</td>
<td>Interv</td>
</tr>
<tr>
<td>TRIAL</td>
<td>1.9</td>
<td>2.1</td>
<td>0.2</td>
<td>6.9</td>
</tr>
<tr>
<td>ECHO</td>
<td>2.2</td>
<td>2.6</td>
<td>0.4</td>
<td>8.1</td>
</tr>
<tr>
<td>UKPDS-OM</td>
<td>1.7</td>
<td>1.9</td>
<td>0.2</td>
<td>6.7</td>
</tr>
<tr>
<td>UKPDS-RE</td>
<td>1.9</td>
<td>2.1</td>
<td>0.2</td>
<td>6.3</td>
</tr>
<tr>
<td>IMS</td>
<td>1.0</td>
<td>1.2</td>
<td>0.2</td>
<td>--</td>
</tr>
<tr>
<td>Michigan</td>
<td>2.3</td>
<td>2.8</td>
<td>0.5</td>
<td>--</td>
</tr>
<tr>
<td>CDC-RTI</td>
<td>1.7</td>
<td>1.9</td>
<td>0.2</td>
<td>--</td>
</tr>
<tr>
<td>Cardiff</td>
<td>1.0</td>
<td>1.1</td>
<td>0.1</td>
<td>--</td>
</tr>
</tbody>
</table>

ACCORD BP and ACCORD GL: composite CVD endpoint

5th Mount Hood Challenge Results

- Results of models varied from each other and, in some cases, from the published trial data
- Models generally predicted relative benefit of interventions, but performed less well in terms of predicting absolute risks
  - ASPEN: Models generally overpredicted absolute risk reductions, with 1 substantially underpredicting
  - Advance: Models generally underpredicted absolute risk reductions
  - Accord BP: Models generally correctly predicted absolute risk reductions
  - Accord GL: Models generally overpredicted absolute risk reductions

Advantages of Decision Analysis

- Forces a systematic examination of the problem
- Forces the assignment of explicit values
- Controls complexity and thus avoids processing errors
Disadvantages of Decision Analysis

• Time consuming
• Results difficult to explain
• Methods not well understood or trusted by policy makers

Use of Models to Transfer Results To Local Settings

• Usefulness depends on how flexible a model is
  – If health care prices are all that can be changed, results unlikely to illuminate actual impact of therapy in local setting
    • Within levels of economic development, little evidence that local prices drive economic value
• What should we be able to change?
  – Epidemiology
  – Clinical practice “style”
  – “Unit costs” / “Price weights”
  – Odds ratios / relative risks
  – Preference scores

How to Use Decision Analysis

• To organize the issues for traditional decision making
• To identify a critical element for intensive study
• To provide information (not answers) for decision making