




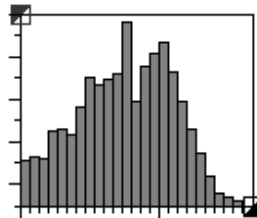
Module 5: Monte Carlo Simulation



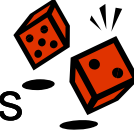
1. Probabilistic Sensitivity Analysis 
2. Cost-Effectiveness Uncertainty 
3. Simulation and Distribution Options 

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Probabilistic Sensitivity Analysis



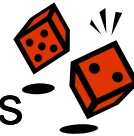
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Probabilistic Sensitivity Analysis

- Several forms of Monte Carlo simulation are supported by TreeAge Pro
 - Probabilistic Sensitivity Analysis (Sampling)
 - 2nd-order, parameter uncertainty
 - Microsimulation (Trials)
 - 1st-order, individual variability
 - Two-Dimensional (Sampling + Trials)
 - Three-Dimensional (Partial EVPI)
- We will focus on Probabilistic Sensitivity Analysis within this training module

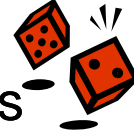
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Probabilistic Sensitivity Analysis

- Deterministic Sensitivity Analysis (prior modules)
 - Requires variables
 - Calculate EV based on range/intervals for uncertain inputs
 - Repeating gives same results
- Probabilistic Sensitivity Analysis (stochastic)
 - Requires distributions
 - Calculate EV based on random samples for uncertain inputs
 - Repeating yields different results from different sampled input values

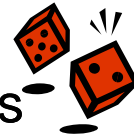
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Probabilistic Sensitivity Analysis

- Advantages of PSA over Deterministic SA
 - More robust
 - More parameters
 - More recalculations
 - More interpretation
 - Confidence intervals, value of information, etc.
- Non-PSA applications of Monte Carlo simulation with sampling:
 - Non-linear models, parameters
 - Where rollback EVs, using best estimates (i.e., means), might not be the same as simulation mean results (due to non-linearities)...
 - In this case, the mean from the sampling simulation is a better estimate of EV than rollback using estimates/means

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Probabilistic Sensitivity Analysis

- Requires defining parameters using probability **distributions** instead of simple variables
- Calculation Loop:
 - Sample parameter value from each distribution
 - Calculate expected value for tree using sampled values
 - Repeat for predefined number of samples
- Examine set of resulting EVs
 - **Mean/median** of EVs
 - **Distribution** of EVs
 - **High/low** EVs
 - Confidence intervals

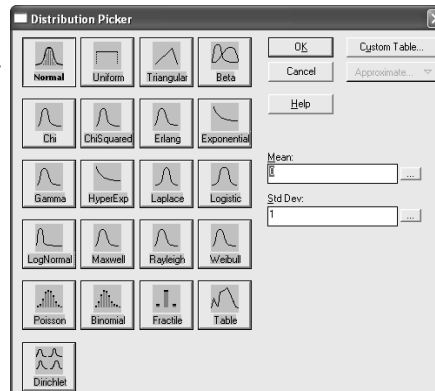
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Probabilistic Sensitivity Analysis

- Distributions

- Several types supported by TreeAge Pro
- Each type has parameters appropriate for that distribution
- E.g., Normal dist. has a mean and a standard deviation
- Will look at sampling rate later



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Probabilistic Sensitivity Analysis

- Distributions – Common Types

- Normal
 - Standard bell curve
- Uniform
 - Equal likelihood of all values in range
 - Option to limit to integers
- Beta
 - Frequently used for probabilities
 - Restricted to between 0 and 1
- Triangular
 - Provide min, max and most likely
- Dirichlet
 - Sample multiple complementary probabilities
- Table
 - For “empirical” data:
 - Column of “values” and corresponding probability
 - Will cover in detail during Microsimulation

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Probabilistic Sensitivity Analysis

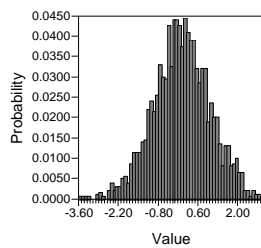
- Distributions

- Can test distribution by graphing a set of samples
- Resulting distribution of 2000 samples strongly resembles normal distribution

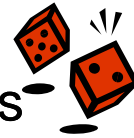
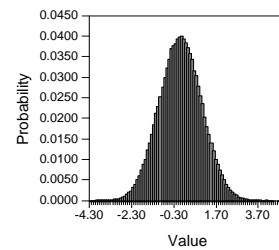
Graph It...

Even more so with
200,000 samples

Dist(1) - Normal distribution example
Normal, Mean = 0, Std Dev = 1; Expected value: 0



Dist(1) - Normal distribution example
Normal, Mean = 0, Std Dev = 1; Expected value: 0



Probabilistic Sensitivity Analysis

- Let's setup our Example 2 tree for PSA and run a simulation
- We will use a distribution to measure the initial mortality of Tx A
- Open Example2-Variables.tre and save under a new name (Example5-?????.tre)





Probabilistic Sensitivity Analysis

● Example 5: Define and use distributions

- Add a distribution to the tree

- Menu: VALUES > Distributions...

- Choose the type Beta

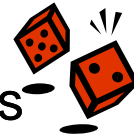
- Enter parameters...

- Select "Integer parameters only"
 - $n = 10$
 - $r = 1$
 - Note: $EV = 0.1$

- Enter name, description



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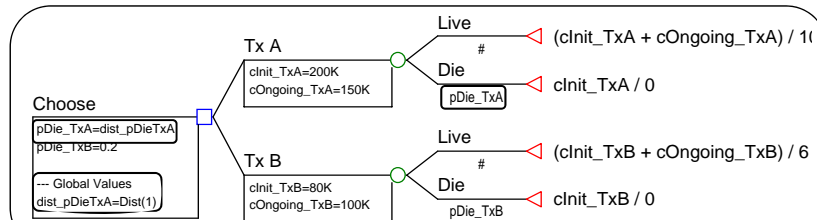
Probabilistic Sensitivity Analysis

● Example 5: Define and use distributions

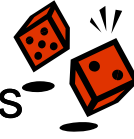
- Use the new distribution in tree:

- Change variable definition for pDie_TxA

- $pDie_TxA = dist_pDieTxA$ (by name), **OR**
 - $pDie_TxA = Dist(1)$ (by index)
 - Could also have placed distribution directly in probability rather than using variable and definition

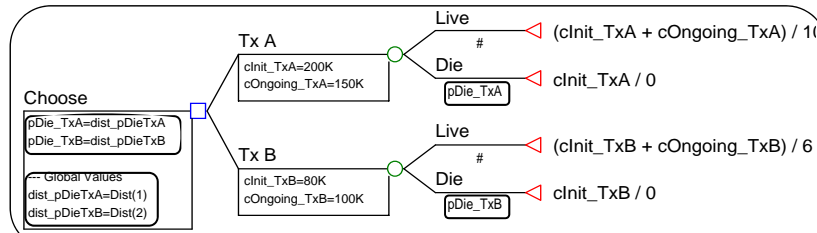


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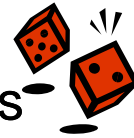


Probabilistic Sensitivity Analysis

- Example 5: Define and use distributions
 - Repeat use of distribution for pDie_TxB
 - Beta distribution dist_pDieTxB
 - “Integer parameters only”
 - n = 500
 - r = 100
 - Note: EV = 0.2

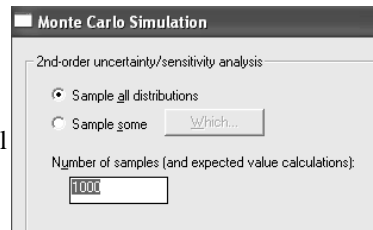


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Probabilistic Sensitivity Analysis

- Example 5: Run PSA
 - Menu: Analysis > Monte Carlo Simulation > Sampling (PSA)
 - Will look at Microsimulation on Day 2
 - Monte Carlo Simulation options...
 - How many iterations?
 - More if more distributions sampled
 - More if skewed/non-normal



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Probabilistic Sensitivity Analysis

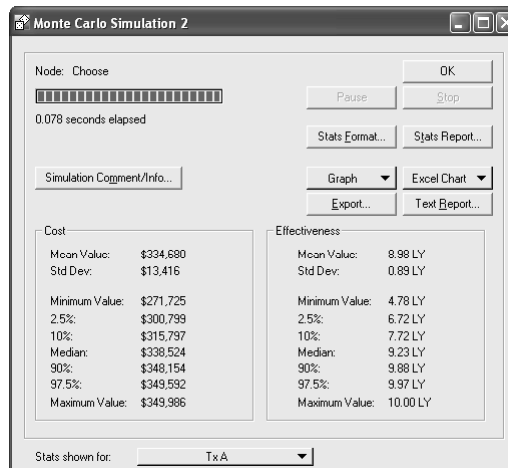
- Example 5: Run PSA
 - How PSA runs...
 - Step 1
 - Sample **random values** from each distribution and update tree with the samples
 - Step 2
 - Analysis: get Cost and Effectiveness for all strategies
 - Return to Step 1, **repeat N times...**

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Probabilistic Sensitivity Analysis

- Example 5: Run PSA
 - Simulation output:

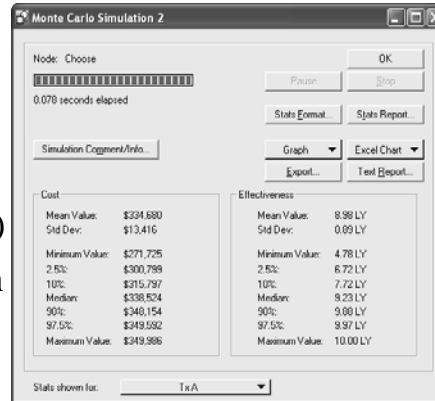


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Probabilistic Sensitivity Analysis

- Simulation key outputs
 - Text Report
 - Full listing of results
 - Stats Report
 - Distribution Graphs (outcomes, inputs, etc.)
 - C/E models have much to analyze...
 - *Next section*



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Probabilistic Sensitivity Analysis

- MCS simulation document
 - Can be saved as independent document (like graphs)
 - Creates *.MCS file (not a text file) which can be shared, e-mailed
 - Output is temporarily associated with tree within TreeAge Pro
 - When closing tree, TreeAge Pro will close MCS files too
 - Prompted to save MCS file(s) (if desired)



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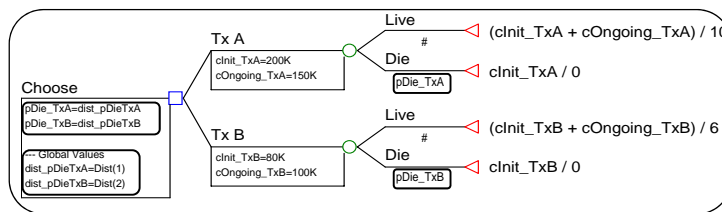
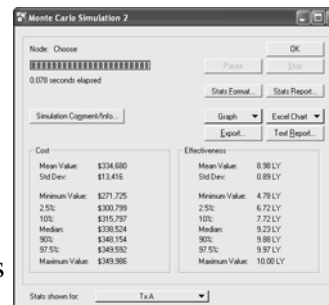
Cost-Effectiveness PSA and Uncertainty



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Cost-Effectiveness PSA...

- We have run the PSA on our cost-effectiveness model
 - How do we interpret the results?
 - We now have N individual EV calculations to consider
 - Need to review the EV calculations balancing each strategy's cost and effectiveness with our overall WTP



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Cost-Effectiveness PSA...

- There are many graphs/reports for interpreting the results
 - We will focus on a few of these
- Text Report
 - Data listed for each iteration of the simulation
 - Sampled values from distributions
 - Expected values (C & E) for each strategy

TreeAge Pro Monte Carlo Simulation
Ordered List of 1000 Outcomes

Sample	C(TxA)	E(TxA)	NMB(TxA)	C(TxB)	E(TxB)	NMB(TxB)	Dist(1)	Dist(2)
1	341840.242...	9.456016135	130960.564...	160315.645...	4.818938722	80631.2907...	0.054398366	0.196843546
2	348329.648...	9.888643247	146102.513...	158956.117...	4.737367072	77912.2357...	0.011135675	0.210438821
3	339288.575...	9.285905004	125006.675...	160712.914...	4.842774854	81425.8284...	0.0714095	0.192870858

Notes:
Dist(1) - Beta distribution, uncertain prob. of mortality
Dist(2) - Beta distribution, uncertain prob. of mortality

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Cost-Effectiveness PSA...

- Statistics Report
 - Statistics gathered from the set of iterations/EVs (mean, std dev, min, max, etc.)
 - Calculated for cost and effectiveness (optional net benefits) for each strategy

TreeAge Pro Monte Carlo Simulation
Statistics for 1000 outputs.
WTP=\$1000 (for NMB stats)

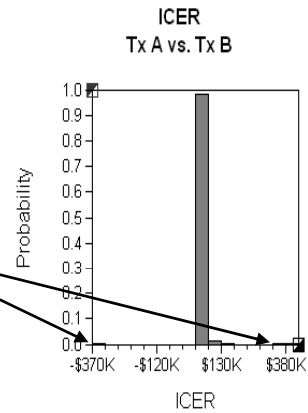
Statistic	C(TxA)	E(TxA)	NMB(TxA)	C(TxB)	E(TxB)	NMB(TxB)	Dist(1)	Dist(2)
Mean	\$334,680	8.98 LY	\$114,253	\$160,102	4.81 LY	\$80,204	0.102135184	0.198377998
Std Dev	\$13,416	0.89 LY	\$31,303	\$1,791	0.11 LY	\$3,501	0.089436668	0.017506523
Minimum	\$271,725	4.78 LY	\$32,642	\$154,561	4.47 LY	\$69,122	0.000090052	0.147280405
2.5%	\$300,799	6.72 LY	\$35,197	\$156,720	4.60 LY	\$73,441	0.002722375	0.165373541
10%	\$315,797	7.72 LY	\$70,192	\$157,916	4.67 LY	\$75,831	0.012234065	0.176750693
Median	\$338,524	9.23 LY	\$123,222	\$160,073	4.80 LY	\$80,146	0.076475103	0.199243566
90%	\$348,154	9.88 LY	\$145,693	\$162,291	4.94 LY	\$84,581	0.225689269	0.220826844
97.5%	\$349,592	9.97 LY	\$149,047	\$163,463	5.01 LY	\$86,925	0.329007859	0.232797075
Maximum	\$349,986	10.00 LY	\$149,988	\$165,272	5.12 LY	\$90,544	0.521635653	0.254332194

Notes:
Dist(1) - Beta distribution, uncertain prob. of mortality
Dist(2) - Beta distribution, uncertain prob. of mortality

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Cost-Effectiveness PSA...

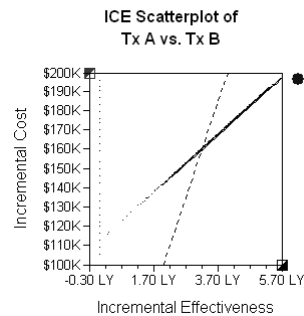
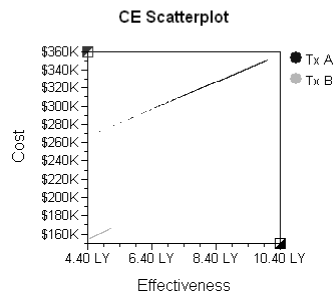
- Distribution of ICERs
 - Graph > Distribution of Incrementals > Incremental CE Ratio
 - Potential problem remains with undefined ratios, small effect differences
 - Creates outliers in graph
 - Remember asymptotes in 1-way sensitivity analysis



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Cost-Effectiveness PSA...

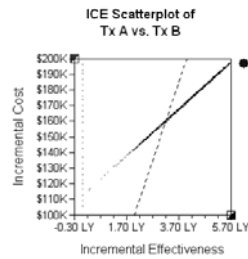
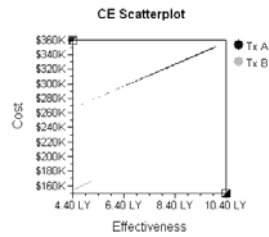
- CE and Incremental CE Scatterplots
 - Plot each iteration as a point in the CE plane
 - CE for each strategy ($x=E, y=C$)
 - ICER for comparator ($x=IE, y=IC$) vs. baseline ($x=0, y=0$)



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Cost-Effectiveness PSA...

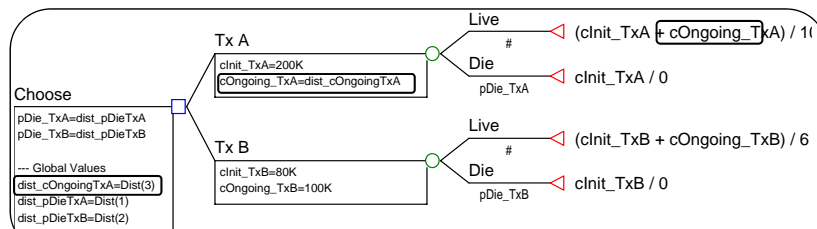
- CE and Incremental CE Scatterplots
 - Results appear to be linear because both C & E are functions of (pDie...) for both strategies
 - No independent parameter uncertainty in cost
 - Tx B:
 - $Eff = 6 * (1 - pDie_TxB)$
 - $Cost = 80K + 100K * (1 - pDie_TxB)$



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Cost-Effectiveness PSA...

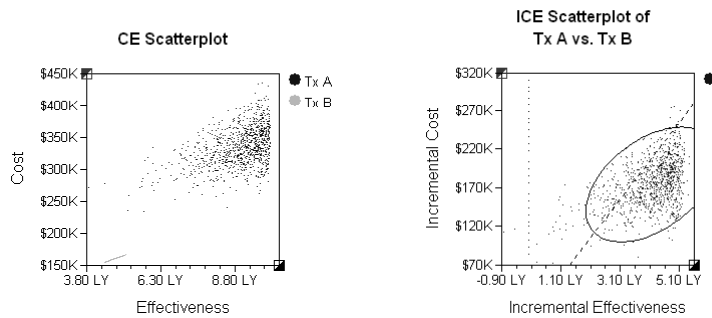
- To get more varied results, add a distribution that impacts the cost of Tx A, but not the effectiveness
 - Save Example 5 tree as Example 6 tree
 - Add Normal Distribution – dist_cOngoingTx A
 - Mean = 150K
 - Std dev = 30K
 - Define ongoing cost of Tx A using new distribution



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Cost-Effectiveness PSA...

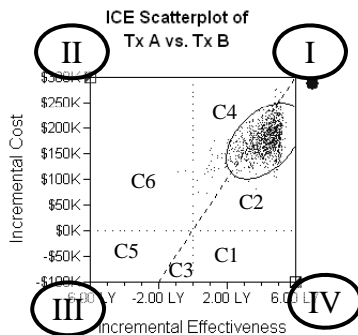
- Rerun PSA on new tree
- CE and Incremental CE Scatterplots
 - More variation now for Tx A and ICER, but not for Tx B



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Cost-Effectiveness PSA...

- ICER Scatterplot in detail...
 - Iteration points scattered among 4 quadrants and 6 components
 - QII/C6 (IC>0, IE<0): Tx A is dominated by Tx B
 - QIV/C1 (IC<0, IE>0): Tx A dominates Tx B
 - Q1 (IC>0, IE>0) and Q3 (IC<0, IE<0): cannot recommend Tx without factoring in WTP



From graph's Text Report

Component	Quadrant	Incr. Eff.	Incr. Cost	ICER	# Points	Percent
C1	IV	IE>0	IC<0	Superior	0	0%
C2	I	IE>0	IC>0	<50000	809	80.9%
C3	III	IE<0	IC<0	>50000	0	0%
C4	I	IE>0	IC>0	>50000	189	18.9%
C5	III	IE<0	IC<0	<50000	0	0%
C6	II	IE<0	IC>0	Inferior	2	0.2%

What does the above table mean?

Quadrants begin at "I" in the upper right, and increment counter-clockwise to "IV" in the lower right.

To identify cost-effective points, a different component labeling system is used. Cost-effective points for "Tx A" lie below the WTP line, in components 1-3.

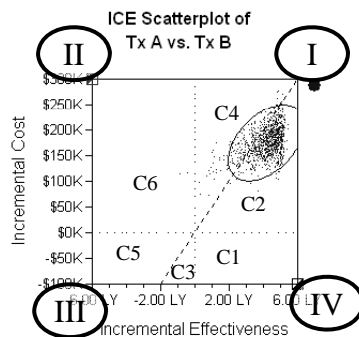
Component 1 (C1) is where the comparator is dominant ("Superior").
Component 2 (C2) is where the comparator is more costly, but lies below the WTP.
Component 3 (C3) is where the comparator is less costly, but lies below the WTP.

Component 4 (C4) is where the comparator is more costly, and lies above the WTP.
Component 5 (C5) is where the comparator is less costly, and lies above the WTP.
Component 6 (C6) is where the comparator is dominated ("Inferior").

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Cost-Effectiveness PSA...

- ICER Scatterplot in detail...
 - 95% Confidence elipsis
 - Most points in Q1 ($IC > 0, IE > 0$)
 - C2: $ICER < WTP$, recommend Tx A
 - C4: $ICER > WTP$, recommend Tx B



From graph's Text Report

Component	Quadrant	Incr. Eff.	Incr. Cost	ICER	# Points	Percent
C1	IV	IE > 0	IC < 0	Superior	0	0%
C2	I	IE > 0	IC > 0	< 50000	809	80.9%
C3	III	IE < 0	IC < 0	> 50000	0	0%
C4	I	IE > 0	IC > 0	> 50000	189	18.9%
C5	III	IE < 0	IC < 0	< 50000	0	0%
C6	II	IE < 0	IC > 0	Inferior	2	0.2%

What does the above table mean?

Quadrants begin at "I" in the upper right, and increment counter-clockwise to "IV" in the lower right.

To identify cost-effective points, a different component labeling system is used. Cost-effective points for "Tx A" lie below the WTP line, in components 1-3.

Component 1 (C1) is where the comparator is dominant ("Superior").
 Component 2 (C2) is where the comparator is more costly, but lies below the WTP.
 Component 3 (C3) is where the comparator is less costly, but lies below the WTP.

Component 4 (C4) is where the comparator is more costly, and lies above the WTP.
 Component 5 (C5) is where the comparator is less costly, and lies above the WTP.
 Component 6 (C6) is where the comparator is dominated ("Inferior").

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Cost-Effectiveness PSA...

- ICER Scatterplot is a little difficult to interpret, easier with Net Benefits
- Advantages of Net Benefits approach
 - Net Benefits combines cost, effectiveness, and WTP (threshold ICER) into a single measurement for CEA
 - Makes recommendation among strategies easy to see, just maximize the Net Benefits value
 - Enables **acceptability curve** (probability cost-effective)
 - Value of information / EVPI

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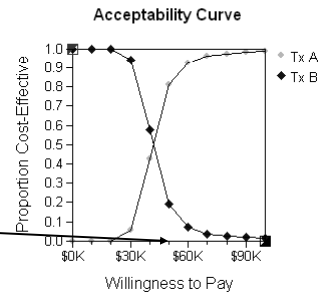
Cost-Effectiveness PSA...



- Acceptability Curve:
 - Sensitivity analysis on WTP
 - Evaluates strategies based on Net Benefits calculations at different WTP values
 - Changes the percentage of points (i.e., probability) where comparator is cost-effective
 - At WTP = \$50K, 80% of our simulation points recommend Tx A

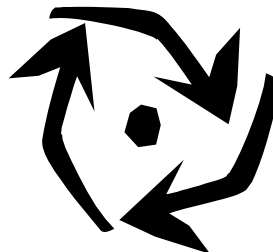


Willingness to Pay	TxA	TxB
0	0.0	1.0
10000	0.0	1.0
20000	0.0	1.0
30000	0.1	0.9
40000	0.4	0.6
50000	0.8	0.2
60000	0.9	0.1
70000	1.0	0.0
80000	1.0	0.0
90000	1.0	0.0
100000	1.0	0.0



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Simulation and Distribution Options



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Simulations and Distributions

- Distribution **sampling rate**:

- Once per EV or set of trials... (default)

- 2nd-order parameter uncertainty

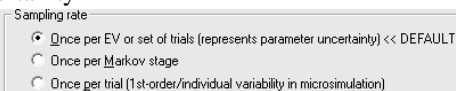
... versus ...

- Once per trial...

- 1st-order *individual variability*

- Distinction is critical:

- Models may need to **sample** patient characteristics (age, BMI, histologic values, etc.), instead of or in addition to parameter uncertainties
- Sampling in microsimulation loop (e.g., inner loop in PSA) requires distribution to be flagged



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Simulations and Distributions

- Dist() function variations:

- Dist()

- Value of sample from distribution
- Assuming default sampling rate, same value wherever used in the calculation loop

- DistForce()

- Force a fresh sample from the distribution

- DistTrim()

- Limit outliers by restricting the range of possible values returned (min, max)
- Will only try 10 times before returning a value that may be outside range

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Simulations and Distributions

- Dirichlet (multivariate):
 - Sampling probabilities for 3 or more branches of a chance node
 - Keeps total probability sum at 100% (coherent)
 - Use Dist(index; 1), Dist(index; 2), etc. to get multiple values back from the distribution
- Table-type distributions
 - Discrete, user-defined data to select with probability associated with each selection
 - Useful when assigning patient demographic data based on percentages in population
 - Used in 1st-order, microsimulation ... later

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Simulations and Distributions

- Correlations:
 - Real/robust correlation not built-in/automatic
 - User-defined functions: **Python** modules, scripting

Note:
Requires installations of Python and NumPy,
for the multivariate_normal function.
(free downloads: <http://numpy.scipy.org/>)

PSA / Simulation:
* Populate table "mvm" with multivariate normal samples using Python / NumPy.
* TreeAge converts normal variate pairs to correlated beta variates, using DistProb and DistValue

```
[F] def correTwo(coeff=0.8, samps=1000, clear=1):
    from numpy.random import multivariate_normal,
    from numpy import array
    # parameters for: multivariate_normal(mean, covar)
    a=[0.0]; # means
    b=[[1,coeff],[coeff,1]]; # covariance matrix
    tt=[]; # results list
    # loop for random pairs
    for i in xrange(1, samps+1):
        c=multivariate_normal(array(a), array(b));
        t=[i,c[0],c[1]];
        tt.append(t);
    # copy results list into a TreeAge table "mvm[]"
    return treeage.addTableRows(tt, "mvm", bool(clear));
# end
```

Tx A (new drug, e.g. for aggressive CA tx)

```
coeff_AB=1
initTable=([_sample=1; user("correTwo"; coeff_AB; 10k; 1); 0]
pDieTxA_corr=DistValue(1; DistProb(3; mvm[_sample; 1]))
```

Long-term survival # (200K + 150K) / 10
Die (base p=.1) 200K / 0
pDieTxA

Tx B (standard Tx)

```
pDieTxB_corr=DistValue(2; DistProb(3; mvm[_sample; 2]))
```

Long-term survival # (80K + 100K) / 6
Die (base p=.2) 80K / 0
pDieTxB

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Simulations and Distributions

- Nested loops:
 - Probabilistic sensitivity analysis on models using microsimulation/trackers/1st-order distributions...
 - 2-dimensional:

```
{ Sampling loop: { Microsimulation loop (avg. trials) ... } ... }  
-- instead of --  
{ Sampling loop: EV ... }
```

- ... Also, Value of Information / **EVPI (3-dimensional)**
- Computational costs with nested loops

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Simulations and Distributions

- Dealing with long run times:
 - Distributed simulations
 - Multi-processor simulations
- Batching simulations
 - Analysis > Storage...
 - Sequences
 - TreeAge Pro library and macros
 - Excel module, TreeAge menu...

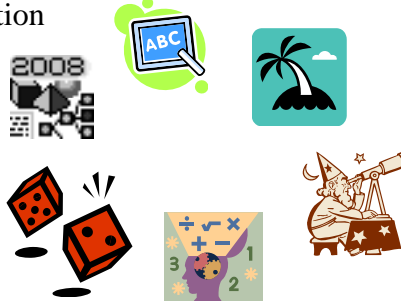


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Summary

- Today we covered...
 - Introduction to Decision Trees and TreeAge Pro
 - Defining and Using Variables in TreeAge Pro
 - Health Economic Decision Analysis
 - Sensitivity Analysis and CEA Thresholds
 - Monte Carlo Simulation

- Questions?



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