Introduction to Markov Models

Henry Glick

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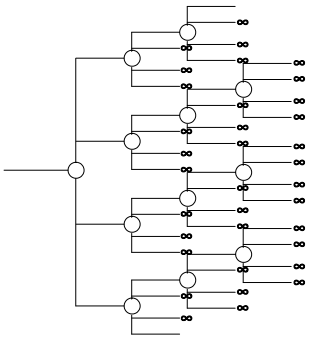
Outline

- Introduction to Markov models
- 5 steps for developing Markov models
- Constructing model
- Analyzing model
  - Roll back and sensitivity analysis
  - Second-order Monte Carlo

Decision Trees and Markov Models

- Markov models are repetitive decision trees
- Used for modeling conditions that have events that occur over time
  - e.g., Cycling among heart failure classes or repeated screening for colerectal cancer
- Simplify presentation of repetitive tree structure
- Explicitly account for timing of events, whereas time usually less explicitly accounted for in decision trees

"Bushiness" of Repetitive Trees



State Transition or Markov Models

- Develop description of disease by simplifying it into a series of states
  - e.g., models of heart failure (HF) might be constructed with five or six health states
    - Five state model (if everyone in model begins with HF): HF subdivided into New York Heart Association (NYHA) classes I through 4, and death (either from heart failure or other causes)
    - Six state model (if model predicts onset of disease): No disease, HF subdivided into New York Heart Association (NYHA) classes I through 4, and death (either from heart failure or other causes)

Progression in Model

- 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 by a set of transition probabilities

Outcomes of Model

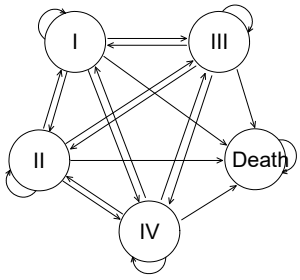
- Assess outcomes such as resource use, cost, and QALYs based on resource use, cost, and QALY weights experienced:
  - Method 1: by making transition from one state to another
    - e.g., average cost among patients who begin a period in NYHA class 1 and begin next period in NYHA class 2 OR
  - Method 2: by being in a state for a period
    - e.g., average cost of being in NYHA class 1 for a year

Modeling an Intervention

- Develop mathematical description of effects of intervention as a change in:
  - Transition probabilities among states
    - e.g., by reducing probability of death OR
  - Outcomes within states
    - e.g., with intervention, cost of being in NYHA class 1 $500 less than without intervention

State Transition Model, NYHA Class and Death

Heart Failure Model



5 Steps in Developing Markov Model

1. Imagine model, draw "tree"
   - 1A. Enumerate states
   - 1B. Define allowable state transitions
2. Identify probabilities
   - 2A. Associate probabilities with transitions
   - 2B. Identify cycle length and number of cycles
   - 2C. Identify initial distribution of patients within states
3. Identify outcome values
4. Calculate expected values
5. Perform sensitivity analysis

Systemic Lupus Erythematosus (SLE) (I)

- Markov model used for illustration predicts prognosis in SLE *
- Study sample for natural history probabilities
  - 98 patients followed from 1950-1966 (steroid period), 58 of whom were treated with steroids
  - All patients were seen more than once and were followed at least yearly until death or study termination
  - No patient was lost to follow-up
  - Time 0 was time of diagnosis

* Silverstein MD, Albert DA, Hadler NM, Ropes MW. Prognosis in SLE: comparison of Markov model to life table analysis. J Clin Epi. 1988;41:623-33.

SLE (II)

- Diagnosis was based on presence of 3 of 4 criteria:
  - Skin rash
  - Nephritis (based on urinary sediment abnormality, with greater than 2+ proteinuria on two or more successive visits)
  - Serositis
  - Joint involvement
- All patients would have fulfilled 1982 ARA diagnostic criteria for SLE
- A set of 11 clinical findings and 9 laboratory values were used to classify patients' disease into four severity grades, 1 through 4

Diagnosing SLE, 2012

- Criteria have changed twice since publication of source data
  - 1997 revision of 1982 criteria cited in paper
  - 2012 revision of criteria
- In 2012, 17 Systemic Lupus International Coordinating Clinics (SLICC) categories
  - Reduced weight of rash/photosensitivity
  - Increased weight of hemotology
  - Increased weight of immunology
- SLE diagnosis requires presence of 4 criteria, including at least one clinical and one immunologic criterion OR biopsy-proven lupus nephritis in presence of antinuclear antibodies or anti–double-stranded DNA antibodies.

2012 SLICC Criteria for Classification of SLE

Clinical Criteria
Acute cutaneous lupus
Chronic cutaneous lupus
Nonscarring alopecia
Oral or nasal ulcers
Joint disease
Serositis
Renal
Neurologic
Hemolytic anemia
Leukopenia or lymphopenia
Thrombocytopenia
Immunologic Criteria
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid
Low complement
Direct Coombs' test

"Test" Characteristics

	2012	1997
Sensitivity (%)	97	83
Specificity (%)	84	96
Accuracy (%)	90.6	89.4

- Reported accuracy calculated in convenience sample with D+ = 349 with SLE and D- = 341 with active control conditions
  - p=0.24

But Does 349/690 Represent Correct Prevalence?

- Prevalence of SLE, 161-322/100,000
- Prevalence of subset of candidate control conditions, 2700-5056/100,000
- Representative testing sample would be more like D+ = 41 with SLE and D- = 349 with active control conditions

	2012	1997
Sensitivity (%)	97	83
Specificity (%)	84	96
Accuracy (%)	90.6	89.4
Accuracy (%) †	84.8	95.2

† p value, 41 vs 349 sample: p<0.0000

Step 1: Imagine model, draw "tree"

Step 1.A Enumerate States

- Markov models made up of states
- In standard Markov models, states are all inclusive and mutually exclusive (all patients must be in one and only one state at all times in model)
- Clearly defined, usually according to standard literature-based notions of disease
- Distinguished by their prognosis, transition probabilities, or payoffs
- Transition probabilities per unit time estimable from data or literature
- Able to assign costs / outcome weights (e.g., QALYs, etc.)

States for Modeling Systemic Lupus

- Four disease states
  - State 1: Remission
    - No disease activity
  - State 2: Active
    - Severity grades 1 through 3
  - State 3: Flare
    - Severity grade 4
  - State 4: Death (from any cause)

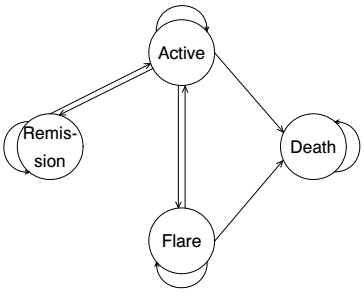
States for Modeling Systemic Lupus (II)

- Each patient year was classified by greatest severity of disease activity during year, even if severity was only present during a portion of year
  - e.g., patients whose disease activity was severity grade 4 during any visit in a calendar year were considered to have a flare year
  - No patient was observed to have more than 1 flare per year and all patients were seen at least once a year

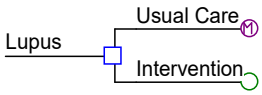
Step 1.B Define Allowable State Transitions

- Nonabsorbing states: once in state, can move out of it
- Absorbing states: once in state, cannot move out of it (e.g., death)

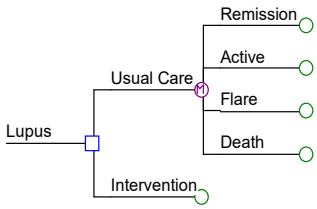
SYSTEMIC LUPUS



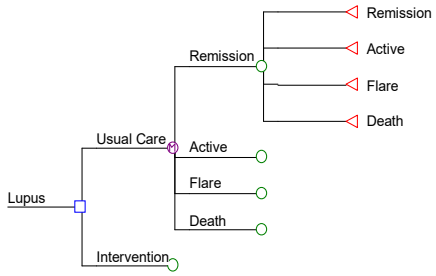
Developing Treeage Lupus Model



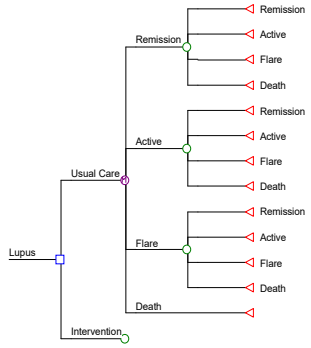
Add 4 States



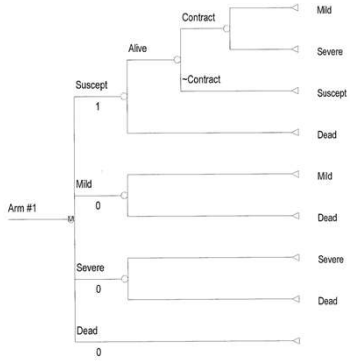
Add Transitions from Remission



Add Remaining Usual Care Transitions



Markov Model / Decision Tree Format



Tree-Like Markov Construction

- Potentially makes path through model more understandable to audience
- Also can simplify model equations if, from same initial state, there are several pathways to one transition state
  - E.g., there may be less traumatic transitions to death (with lower costs and higher QALYs) and more traumatic transitions to death (with higher costs and lower QALYs
    - Can be modeled with a single transition to death accruing a weighted average of 2 QALY estimates and of 2 cost estimates
    - Also can be modeled as two branches both transitioning to death (no need for weighted avg)

Step 2: Identify probabilities

Step 2.a Associate Probabilities with Transitions

- Suppose you had data from a lupus registry that was following 98 patients
  - Observations were made at beginning and end of each year
  - During period of observation, you had 1117 patient years of observation
  - Pooling across years of observation, you identified
    - 100 patient years classified as remission
    - 937 patient years classified as active disease
    - 80 patient years classified as flare

Remission Transition Probabilities

- Suppose that among 100 classified as having spent a year in remission
  - 59 classified as having spent following year in remission
  - 41 classified as having spent following year with active disease
  - None classified as having spent following year with flare or dead
- What are annual transition probabilities?

Active Transition Probabilities

- Suppose that among 937 classified as having spent a year with active disease
  - 66 classified as having spent following year in remission
  - 806 classified as having spent following year with active disease
  - 56 classified as having spent following year with flare
  - 9 died
- Probabilities?

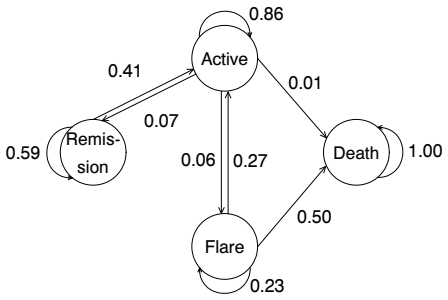
Flare Transition Probabilities

- Suppose that among 80 classified as having spent a year with flare
  - 0 classified as having spent following year in remission
  - 22 were classified as having spent following year active disease
  - 18 classified as having spent following year flare
  - 40 died
- Probabilities?

Transition	Data *	Prob	95% CI
Remission ⇗ Remission	59 / 100	0.59	(0.49 to 0.69)
Remission ⇗ Active	41 / 100	0.41	(0.31 to 0.51)
Remission ⇗ Flare	0 / 100	0.00	(0.00 to 0.03)
Remission ⇗ Death	0 / 100	0.00	(0.00 to 0.03)
Active ⇗ Remission	66 / 937	0.07	(0.06 to 0.09)
Active ⇗ Active	806 / 937	0.86	(0.83 to 0.88)
Active ⇗ Flare	56 / 937	0.06	(0.05 to 0.08)
Active ⇗ Death	9 / 937	0.01	(0.00 to 0.02)
Flare ⇗ Remission	0 / 80	0.00	(0.00 to 0.06)
Flare ⇗ Active	22 / 80	0.27	(0.18 to 0.39)
Flare ⇗ Flare	18 / 80	0.23	(0.14 to 0.33)
Flare ⇗ Death	40 / 80	0.50	(0.38 to 0.62)

* Counts are approximations of actual data (not provided in article)

SYSTEMIC LUPUS



?? Rule of Thumb When No Transitions Observed ??

- No transitions observed from remission to flare, remission to death, and flare to remission
- Proposed rule of thumb: add 1 to count for each possible transition
  - Remission
    - Original: 59, 41, 0, 0; Revised: 60, 42, 1, 1
  - Flare:
    - Original: 0, 22, 18, 40; Revised: 1, 23, 19, 41
- Resulting probabilities
  - Remission: 0.58, 0.4, 0.01, 0.01 (0.59, 0.41, 0, 0)
  - Flare: 0.01, 0.27, 0.23, 0.49 (0, 0.27, 0.23, 0.50)

Rule of Thumb When No Transitions Observed (2)

- Why add 1 (and not 0.5 or 1.5)?
  - For remission, 0.01 (0.009569) represents approximately 27% of upper limit of Wilson CI for 0 successes among 104 tries (0.0356214)
  - For flare, 0.01 (0.0119048) represents approximately 27% of upper limit of Wilson CI for 0 successes among 84 tries (0.0437317)
- What is basis for adopting ~27% of upper limit?

Rates vs Probabilities

- Large number of methods exist for estimating transition probabilities
  - Simple methods as suggested in Lupus example
  - If available data are hazard rates (i.e., instantaneous failure rates) per unit of time ($R_{ij}[t]$), can be translated into probabilities as follows:

$$P_{ij}(t) = 1 - e^{-R_{ij}t}$$

where $P_{ij}(t)$ equals probability of moving from state i at beginning of period t to state j at beginning of period t+1; Rij equals instantaneous hazard rate per period (e.g., per year); and t equals length of period

Step 2.B Identify a Cycle Length and Number of Cycles (Markov Termination)

- Currently accepted practice for cycle length:
  - Strategy 1: Have cycle length approximate clinical follow-up
  - Strategy 2: Allow cycle length to be determined by study question or available data; ignore differences that don't make a difference
- Current probabilities are for annual cycles
- Markov Termination : _stage > 1999

Step 2.C Identify an Initial Distribution of Patients Within States

- Use a population approach: e.g., one might want to use distribution in which patients present to registry

Remis	Active	Flare
0.10	0.85	0.05

Step 2.C Identify an Initial Distribution of Patients Within States (II)

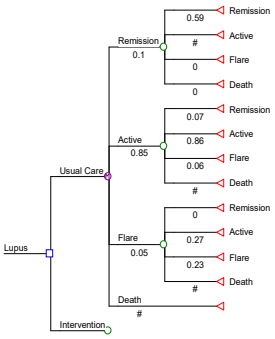
- Alternatively, start everyone in one state, (e.g., to determine what will happen to patients who begin in remission, make probability of being in remission 1.0)

	Remis	Active	Flare
Start in Remission	1.0	0.0	0.0
Start in Active	0.0	1.0	0.0
Start in Flare	0.0	0.0	1.0

Hypothetical Lupus Initial Distribution

Remission:	0.10
Active:	0.85
Flare:	0.05

Insert Initial Distribution, Probabilities, and Number of Cycles in Tree



Step 3: Identify outcome values

Step 3. Identify Outcome Values

- Basic result of model calculation is cycles of survival in different states
- Also should identify:
  - Costs of making a transition from one state to another state or of being in a state
  - Health outcomes other than survival (e.g., quality-adjusted life expectancy)

Outcomes for Transitions

- For current analysis, outcomes are modeled as a function of making a transition from one state to another
  - Number of hospitalizations, cost, and QALYs experienced by patients who at beginning of time t are in state i and at beginning of time t+1 are in state j
    - e.g., transition from remission to active disease

Lupus Outcome Variables

- Hypothetical Cost Data
  - Costs modeled as # of hospitalizations × $
    - cHosp assumed to equal 10,000 *
  - Suppose that our hospitalization data were derived from observation of subjects for a year
    - We recorded their disease status at beginning and end of year and measured number of times they were hospitalized during year
  - We use these data to estimate (hypothetical) mean number of hospitalizations for those who begin in state i and end in state j:

* Krishnan, Hospitalization and mortality of patients with systemic lupus erthematosus. J Rheumatol. 2006;33:1770-4.

Numbers of Hospitalizations

	Remis.	Active	Flare	Death
Remission	0.05	0.25	0.00	0.00
Active	0.10	0.20	1.00	0.50
Flare	0.00	0.25	1.25	0.75

- e.g., Patients who begin in remission and remain in remission will have 0.05 hospitalizations during year; those who begin with active disease and develop a flare will have 1 hospitalization during year

Hypothetical QALY Data (I)

- Suppose you found a study that reported preference weights from cross sectional observation of subjects (i.e., authors assessed preference for current health among cohorts of patients who were in remission, active disease or flare)
- We observed following (hypothetical) QALY weights (NYHA class weights provided for reference):

SLE Stage	QALY Weight	NYHA Class	QALY Weight
Remission	0.90	--	--
Active	0.70	1	0.71
Flare	0.50	3	0.52

Hypothetical QALY Data (II)

- Hypothetical preference weights can be used to estimate QALYs for those who begin in state i and end in state j:
  - For transition between remission and active disease, we know that people in remission experience 0.9 QALYs and those in active disease experience 0.7
  - If we assume that transition between remission and active disease occurs at mid-interval, mean QALYs among those who begin period in remission and end it in active disease are:

$$(0.5 \times 0.9) + (0.5 \times 0.7)$$

Hypothetical QALY Transition Rewards

Transition	Preference Score
R to R	0.9
R to A	(0.9+0.7)/2
A to R	(0.7+0.9)/2
A to A	0.7
A to F	(0.7+0.5)/2
A to D	0.7/2
F to A	(0.5+0.7)/2
F to F	0.5
F to D	0.5/2

Other Outcomes

- Years of life
  - 1 for every transition other than transition to death
  - 0.5 for every transition to death
- Discounted years of life
  - Years of life rewards that include discounting
- Number of discounted hospitalizations
  - Calculated by setting cHosp = 1

Discounting

- Rewards experienced over time, and thus must be discounted
- **Old Methods**
  - Write out discounting equation as part of reward
    - e.g., for annual transition from REM to REM

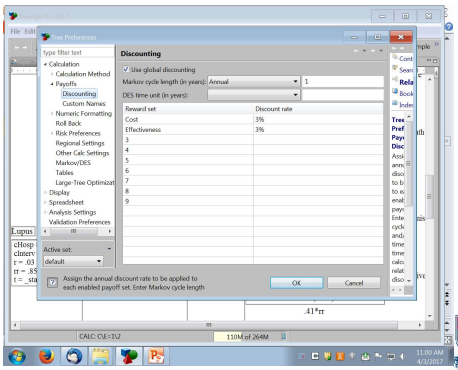
      (cHosp * 0.05) / ((1+r)^_stage)
    - where r = discount rate (e.g., 0.03) and _stage represents Treeage's cycle counter (first cycle = 0)
  - Can use Treeage's discounting function

    Discount(payoff; rate; time) = payoff / $((1 + rate)^{time})$
    - e.g., Discount(cHosp * 0.05;***0.03***;_stage)

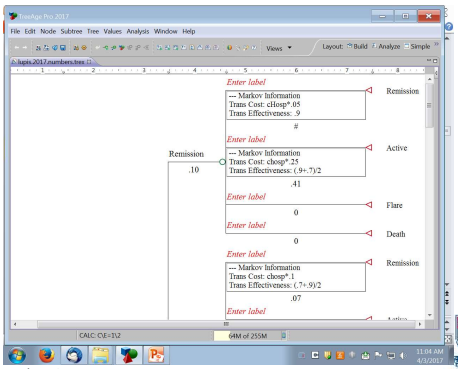
Discounting

- **Relatively New Method**
  - Do not use "Discount" function or add discounting denominators into tree
  - Use "General Discounting" Function
    - \Edit\Tree Preferences\Calculation\Payoffs \Discounting\"Use global discounting"
      - Markov cycle length (in years):
        - » For current model: Annual 1
      - Discount rate
        - » For current model: Cost 3%
          Effect 3%

General Discounting Function



Remission Transition Rewards



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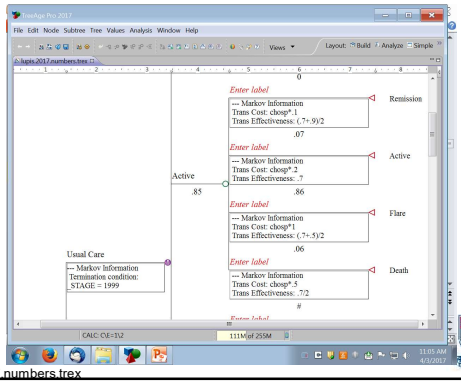
Active Transition Rewards



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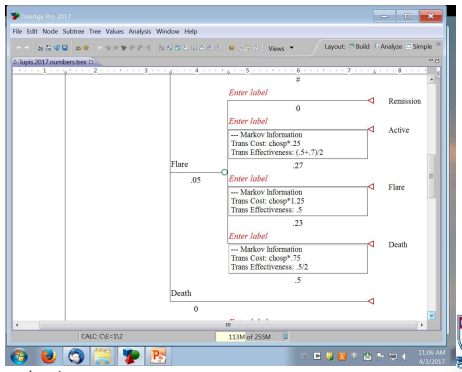
Flare Transition Rewards



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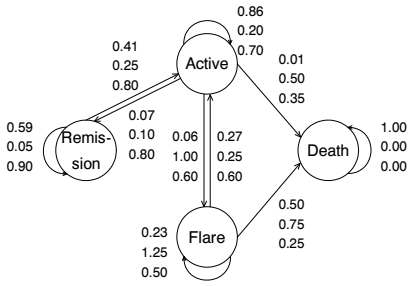
Systemic Lupus



- Row 1, Transition probabilities; Row 2, Number of hospitalizations; Row 3, QALYs

Hypothetical Intervention

- (Simplification) Hypothetical intervention **must be taken by everyone in all states for life, but affects only transition from remission to active disease**
  - Relative risk = 0.8537 (0.35 / 0.41)

    R to A: 0.8537 * 0.41
  - Where does 0.1463 * 0.41 go?
    - In this case it remains in remission. **MAKE SURE residual of changed probability goes to correct state**
- Cost of hypothetical intervention per year: 365
  - Benlysta: “first new lupus treatment in 50 years”, ~25 mg/day; 2014 FSS, 3.69/mg, 365*25*3.69 = 34K

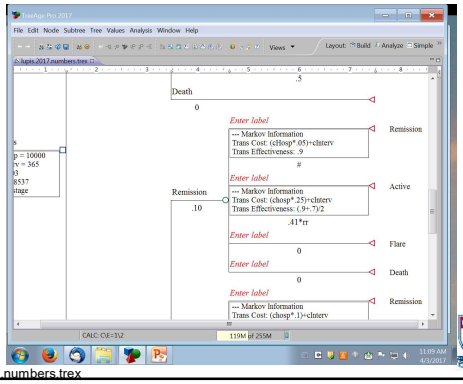
Construct Intervention Subtree

- Change “Intervention” node to a Markov node
- Place cursor on “Usual Care” node
- \Subtree\Select Subtree OR Right click: Select Subtree
- \Edit\Copy
- Place cursor on intervention node
- \Edit or Right click \ Paste

Construct Intervention Subtree (2)

- Everything should have copied EXCEPT Markov termination condition
  - If pay-offs aren’t copied, check to make sure that you changed “Intervention” node to a Markov node
- Open either “Markov Info” view or “node properties” view
  - Revise termination condition: (_stage>1999)
- Revise Remission probabilities
- Add intervention cost (cInterv = 365)

Remission Transition Probabilities and Rewards



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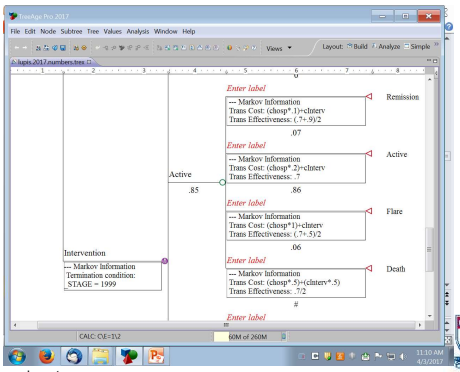
Active Transition Probabilities and Rewards



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Step 4: Calculate expected values

Calculate Expected Values

- Principal analysis can be performed in 1 of 3 ways:
  - "Iterate" model
  - Monte Carlo simulation
  - Matrix algebra solution (Not discussed)

Iterate Model

- Use data on initial distribution and transition probabilities to estimate distribution of patients in later periods (e.g., years) of model
- Initial Distribution:

  Remission: 0.10; Active: 0.85; Flare: 0.05
- Disease Transition Probabilities:

	Time t+1		
Time t	Remission	Active	Flare
Remission	0.59	0.41	0.00
Active	0.07	0.86	0.06
Flare	0.00	0.27	0.23

Transition to Remission

- Assuming that probability that patient is in three states at beginning of model is 0.1, 0.85, and 0.05, what is probability a patient will be in remission next year?

$State_{i,t}$	$P_{i,t}$	$P_{i,Rem}$	P_{t+1}
Remission	0.10	0.59	0.059
Active	0.85	0.07	0.0595
Flare	0.05	0.00	0.00
$P_{Rem,t+1}$			0.1185

(i.e., multiply initial distribution times first column of transition matrix)

Transition to Active

- Will have Active disease?

$State_{i,t}$	$P_{i,t}$	$P_{i,Act}$	P_{t+1}
Remission	0.10	0.41	0.041
Active	0.85	0.86	0.731
Flare	0.05	0.27	0.0135
$P_{Act,t+1}$			0.7855

Transition to Flare

- Will experience a Flare?

$State_{i,t}$	$P_{i,t}$	$P_{i,Flr}$	P_{t+1}
Remission	0.10	0.00	0.00
Active	0.85	0.06	0.051
Flare	0.05	0.23	0.0115
$P_{Flr,t+1}$			0.0625

Transition to Death

- Will die?

$State_{i,t}$	$P_{i,t}$	$P_{i,Dth}$	P_{t+1}
Remission	0.10	0.00	0.00
Active	0.85	0.01	0.0085
Flare	0.05	0.50	0.0250
$P_{Dth,t+1}$			0.0335

Expected Cost of Hospitalization

- Use data on initial distribution, transition probabilities, and number of hospitalizations per transition/period to estimate expected number of hospitalizations in each period of model
- Number of Hospitalizations

	Remis.	Active	Flare	Death
Remission	0.05	0.25	0.00	0.00
Active	0.10	0.20	1.00	0.50
Flare	0.00	0.25	1.25	0.75

Expected Cost of Hospitalization for Usual Care Patients Who Transition to Remission in Period 2?

- What is expected cost of hospitalization for patients who make transition to remission next year?

$State_i$	P_i	P_{ij}	H_{ij}	N_{hosp}	* 10,000
Remission	0.10	0.59	0.05	.00295	29.50
Active	0.85	0.07	0.10	.00595	59.50
Flare	0.05	0.00	0.00	0	0
Total	1.0	--	--	.0089	89.00

Expected Cost of Hospitalization for Usual Care Patients who Transition to Active in Period 2?

- Who make transition to active disease?

$State_i$	P_i	P_{ij}	H_{ij}	N_{hosp}	* 10,000
Remission	0.10	0.41	0.25	.01025	102.5
Active	0.85	0.86	0.20	.1462	1462
Flare	0.05	0.27	0.25	.003375	33.75
Total	1.0	--	--	.159825	1598.25

Expected Cost of Hospitalization for Usual Care Patients who Transition to Flare in Period 2?

- Who make transition to flare?

$State_i$	P_i	P_{ij}	H_{ij}	N_{hosp}	* 10,000
Remission	0.10	0	0	0	0
Active	0.85	0.06	1.0	.051	510
Flare	0.05	0.23	1.25	.014375	143.75
Total	1.0	--	--	.065375	653.75

Expected Cost of Hospitalization for Usual Care Patients who Transition to Death in Period 2?

- Who make transition to death?

$State_i$	P_i	P_{ij}	H_{ij}	N_{hosp}	* 10,000
Remission	0.10	0	0	0	0
Active	0.85	0.01	0.5	.00425	85.00
Flare	0.05	0.5	0.75	.01875	187.50
Total	1.0	--	--	.023	230.00

- Total cost of hospitalization, Usual Care:
  89 +1598.25 + 653.75 + 230 = 2571

Expected QALYs

- Use initial distribution, transition probabilities, and QALY weights to estimate expected QALYS / period

Transition	Preference Score
R to R	0.9
R to A	(0.9+0.7)/2 = 0.8
A to R	(0.7+0.9)/2 =0.8
A to A	0.7
A to F	(0.7+0.5)/2 = 0.6
A to D	0.7/2 = 0.35
F to A	(0.5+0.7)/2 = 0.6
F to F	0.5
F to D	0.5/2 = 0.25

Expected QALYs for Usual Care Patients Who Transition to Remission in Period 2?

- What are expected QALYs for patients who make transition to remission next year?

$State_i$	P_i	P_{ij}	Q_{ij}	Q_{Rem}
Remission	0.10	0.59	0.9	.0531
Active	0.85	0.07	0.8	.0476
Flare	0.05	0.00	0.00	0
Total	1.0	--	--	.1007

Expected QALYs, Period 1 (cont.)

- And so on...
- Total QALYS:

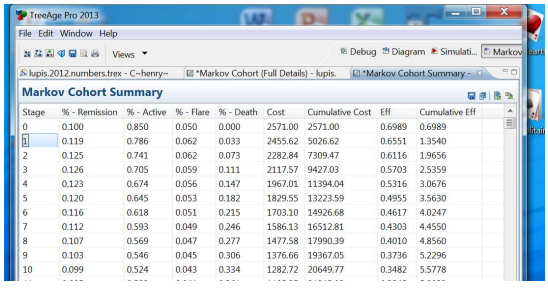
  0.1007 + 0.5526 + 0.03635 + 0.009225 = 0.698875

Iterating Model for Cycles 0-5

- Distribution at beginning of period

Cycle	Remission	Active	Flare	Death
Initial (0)	.10	.85	.05	.00
Second	.1185	.7855	.0625	.0335
Third	.1249	.7410	.0615	.0726
Fourth	.1256	.7051	.0586	.1108
Fifth	.1234	.6737	.0558	.1471
Sixth	.1200	.6450	.0532	.1817

TreeAge Output for Iterated Model



lupis.2017.numbers.trex

Roll Back Results

- For a patient who initially has a 0.1, 0.85, and 0.05 probability of being in three states, respectively

	Nat Hist	Interv
Life expectancy (undisc)	24.48	25.10
Life expectancy (disc)	14.44	14.63
QALYs (disc)	10.34	10.53
Cost (disc)	38,188	43,300
Hospitalization, N (disc)	3.82	3.80

lupis.2017.numbers.trex

Roll Back, Patients Beginning in Remission

	Nat Hist	Interv
Life expectancy (undisc)	27.44	28.46
Life expectancy (disc)	16.08	16.45
QALYs (disc)	11.83	12.21
Cost (disc)	39,398	44,953
Hospitalization, N (disc)	3.94	3.89

lupis.2017.numbers.trex

Roll Back, Patients Beginning with Active Disease

	Nat Hist	Interv
Life expectancy (undisc)	27.44	25.60
Life expectancy (disc)	16.08	14.92
QALYs (disc)	10.53	10.71
Cost (disc)	38,965	44,201
Hospitalization, N (disc)	3.90	3.88

lupis.2017.numbers.trex

Roll Back, Patients Beginning with Flare

	Nat Hist	Interv
Life expectancy (undisc)	9.74	9.95
Life expectancy (disc)	5.94	6.00
QALYs (disc)	4.07	4.13
Cost (disc)	22,549	24,669
Hospitalization, N (disc)	2.25	2.25

lupis.2017.numbers.trex

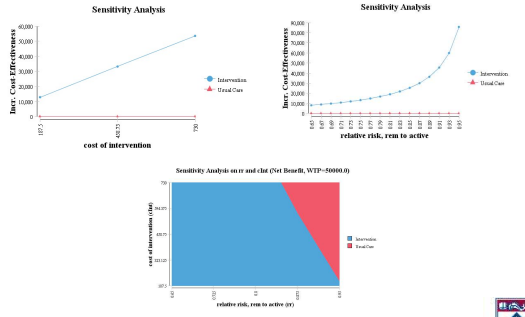
(CEA)/Analysis/Cost-Effectiveness/Text report

Strat	Cost	Incr Cst	Eff	Incr Eff	Incr C/E	~~C/E~~
UC	38188		10.3388			~~3694~~
Int	43300	5112	10.5342	0.1955	26155	~~4110~~

lupis.2017.numbers.trex

Step 5: Perform sensitivity analysis

One- and Two-Way Sensitivity Analyses



lupis.2017variables.trex

Second Order Monte Carlo Simulation

5 Steps in Developing Probabilistic Markov Model

1. Imagine model, draw "tree"
   - 1A. Enumerate states
   - 1B. Define allowable state transitions
2. Identify probabilities
   - 2A. Associate probability distributions with transitions
   - 2B. Identify cycle length and number of cycles
   - 2C. Identify distribution of initial distribution of patients within states
3. Identify outcome distributions
4. Calculate expected values and SEs
5. Perform sensitivity analysis

Distribution for Probabilities If More than 2 Branches?

- Problem: Using separate beta distributions for each branch (or n-1 distributions plus #) should work for point estimate
- For probabilistic sensitivity analysis, separate draws from n-1 of the distributions need not sum to less than 1
- Need distribution that ensures that probabilities for the branchs sum to 1

Dirichlet Distribution

- Dirichlet Distribution is multinomial (more than 2 categories) extension of binomial Beta distribution
- Defined by counts for each of outcomes
  - e.g., For transitions from Remission (tRemiss)
    List(59;41;0;0) OR List(59;41) OR Beta distribution
  - e.g., For transitions from Active (tActive)
    List(66;806;56;9)
  - e.g., For transitions from Flare (tFlare)
    List(0;22;18;40) OR List(22;18;40)
  - e.g., For initial distribution
    List(100;937;80) (Don't include count for death)

Assigning Dirichlet Distribution to Nodes

- In my tree, tActive is second distribution
- In my tree, the first element of tActive is A to R; the second element is A to A,….
- One adds this distribution to tree as follows:
  - Active to Remission: Dist(2;1)
  - Active to Active: Dist(2;2)
  - Active to Flair Dist(2;3)
  - Active to Dead Either Dist(2;4) or #
- If elements are in a different order (e.g., first element is A to A), need to change number after semicolon (e.g., (2;1) rather than (2;2)

Relative Risk, Remission to Active

- Hypothetical experimental data

	Intervention	Usual Care
Rem to Act	35 (a)	41 (b)
Rem to Rem	65 (c)	59 (d)
	100 (a+c)	100 (b+d)

- Relative risk: 0.35 / 0.41 = 0.8537

Log Relative Risk

- Log(RR) and SE Log(RR)

$$\ln(RR) = \ln(a) + \ln(b+d) - \ln(b) - \ln(a+c)$$

$$se[\ln(RR)] = \sqrt{\frac{1}{a} + \frac{1}{b} - \frac{1}{a+c} - \frac{1}{b+d}}$$

- RR distributed log normal (2 parameters)
  - μ (ln RR): ln(35)+ln(100)-(ln(41)+ln(100)) = -.1582
  - sigma (se ln(RR)): ((1/35)+(1/41)-((1/100)+(1/100)))^.5 = .1816
- NOTE: Mean of distribution (0.8679) is reasonably similar to point estimate for RR (0.8537)

Cost Distributions

- Number of hospitalizations
  - Single parameter Poisson distributions (lambda = point estimate); separate distribution for each possible transition

    e.g., hdAtoA, poisson, 0.2; hdAtoF, poisson 1.0
- Cost per hospitalization
  - Normal distribution (mean, SE)
  - Assume mean = 10,000; SE = 100
- Cost of intervention
  - Normal distribution (mean, SE)
  - Assume mean = 365; SE = 50

Gamma Cost Distributions

- Cost per hospitalization
  - $\alpha = 10{,}000^2 / 100^2 = 10{,}000$
  - $\lambda = 10{,}000 / 100^2 = 1$
- Cost of intervention
  - $\alpha = 365^2 / 50^2 = 53.29$
  - $\lambda = 365 / 50^2 = 0.146$

Log Normal Cost Distributions

- Cost per hospitalization
  - $\mu = 9.21029037$
  - sigma = 0.00999975
- Cost of intervention
  - $\mu = 5.89060168$
  - sigma = 0.13635011

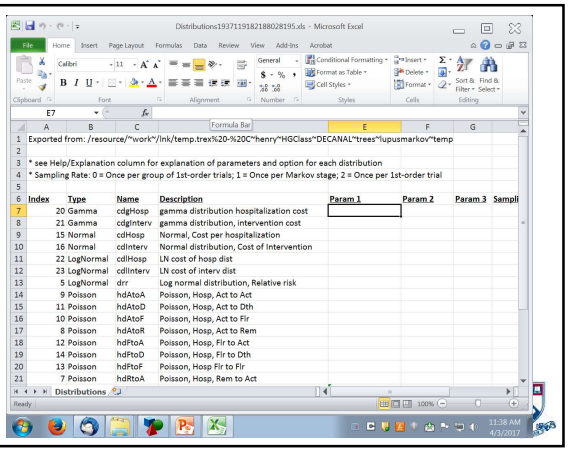
QALY Distributions

- Assume normal distribution (mean, SE)
- Assume SD = 0.1
- Assume QALY scores were measured in 100, 100, and 70 patients in remission, active, and flare, respectively

	Mean	$SD/N^{0.5}$	SE
Remis	0.9	$.1/100^{0.5}$	0.01
Active	0.7	$.1/100^{0.5}$	0.01
Flare	0.5	$.1/50^{0.5}$	0.0141

Creating Distributions in TreeAge

- Create desired distributions in Treeage distributions view
  - Open distributions view and create each of distributions needed for tree. Don't worry about defining parameters for distribution
    - E.g, 4 Dirchelet for probabilities
    - 1 lognormal for RR
    - 3 normal (preference scores)
    - 9 poisson for hospitalizations)
    - 2 normal/gamma/lognormal for cost
- Highlight (click on) one of specific distributions for which you want to enter/edit parameter values. Click "Open in new Excel Spreadsheet" button (fifth button from right in row of icons above "Index | Type....)

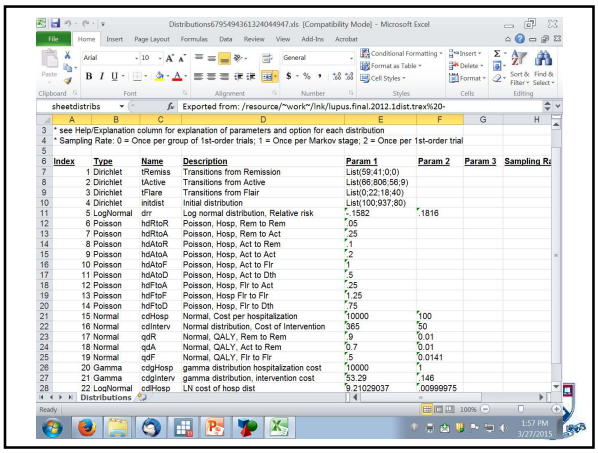


Editing Distributions in Excel

- Enter requested parameters
  - You can edit index, type, name, description or parameter values
- To finish editing in Excel, click on Treeage tab or \Add-Ins\TreeAge Pro. Under "distributions tab, click Add or Update Distributions
- You can, but needn't save resulting treeage file

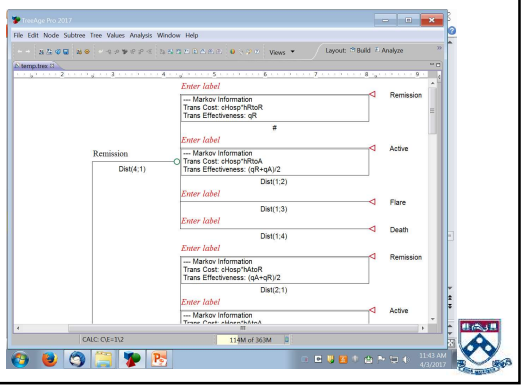
Not sure if it is still required, but I had to install the add-in in Treeage; then I had to update the Excel Trust Center settings (adding the path to the treeage add-in and indicating it was trustworthy)

Google "treeage add-in for excel" for instructions

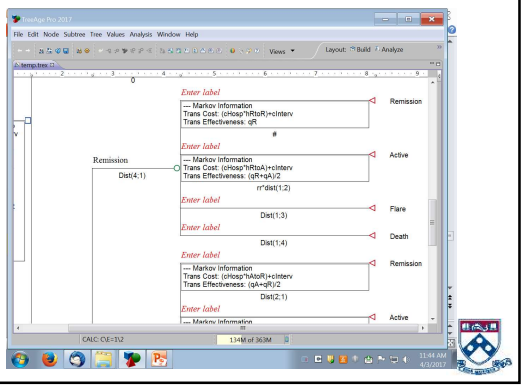


Index	Type	Name	Description	Param 1	Param 2	Param 3	Sampling Ra
1	Dirichlet	tRemiss	Transitions from Remission	List(59;41;0;0)			
2	Dirichlet	tActive	Transitions from Active	List(66;806;56;9)			
3	Dirichlet	tFlare	Transitions from Flair	List(0;22;18;40)			
4	Dirichlet	intdist	Initial distribution	List(100;937;80)			
5	LogNormal	drr	Log normal distribution, Relative risk	-.1582	.1816		
6	Poisson	hdRtoR	Poisson, Hosp, Rem to Rem	.05			
7	Poisson	hdRtoA	Poisson, Hosp, Rem to Act	.25			
8	Poisson	hdAtoR	Poisson, Hosp, Act to Rem	.1			
9	Poisson	hdAtoA	Poisson, Hosp, Act to Act	.2			
10	Poisson	hdAtoF	Poisson, Hosp, Act to Flr	1			
11	Poisson	hdAtoD	Poisson, Hosp, Act to Dth	.5			
12	Poisson	hdFtoA	Poisson, Hosp, Flr to Act	.25			
13	Poisson	hdFtoF	Poisson, Hosp Flr to Flr	1.25			
14	Poisson	hdFtoD	Poisson, Hosp, Flr to Dth	.75			
15	Normal	cdHosp	Normal, Cost per hospitalization	10000	100		
16	Normal	cdInterv	Normal distribution, Cost of Intervention	365	50		
17	Normal	qdR	Normal, QALY, Rem to Rem	.9	0.01		
18	Normal	qdA	Normal, QALY, Act to Rem	0.7	0.01		
19	Normal	qdF	Normal, QALY, Flr to Flr	.5	0.0141		
20	Gamma	cdgHosp	gamma distribution hospitalization cost	10000	1		
21	Gamma	cdgInterv	gamma distribution, intervention cost	53.29	.146		
22	LogNormal	cdlHosp	LN cost of hosp dist	9.21029037	.00999975		

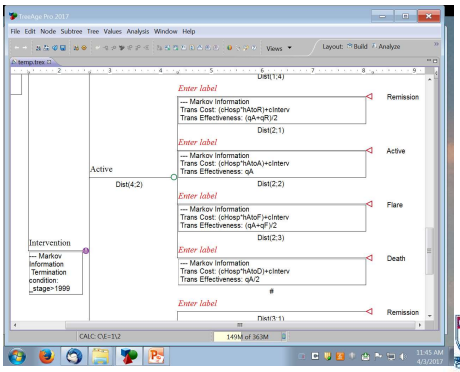
Usual Care Remission Transition Rewards



Intervention Remission Transition Rewards



Intervention Active Transition Probabilities and Rewards



Defined Variables

Lupus

```
cHosp = cdHosp
cInterv = cdInterv
hAtoA = hdAtoA
hAtoD = hdAtoD
hAtoF = hdAtoF
hAtoR = hdAtoR
hFtoA = hdFtoA
hFtoD = hdFtoD
hFtoF = hdFtoF
hRtoA = hdRtoA
hRtoR = hdRtoR
qA = qdA
qF = qdF
qR = qdR
r = 0.03
rr = drr
```

Roll Back CE Analysis, Numbers vs Distributions

2017 V*	Cost	Incr Cost	Eff	Incr Eff	IC/IE	~~C/E~~
UC	38188		10.3388		0	~~3694~~
Int	43300	5112	10.5342	.1955	26,155	~~4110~~

2017 D†	Cost	Incr Cost	Eff	Incr Eff	IC/IE	~~C/E~~
UC	38035		10.2890			~~3697~~
Int	43247	5212	10.4603	.1713	30,425	~~4134~~

* lupis.2017variables.trex † lupus.final.2017.1dis

Running PCEA: Sampling

- To analyze both therapies simultaneously, place cursor on root node
- \Analysis\Monte Carlo Simulation\Sampling (Probabilistic Sensitivity...)
  - Set number of samples
  - Ensure that you are sampling from all distributions
    - \Distributions\Sample all
  - Set seed (optional)
    - \Seeding\Seed random number generator\[#]
  - Begin

Second-Order Monte Carlo Simulation *

	Usual Care		Intervention	
	Cost	QALYs	Cost	QALYs
Mean	36,723	10.3955	41,994	10.5914
SD ***SE***	44,173	0.8737	43,692	0.9189
Min	0	8.1217	4121	8.1345
2.5%	1211	8.7982	6607	8.7982
10%	6348	9.3345	11,783	9.4509
Median	19,484	10.3680	25,187	10.5618
90%	115,489	11.5357	119,757	11.7411
97.5%	139,323	12.1772	141,741	12.5113
Max	321,979	13.7906	322,765	14.6591

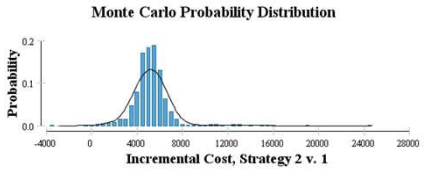
* lupus.final.2017.1dis; 1,000 trials; Seed set to 2

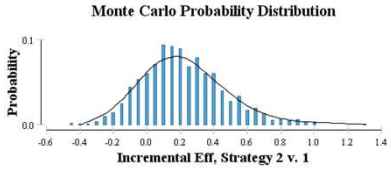
Normal vs Gamma Cost Distributions

	Usual Care	Intervention
Normal distribution †		
Mean	36,723	41,994
SE	44,173	43,692
Gamma distribution †		
Mean	36,739	41,979
SE	44,219	43,764
Log Normal distribution †		
Mean	36,734	41,983
SE	44,173	43,719

† lupus.final.2017.1dis; 1,000 trials; Seed set to 2

\Histograms\Output Distributions\Incremental …





TreeAge Pro Stats Report (Incrementals)

	Cost	QALYs
Mean:	5270	0.1959
SD *:	1647	0.2397
Minimum	-3371	-0.4578
2.5%	**2394**	**-0.2299**
Median	5208	0.1766
97.5%	**8653**	**0.7043**
Maximum:	19690	1.1452

* Represents standard error

† \Charts\Output Distributions\Incremental…\Intervention v. Usual Care\#bars\Stats Report
lupus.final.2017.1dis; 1,000 trials; Seed set to 2

Parametric Tests of Significance *

	Cost	QALYs
Mean:	5270	0.1959
Std Dev †:	1647	0.2397
T-statistic	3.1998	.8173
P-value ‡	0.001	0.41
P-value, z score	0.001	0.41

* By assumption: dof = 1100

† Represents standard error

‡ 2*(1-normal(5270/1647)) | 2*ttail(1100,(5270/1647))
2*(1-normal(.1959/.2397)) | 2*ttail(1100,(.1959/.2397))

Confidence Interval for Cost-Effectiveness Ratio

- Given that $\Delta C=5270$, $SE_c=1647$, $\Delta Q=0.1959$, $SE_q=0.2397$ and $\rho=-0.146$:

Point estimate: 26,901 / QALY gained

Values of WTP included in interval:

$-\infty$ to -15,169 & 6274 to infinity

Values of WTP excluded from interval:

-15,169 to 6274

→ Can't be 95% confident of value if WTP > 6274

Concerns About Standard Error for Difference in Single Distribution Models

Problem with Reported SEs for Difference?

- Reported SEs for cost and QALYs

Treeage Estimates

	Usual Care	Intervention	Difference
Cost	44,173	41,994	1647
QALYs	0.8737	0.9189	0.2397

Usual Formula for Combining SEs for Difference

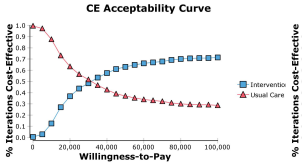
- Common formula for combining SEs for independent outcomes when calculating their difference:

$$SE_{Diff} = \sqrt{SE_0^2 + SE_1^2}$$

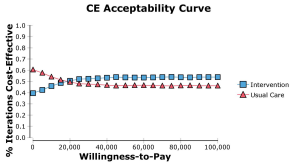
Outcome	Usual Care	Intervention	SE_{Diff} Formula	SE_{Diff} TreeAge
Cost	44,173	41,994	60,949	1647
QALYs	0.8737	0.9189	1.2680	0.2397

Implications for Acceptability Curves

TreeAge



"Formula"



SEs for Difference of Correlated Variables

$$SE_{CorrDiff12} = \sqrt{SE_1^2 + SE_2^2 - 2Cov_{12}}$$

$$Cov_{12} = \frac{44{,}173^2 + 41{,}994^2 - 1647^2}{2} = 1{,}856{,}018{,}000$$

- Simply don't see these magnitudes of covariances / correlations when we look at patient level data in observational studies or randomized trials

SEs for Difference

- Difference between reported and calculated SEs for difference due to fact that use of same draw (e.g., from chosp or from tActive) for both usual care and intervention creates stronger correlations in model data than are ever seen in experimental data
  - ρ for C_0 vs C_1: 0.9994
  - ρ for Q_0 vs Q_1: 0.9655

SEs for Difference (2)

- In actual data, even if underlying transition rates/costs/QALY scores in both Rx groups arise from same distributions, one group is sometimes above mean while other is below, or one group is sometimes a little above mean while other is more above mean; etc.
- If we use same draw for both groups, they both are always exactly same distance above or same distance below mean

A Fix for SEs

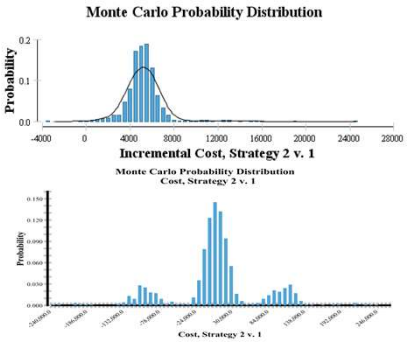
- If you don't think your confidence level is greater than what you would observe in a trial or in observational data from 2 groups, you can generate a proxy for trial/observational data by creating 2 identical distributions, one for UC and one for intervention (e.g., tActiveu and tActivei)

	SEs, 1 Distribution (corr)	SEs 2 Distributions (corr)*
Cost	1647 (0.9994)	63,451 (-.039)
QALYs	0.2397 (0.9655)	1.3216 (0.027)

(vs. calculated 60,949 and 1.2680)

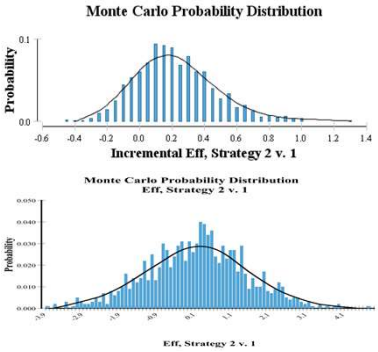
* lupus.final.2017.2dist.trex; 1000 trials; seed set to 6

Comparison of Incremental Cost Distributions *



* "Spikeiness" due to Poisson distribution

Comparison of Incremental QALY Distributions



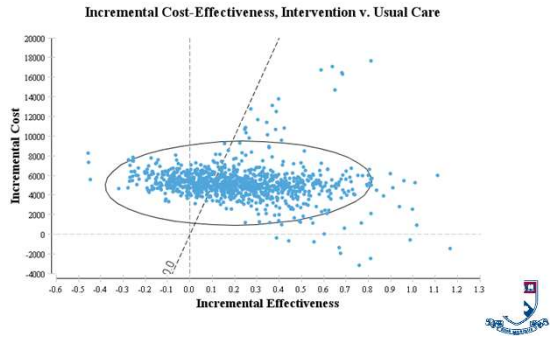
Comparison of Parametric Tests of Significance *

	Cost	QALYs
P-value, 1 distribution	0.001	0.41
P-value, 2 distributions	0.93	0.88

Additional TreeAge Outputs

(We've seen this before)

Cost-Effectiveness Plane
\ICE Scatterplot\Int v UC\WTP



Incremental CE Plot Report

- \ICE Scatter Plot\Intevention v. Usual Care\WTP [$50K]\ICE Report

	QUAD-RANT	INCR EFF	INCR COST		FREQ	PRO-PORTION
C1	IV	IE>0	IC<0	Superior	5	0.005
C2	I	IE>0	IC>0	ICER<50k	625	0.625
C3	III	IE<0	IC<0	ICER>50k	0	0
C4	I	IE>0	IC>0	ICER>50k	157	0.157
C5	III	IE<0	IC<0	ICER<50k	0	0
C6	II	IE<0	IC>0	Inferior	213	0.213
Indiff	origin	IE=0	IC=0	0/0	0	

Distribution of Ratios from Cost-Effect Pairs

- (ALMOST) Never summarize the cost-effectiveness ratios of the 1000 replicates
  - Never report:
    - Mean of ratios
    - SE of ratios
    - P-value for ratios
    - Mean $\pm$ 1.96 * SE
- If all replicates for ICE scatterplot are on one side of the Y-axis, the ratios that represent the 2.5 and 97.5% percentiles represent the nonparametric CI for the ICER