Pharmacoeconomic Modeling

HG1

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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

Slide 1

HG1 add graphic with limited set of transition probabilities for diabetes prevention model;
add discounting for costs of rotavirus
Henry Glick, 11/24/2013

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

- Ortega O, El-Sayed N, Abd-Rabou Z, Antil L, Bresee J, Mansour A, Adib I, Nahkla I, Riddle MS. Cost-benefit analysis of a rotavirus Immunization Program in the Arab Republic of Egypt. Journal of Infectious Diseases. 2009;200:S92-8.

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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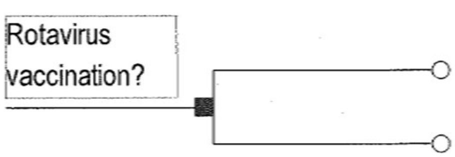
Types of Nodes

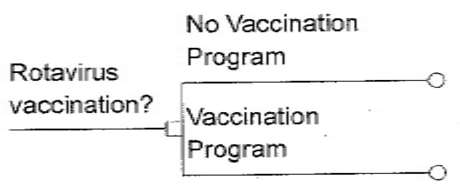
- Decision trees have a (horizontal) “trunk” and “branches”
- Main branch point is a decision, characterized by decision node (square)
- Succeeding branch points usually chances, characterized by chance nodes (circles)
- Terminal nodes (branch endings, commonly triangles)

Initial Decision *

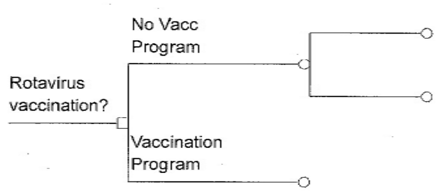


* Tree construction demonstated using TreeAge software

No Vaccination / Vaccination



No Vaccination, Initial Chance



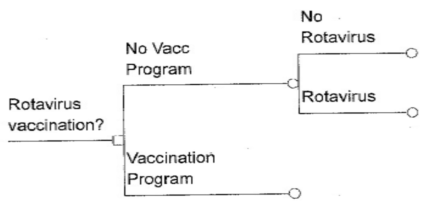
Rule 1

Node branches must be exhaustive and mutually exclusive.

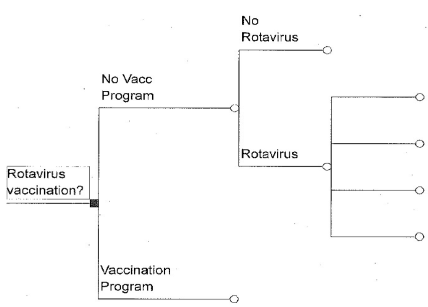
Rule 2

At each chance node, the sum of the branch probabilities must equal 1.0

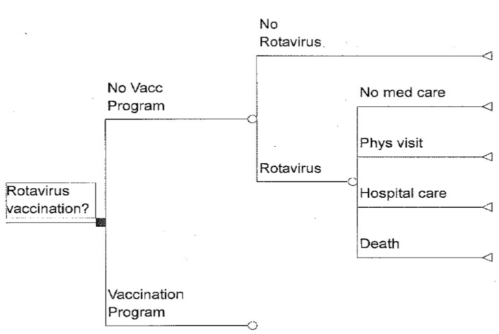
No Rotavirus / Rotavirus



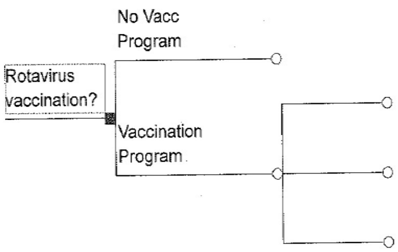
Rotavirus “Terminal Nodes”



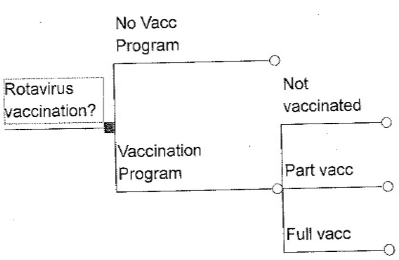
No Vaccination Program Tree



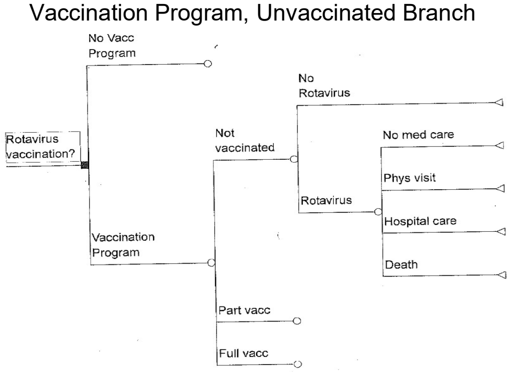
Vaccination, Initial Chance



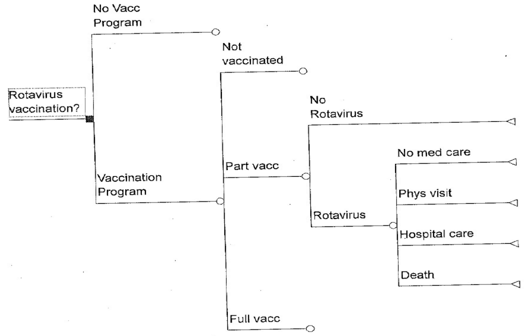
Not-, Partially-, Fully Vaccinated



Vaccination Program, Unvaccinated Branch



Vaccination Program, Partially Vaccinated Branch



Vaccination program, Fully Vaccinated Branch

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 aides 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
4. Calculate expected values
5. Perform sensitivity analyses

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:

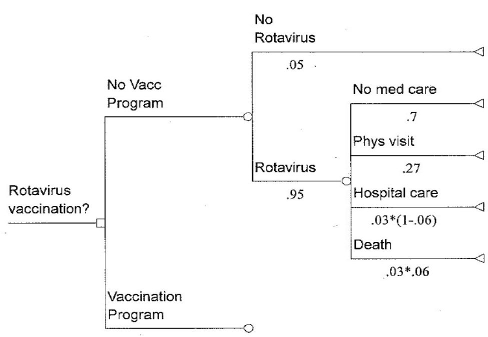
$$P(t) = 1 – e^{R(t)}$$

where P(t) equals the probability R(t) equals the rate 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

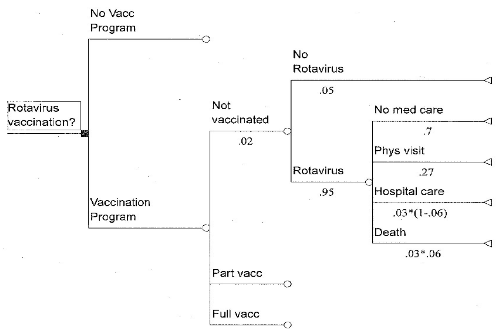
Probabilities, No Vaccination Program



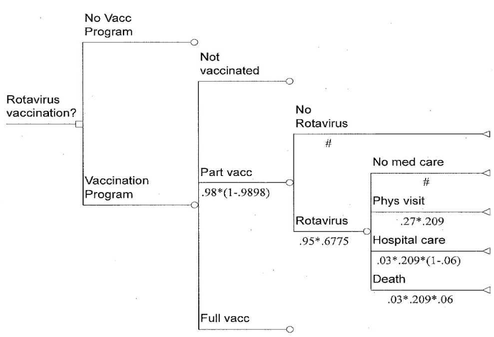
Vaccination Program Probabilities

- 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*

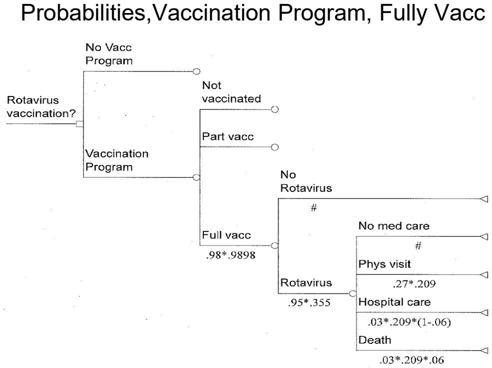
Probabilities, Vaccination Program, Unvaccinated



Probabilities, Vaccination Program, Partially Vacc



Probabilities,Vaccination Program, Fully Vacc



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Outcomes

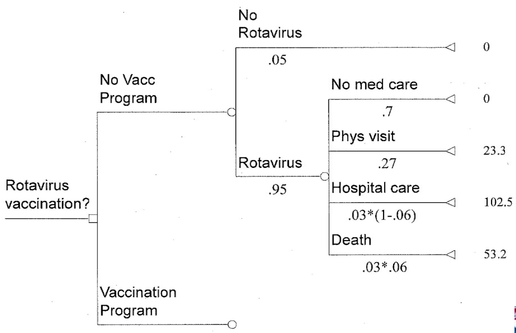
- # of cases of rotavirus
- # physician visits
- # hospital visits
- # deaths
- Costs
- DALYs
- Cost / case averted
- Cost / death averted
- Cost / DALY averted

Costs *

• Physician visit	23.3
• Hospital visit	102.5
• Death	51.3
• 1 dose of vaccine	53.2

* Costs in 2005 Egyptian pounds (LE)

Costs



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Two Methods of Calculation

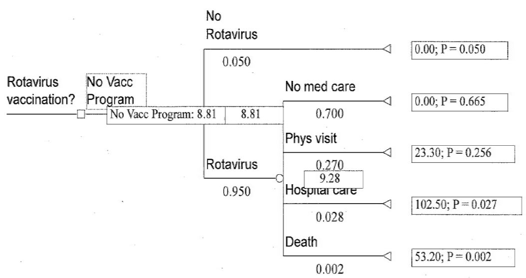
- Average out and fold back
  - Most common method
- Path probabilities

Average Out Formula

Probability$_1$ * Outcome$_1$
+ Probability$_2$ * Outcome$_2$
+ !
+ Probability$_n$ * Outcome$_n$

Expected Value

Roll Back of Cost: No Vaccination Strategy *



.05*0 + .95*.7*0 + .95*.27*23.3 + .95*.028 *102.5 + .95*.002*53.2 = 8.81

Expected Events *

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

* Assumes 1,909,000 birth cohort

Expected Costs *

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

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

Cost-Effectiveness Ratios *

Service	ΔCost	ΔEffect	ICER
Cost/Case	183,668,374	1,140,496	161
Cost/Death	183,668,374	2873	63,929
Cost/DALY	183,668,374	94,993	1933

Assumes 1,909,000 birth cohort
Costs expressed in 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.

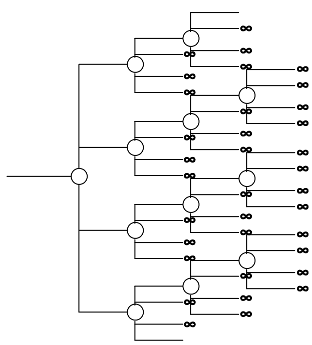
Ratios Without Cost Offsets

Service	Original ICER	Revised ICER
Cost/Case	161	174
Cost/Death	63,929	68,930
Cost/DALY	1933	2085

(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

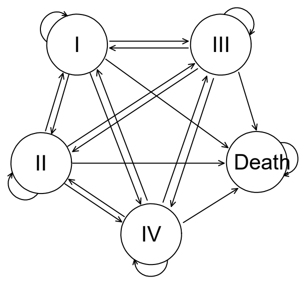


State Transition / Markov Models

- 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

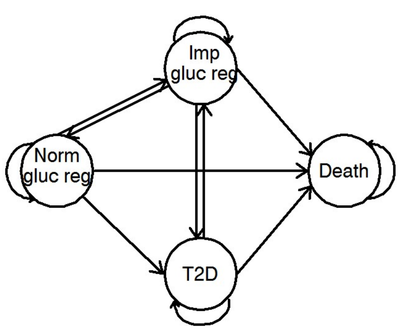
- Develop mathematical description of effects of an intervention as a change in either (or both):
  - Transition probabilities among states (e.g., by reducing probability of death) or
  - Outcomes within states (e.g., after intervention, those in NYHA class 1 cost $500 less than do those without intervention)

"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



- Palmer AJ, Tucker DMD. Cost and clinical implications of diabetes prevention in an Australian setting. Primary Care Diabetes. 2012;6:109-21.

Steps 2-2c: Identify the Probabilities

"Key" Transition Probabilities

	Control	Metformin	Lifestyle
Rates of progression from IGT to T2D/100 patient years			
Years 1-3	11.0	7.8	4.8
Years 4+	5.6	4.9	5.9
Transition probabilities of regression from IGT to NGR			
Year1	10.0	12.0	25.0
Year 2	5.6	6.8	13.3
Year 3	3.5	8.5	6.2
Year 4+	3.5	3.5	3.5
Rates of progression from NGT to T2D/100 patient years			
All years	4.6	4.6	4.6

Step 3: Identify the Outcome Values

“Key” Cost Data

	Control	Metformin	Lifestyle
Annual costs of intervenntion ($AU)			
Year 1	154	998	1487
Year 2	75	898	915
Year 3	75	899	940
Year 4	172	292	120
Year 5+	15	128	39
Cost of states ($AU)			
NGR	1907	1907	1907
IGT	2158	2158	2158
T2D	5018	5018	5018

Step 4: Calculate the Expected Values

Results

- Intensive lifestyle change ($A 62,091) cost less than control ($A 62,380) or metformin ($AU 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)

Andrew J.Palmer J, The Mount Hood 5 Modeling Group. Computer Modeling of Diabetes and Its Complications. *Value Health*. 2013; 16: 670-85.

Mount Hood Results, ASPEN / ADVANCE Trials

	ASPEN			ADVANCE		
	Interv	Cont	Diff	Interv	Cont	Diff
TRIAL	**13.7**	**15.0**	**1.3**	**4.5**	**5.2**	**0.7**
ECHO	12.3	14.8	1.5	6.6	7.5	0.9
UKPDS-OM	9.6	11.1	1.5	6.4	6.5	0.01
UKPDS-RE	--	--	--	--	--	--
IMS	--	--	--	4.2	4.6	0.4
Michigan	2.7	3.3	0.6	5.6	5.7	0.1
CDC-RTI	12.4	14.3	1.9	11.0	11.4	0.4
Cardiff	--	--	--	2.2	2.4	0.2

ASPEN: composite endpoint; ADVANCE: CVD mortality

Mount Hood Results, ACCORD Trials

	ACCORD BP			ACCORD GL		
	Interv	Cont	Diff	Interv	Cont	Diff
TRIAL	**1.9**	**2.1**	**0.2**	**6.9**	**7.2**	**0.3**
ECHO	2.2	2.6	0.4	8.1	9.0	0.9
UKPDS-OM	1.7	1.9	0.2	6.7	7.4	0.7
UKPDS-RE	1.9	2.1	0.2	6.3	7.1	0.8
IMS	1.0	1.2	0.2	--	--	--
Michigam	2.3	2.8	0.5	--	--	--
CDC-RTI	1.7	1.9	0.2	--	--	--
Cardiff	1	1.1	0.1	--	--	--

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 for Transferring Results To Local Setting

- 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