Module 9.2 – Markov models

McGill

Economic evaluation of health programs

Fall 2022

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Today

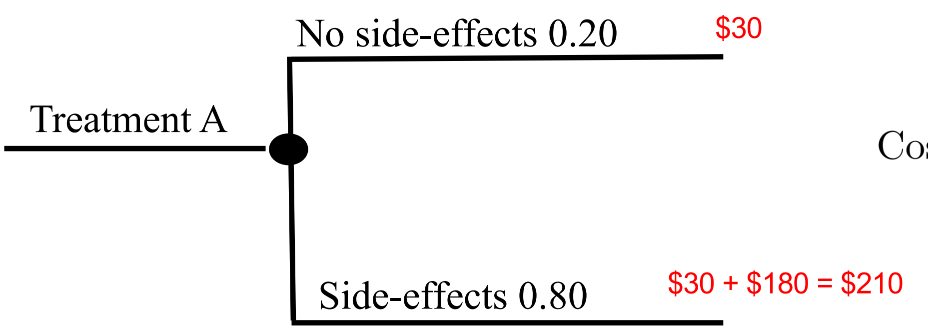
- Another tree example
- Introducing Markov models

Logistics

- By Thursday
  - Create “group” in MyCourses
  - Email me your project topic idea

Discrete probability distribution

- In decision trees each chance node represents a **discrete probability distribution**
- For discrete distributions:
  - There are 2 or more finite possible values
  - Probabilities must sum to 1



$$\text{Cost(treatment A)} = \begin{cases} \$30 & \text{with probability } 0.2 \\ \$210 & \text{with probability } 0.8 \end{cases}$$

Conditional Probability

If we are concerned that event E will occur, and we already know that event F occurred, then what we are actually looking for is the probability that E will occur **given** that F has occurred. We write this as:

$$P(E|F)$$

Another way to consider this is that when we know event F has occurred, our new sample space is simply F. To compute this new conditional probability, we need the fraction of F that is also in E:

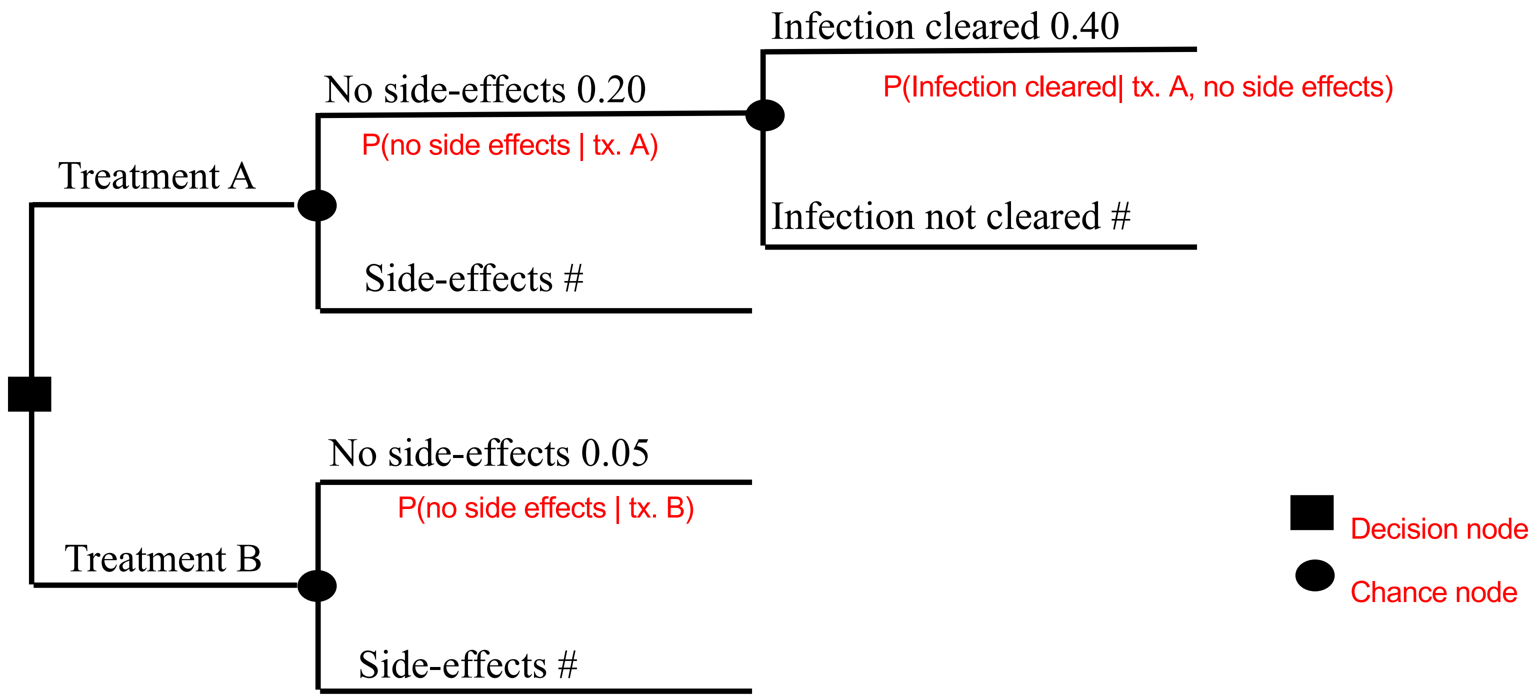
$$P(E|F) = \frac{P(EF)}{P(F)}$$

Can condition on multiple events:

$$P(E|F, G, H)$$

For decision trees

- All probabilities are **conditioned** on prior events



Expected value

- The probability-weighted average of all possible values

$$E(X) = \sum_{i=1}^{n} p_i X_i$$

- X_i is the ith outcome of a decision, p_i is the probability of the i^{th} outcome, and n is the total number of possible outcomes
- Indicates "average" value of the outcomes if the risky decision were to be repeated many times

Problem: Suspected Malignant Tumor

- Patient has a tumor: Could be fatal cancer (10%) or benign (90%)
- Medical or surgical therapy effective
- Medical therapy: Cure 15%
- Surgical therapy:
  - Radical: Periop Death 10%, Cure 90%
  - Palliative: Periop Death 2%, Cure 10%
  - If no tumor: Periop death 1% whether radical or palliative
- Outcomes - life expectancy
  - Cure: 20 years
  - Periop Death: 0 years
  - No cure: 2 years (death from progressive disease)

Structuring the Problem as a Decision Tree

1. Define the decision problem
2. Identify alternatives
3. Identify chance events
4. Represent the time sequence (order of observation)
5. Determine probability of chance events
6. Value the outcomes
7. Calculate the expected utility of each alternative
8. Assess uncertainty with sensitivity analyses

Define the Decision Problem

The decision:

- Medical therapy or surgical therapy

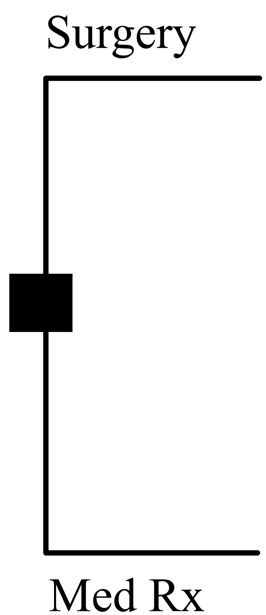
The decision maker

- The patient

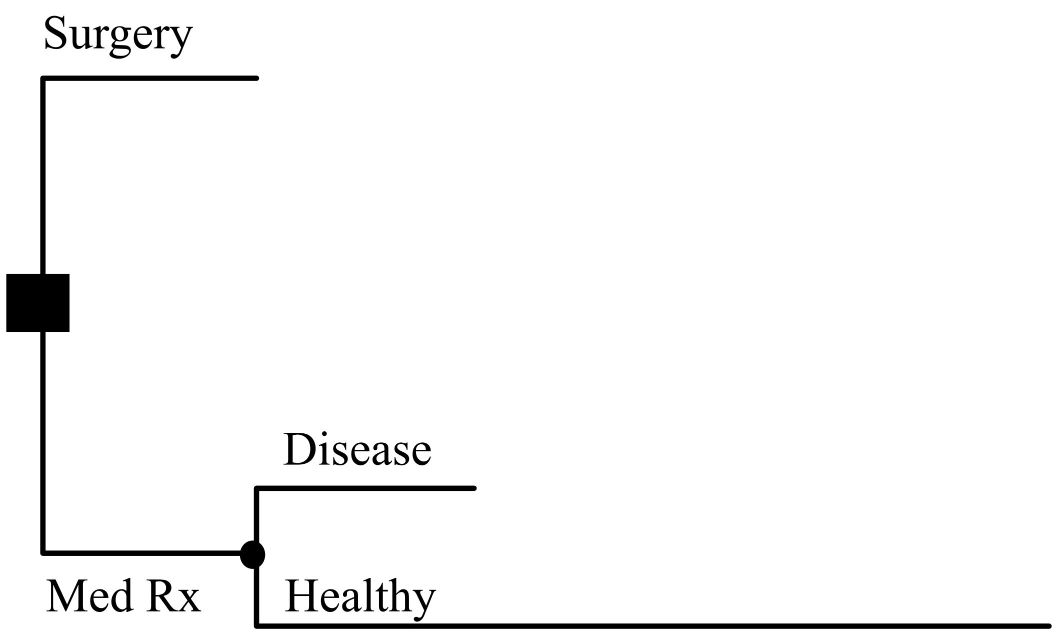
Identify the Alternatives

- Medical therapy
- Surgical therapy
  - Radical surgery
  - Palliative surgery

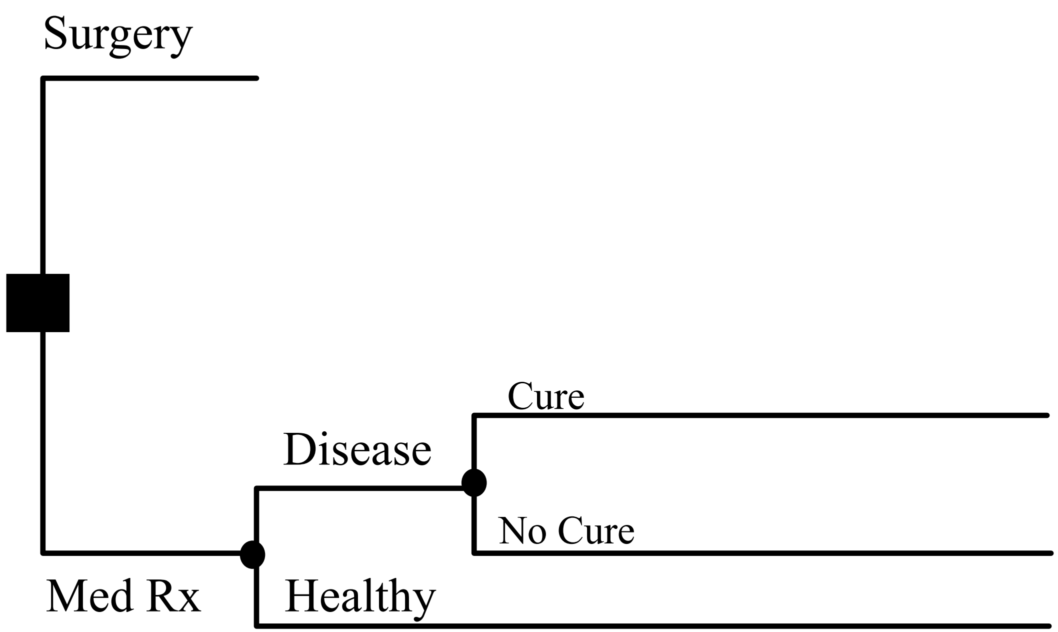
The Decision Alternatives



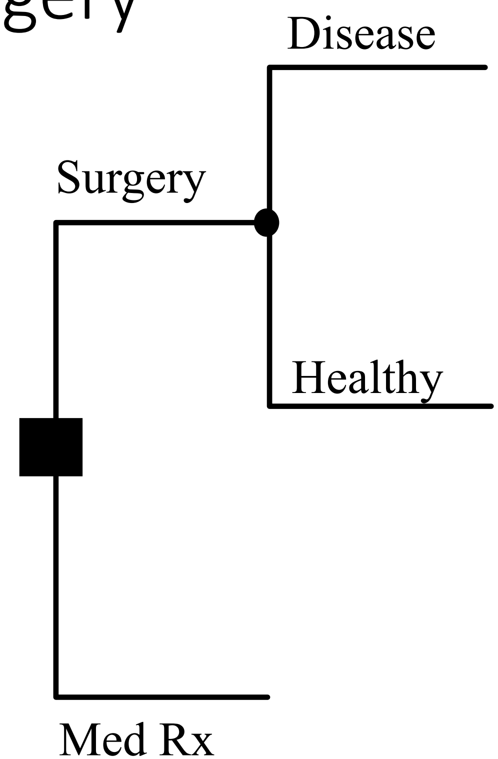
Identify the Chance Events - Medical Rx



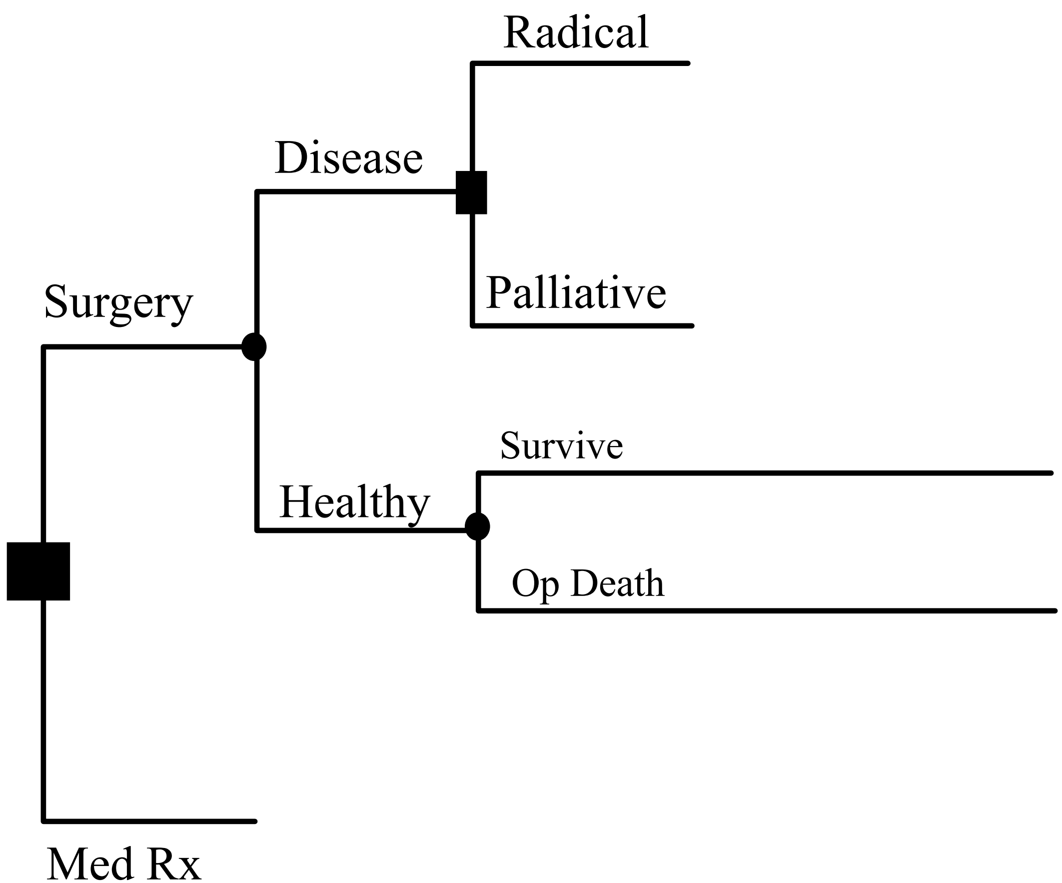
Identify the Chance Events - Medical Rx



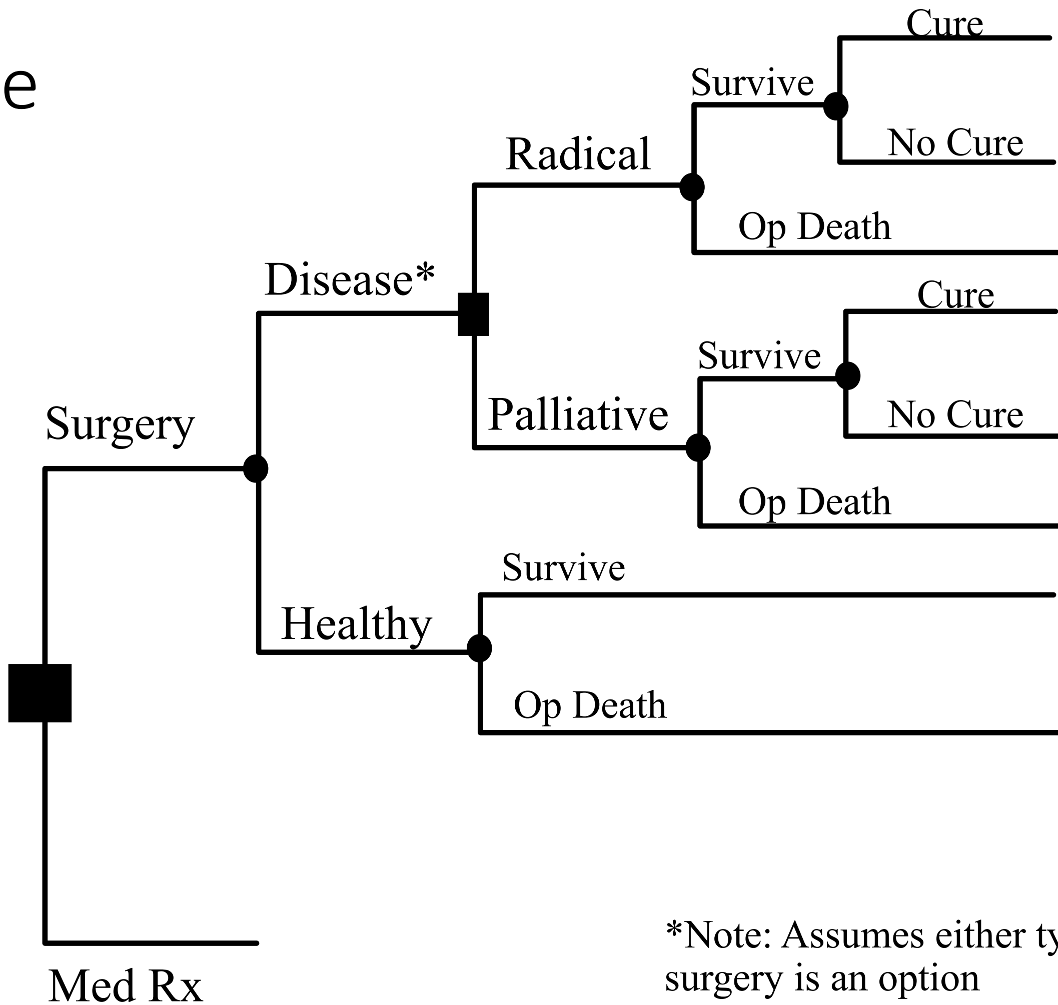
Identify the Chance Events - Surgery



Identify the Chance Events - Surgery

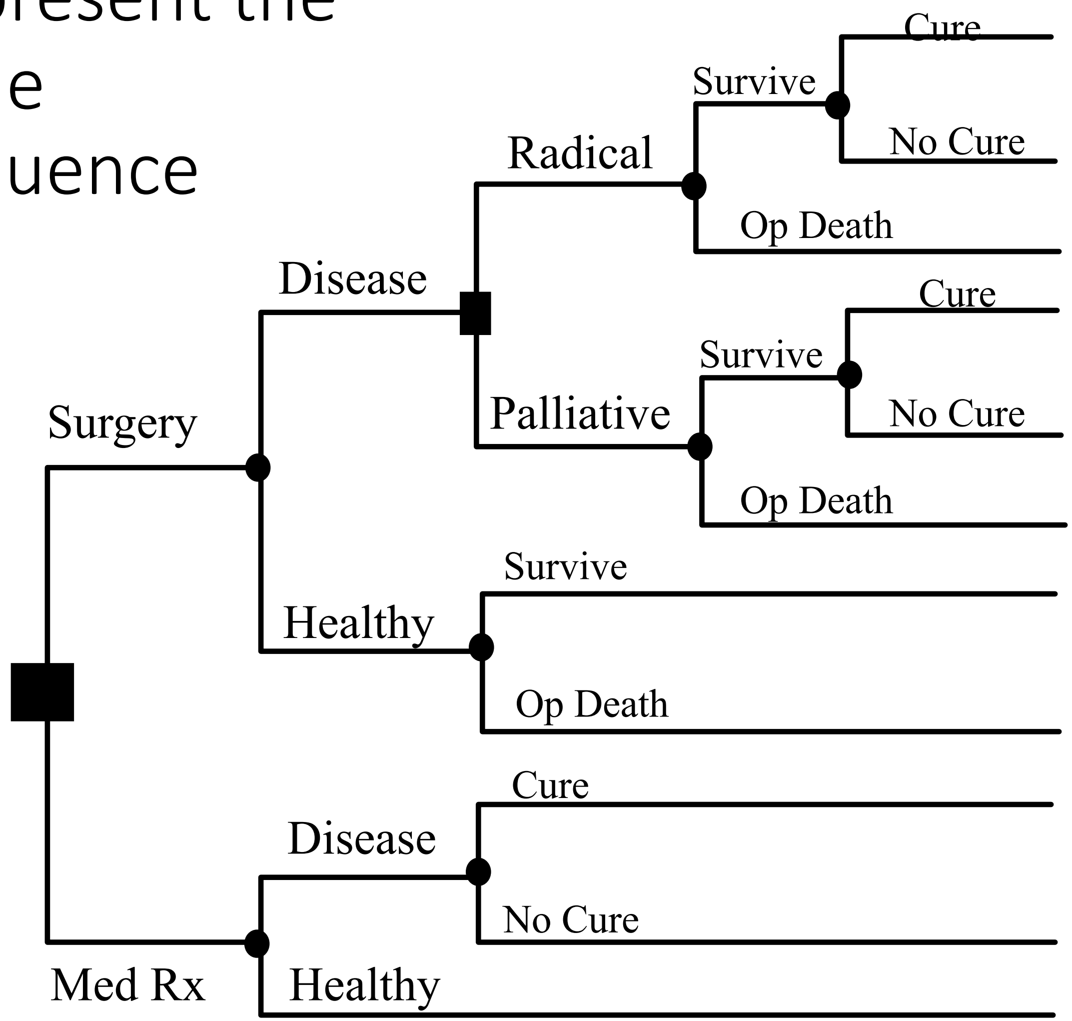


Identify the Chance Events - Surgery

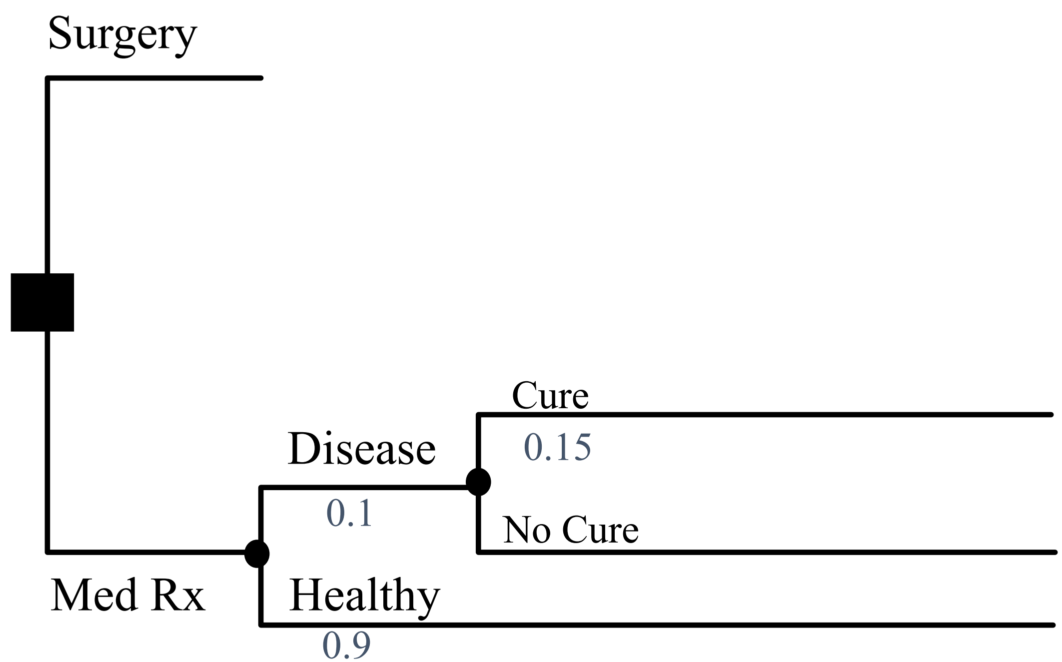


*Note: Assumes either type of surgery is an option

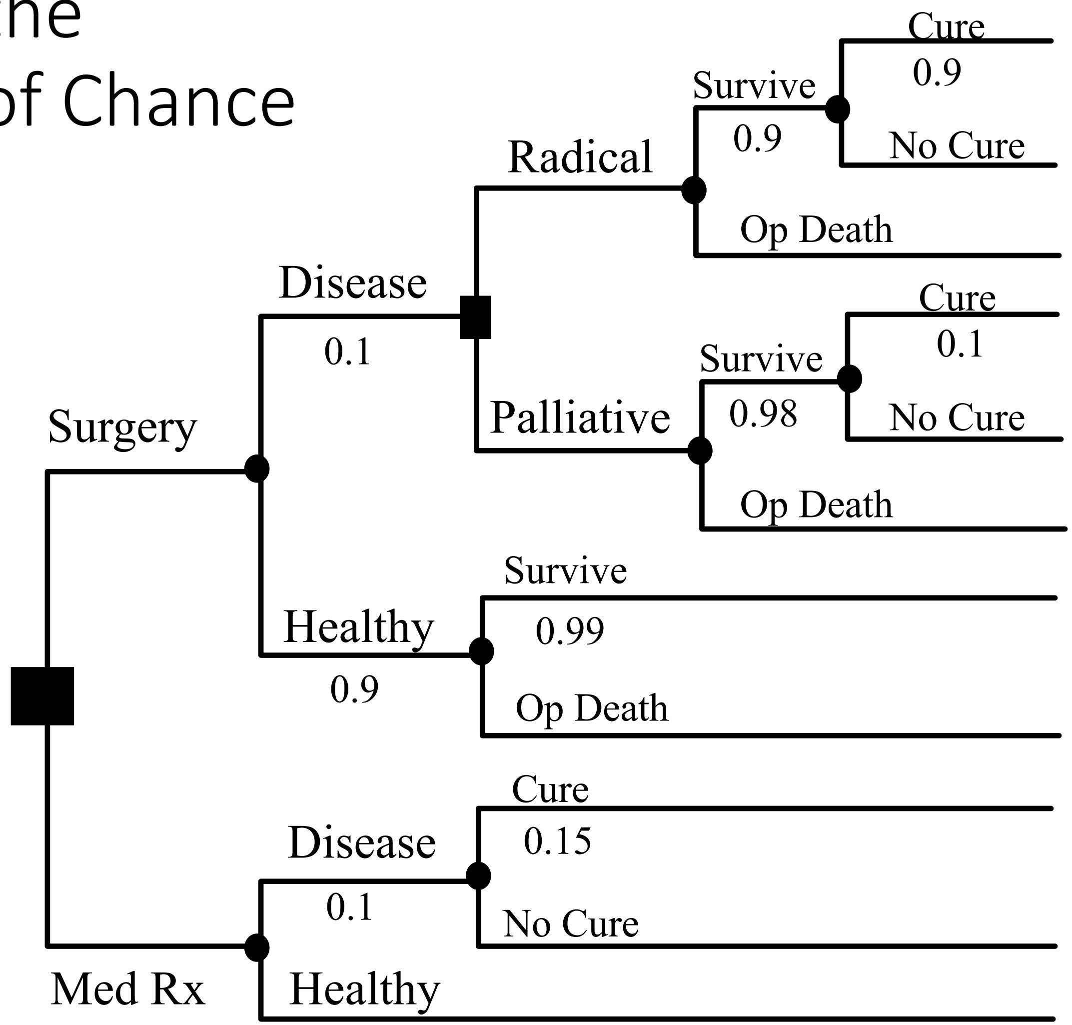
Represent the Time Sequence



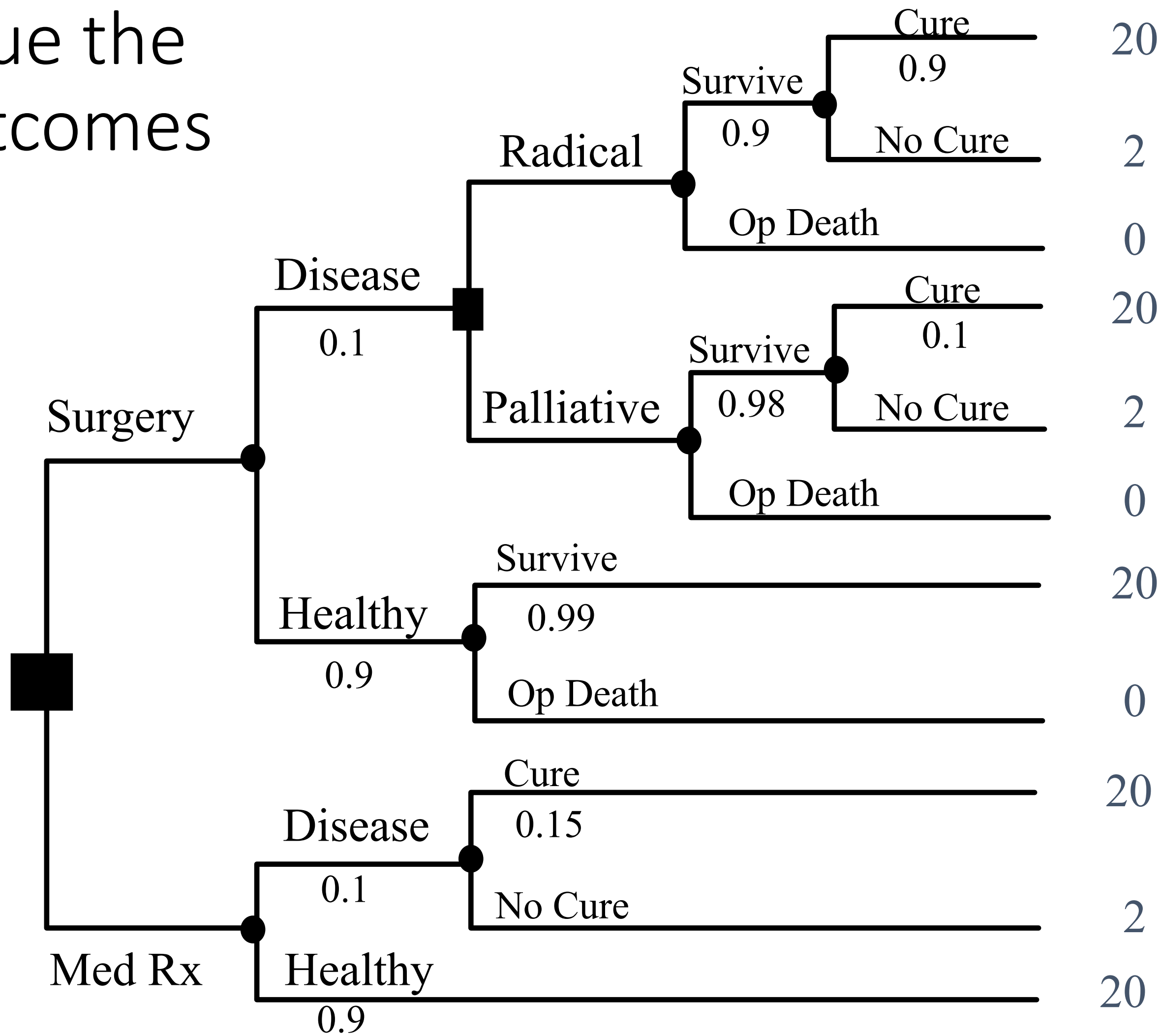
Determine the Probability of Chance Events



Determine the Probability of Chance Events

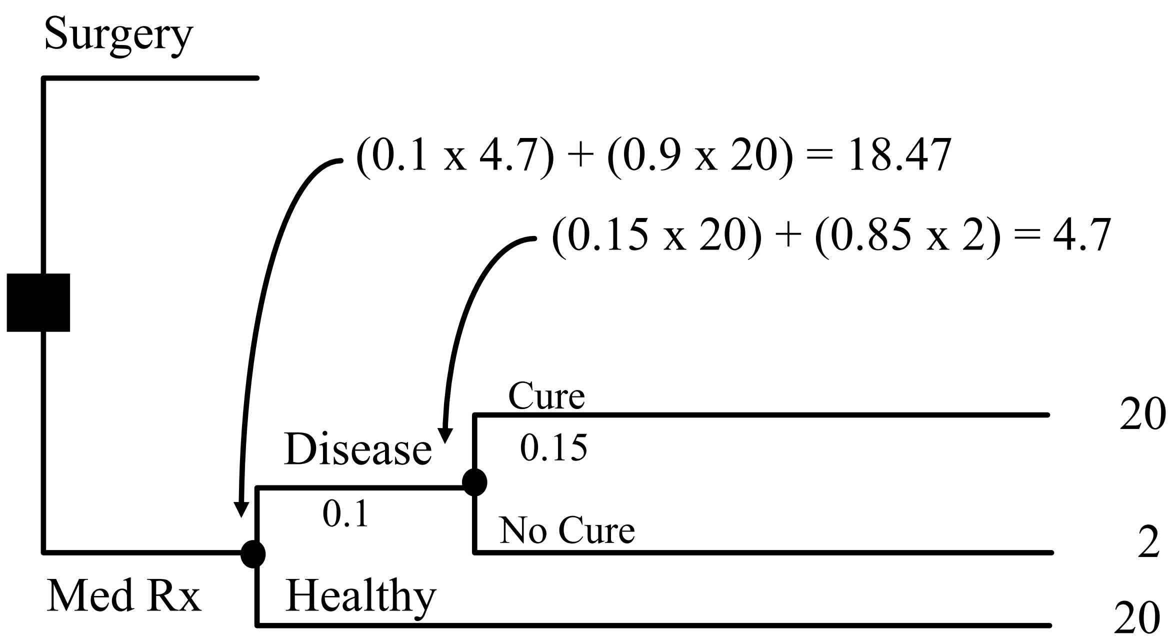


Value the Outcomes

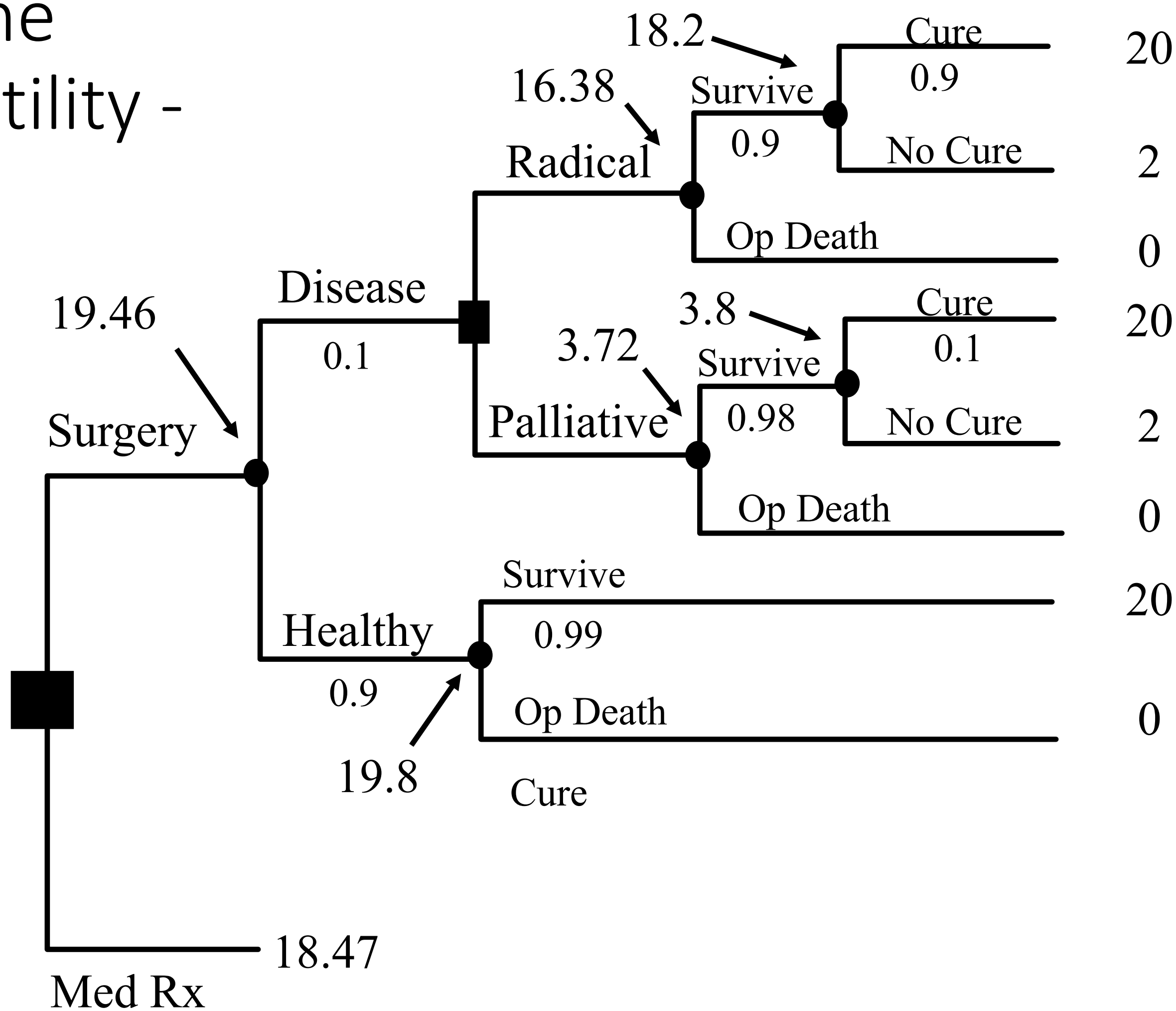


Calculate the Expected Utility - Med Rx

Take the weighted average of years lived



Calculate the Expected Utility - Surgery



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If surgery is begun and a tumor is detected, which type of surgery is preferred?

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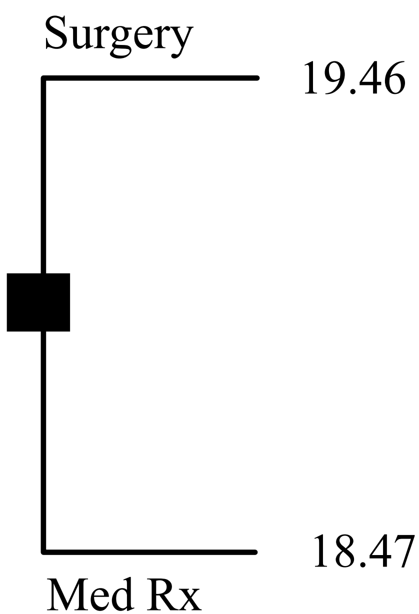
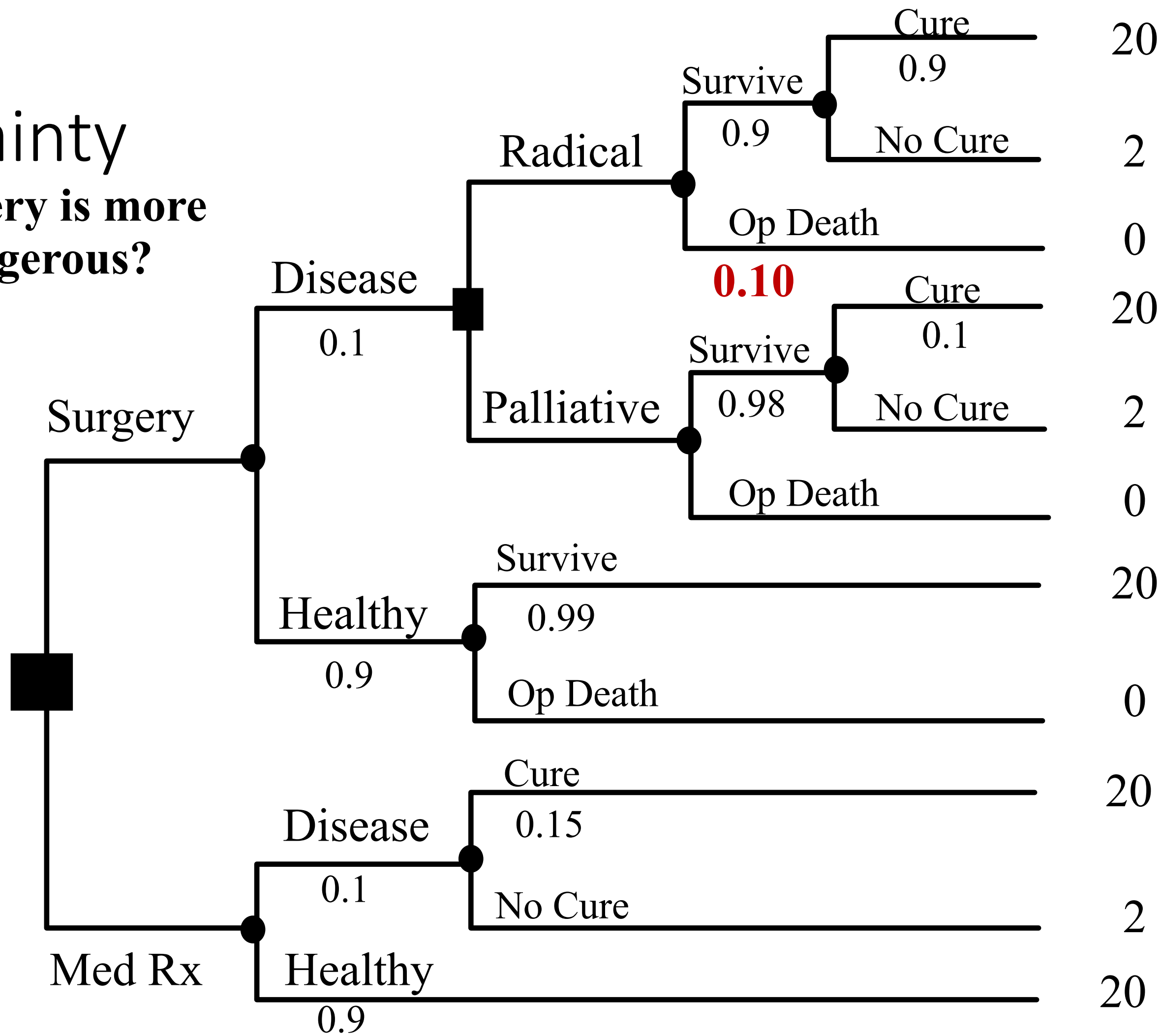
Choose the Alternative with Highest Expected Utility



ON AVERAGE,
surgery is better

Assess Uncertainty

What if surgery is more or less dangerous?



Assess Uncertainty - Sensitivity Analyses

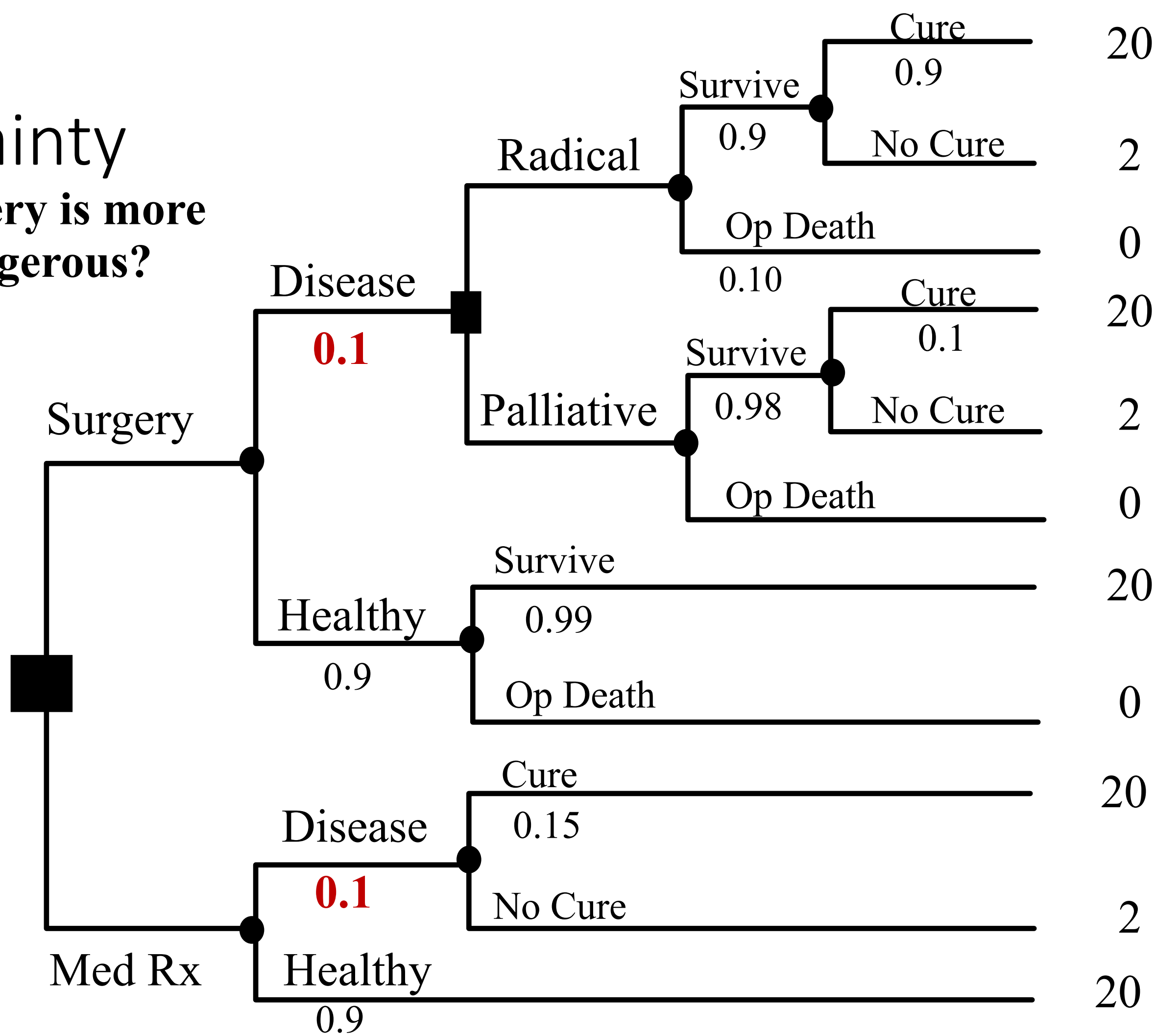
- What if the mortality from radical surgery is different?

p(Death)	LE Surgery	LE Med
0.05	19.55	18.47
0.10	**19.46**	**18.47**
0.15	19.37	18.47
0.20	19.27	18.47

Although surgical mortality may be higher(or lower), surgery is still preferred

Assess Uncertainty

What if surgery is more or less dangerous?



Sensitivity Analyses - Probability of Disease

- What if the probability of disease is higher than 0.1?

p(Disease)	LE Surgery	LE Med
0.05	19.62	19.24
0.10	**19.46**	**18.47**
0.20	19.12	16.94
0.30	18.77	15.41
0.40	18.43	13.88

The decision is ***NOT SENSITIVE*** *to the probability of disease*

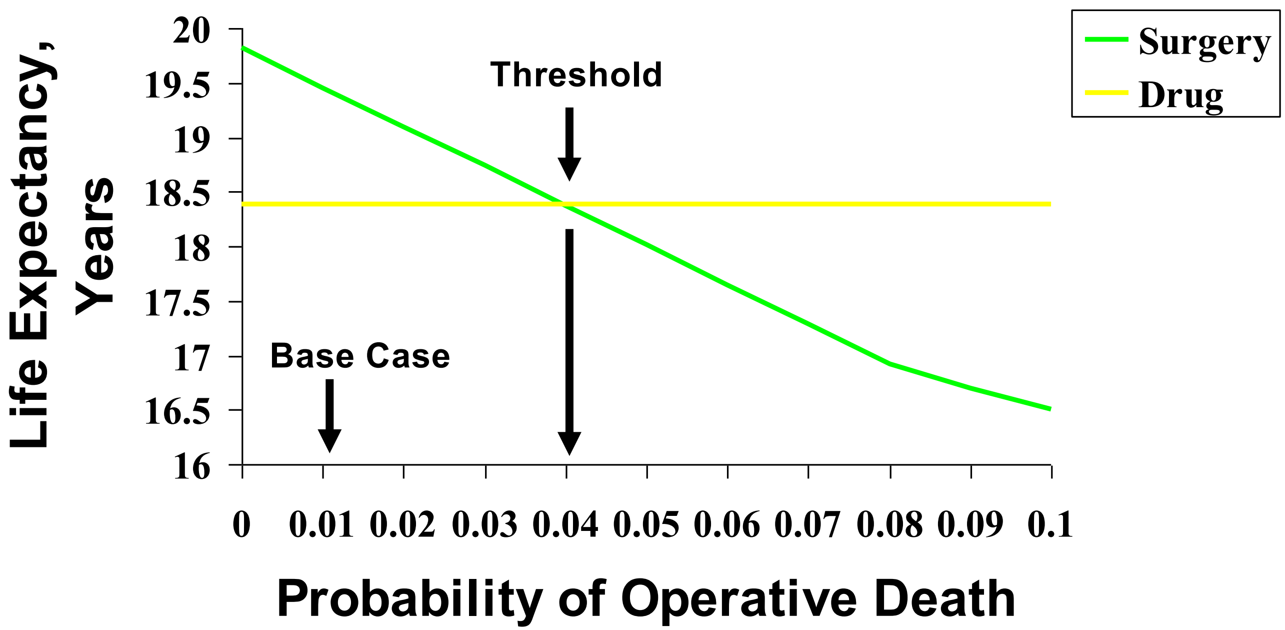
Sensitivity Analyses - Surgical Cure Rate

- What if radical surgery is not as good as we thought (initial estimate of cure rate = 0.9)?

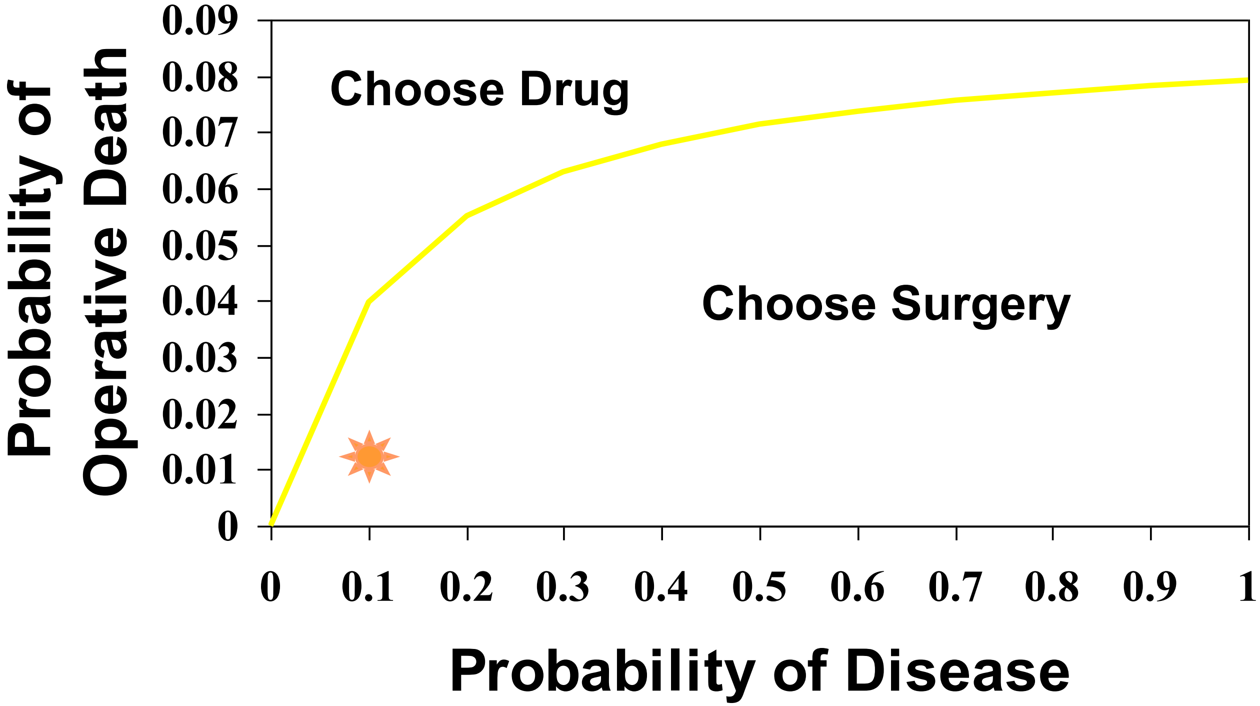
p(Surg Cure)	LE Surgery	LE Med
0.90	**19.46**	**18.47**
0.75	19.22	18.47
0.50	18.81	18.47
0.20	18.32	18.47

*The decision **IS SENSITIVE** to the probability of SURGICAL CURE*

Sensitivity Analysis: Probability of Operative Death



Two-Way Sensitivity Analysis: pDisease vs. pOperativeDeath



Decision Trees: Strengths & Weaknesses

Strengths

- Intuitive, visual form of the model
- Can generate rapid response using available data
- Permits long-term projections

Weaknesses

- Elapsed time not explicit in decision trees
- Tree format can become unwieldy when events repeat

Learning objectives for module 9.2

- The main features of Markov models
- Example
- Extensions
- Strengths and limitations of Markov models

Markov models

- People can be in one of a pre-determined number of *health states* (ex: healthy, HIV+, AIDS, death).
- They remain in that state for a period of time called a *cycle* (ex. of a cycle length: one year)
- At the end of the cycle, they may remain in the same state or change states – according to a set of transition probabilities governing transition from one state to another
- Transition probabilities are not affected by the person's previous path through the different health states

Why use a Markov model instead of a decision tree?

- Decision tree can get too complicated if the sequence of events is too long.
  - Especially likely to occur when modeling treatment of chronic illness
- Passage of time not explicit

Markov models

- Useful when
  - A decision problem involves risk that is continuous and constant over time
  - Times at which events will occur are uncertain
  - Timing of events is important
  - Important events may happen more than once

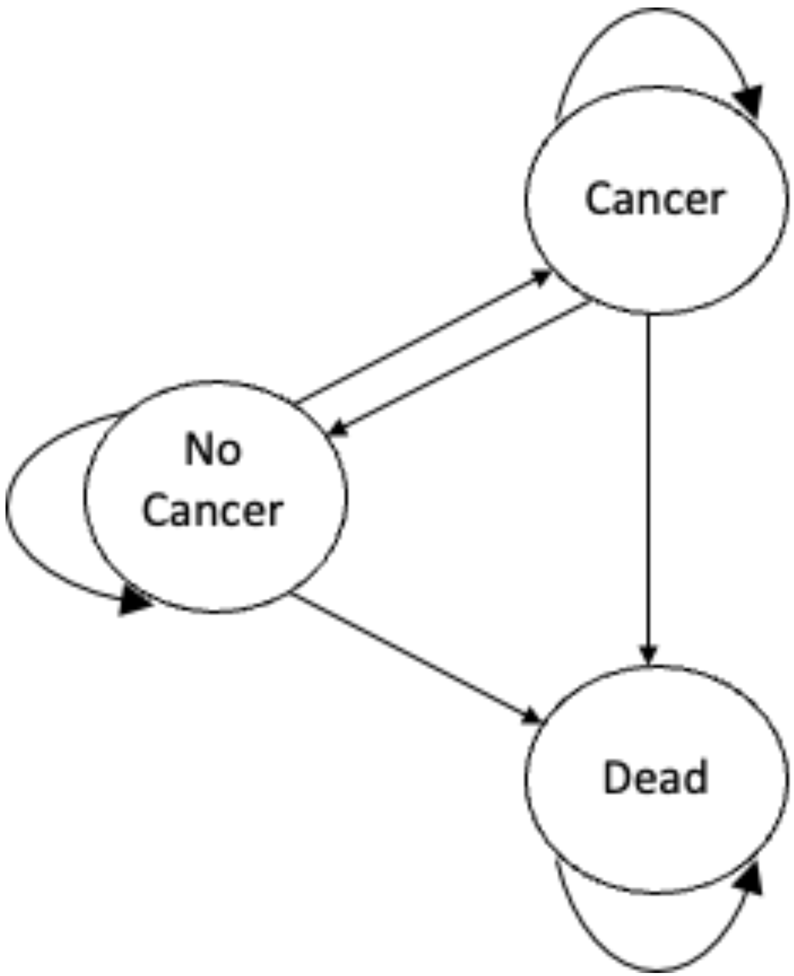
Example applications of Markov models in health

- Modeling disease and treatment in an individual patient
- Modeling disease and treatment in cohorts of patients
- Modeling HIV on needles
- Modeling the queue of patients waiting for organ transplants

Elements of a Markov model

- Markov states
  - Patient/entity is always in one of a finite number of states
- Markov cycles
  - Time horizon is divided into increments of equal length
- State transition probabilities
  - Events of interest are modeled as transitions from one state to another
  - In each cycle, there is a probability of transition from some states to others
  - Transitions satisfy the Markovian assumption

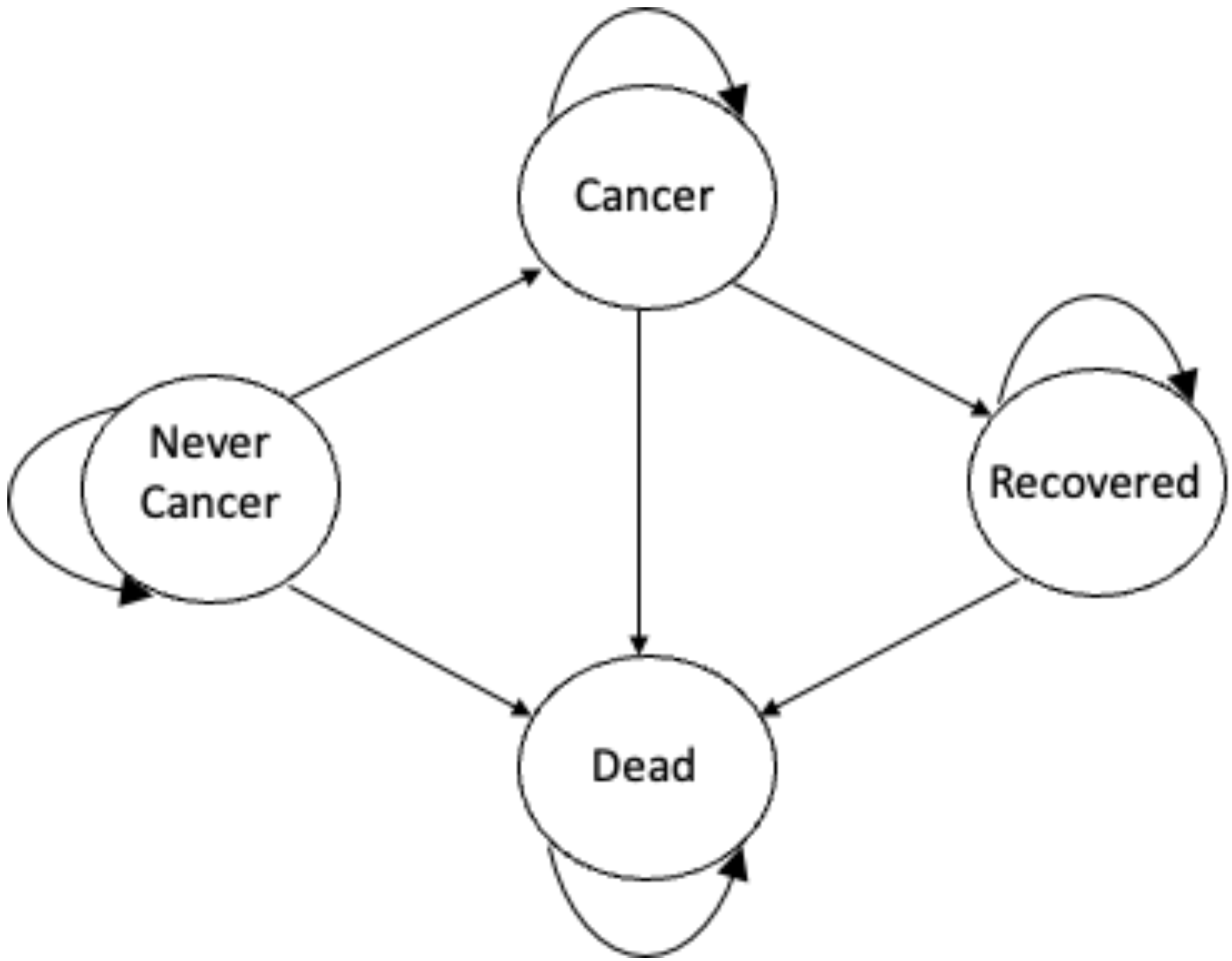
Example of a state-transition diagram



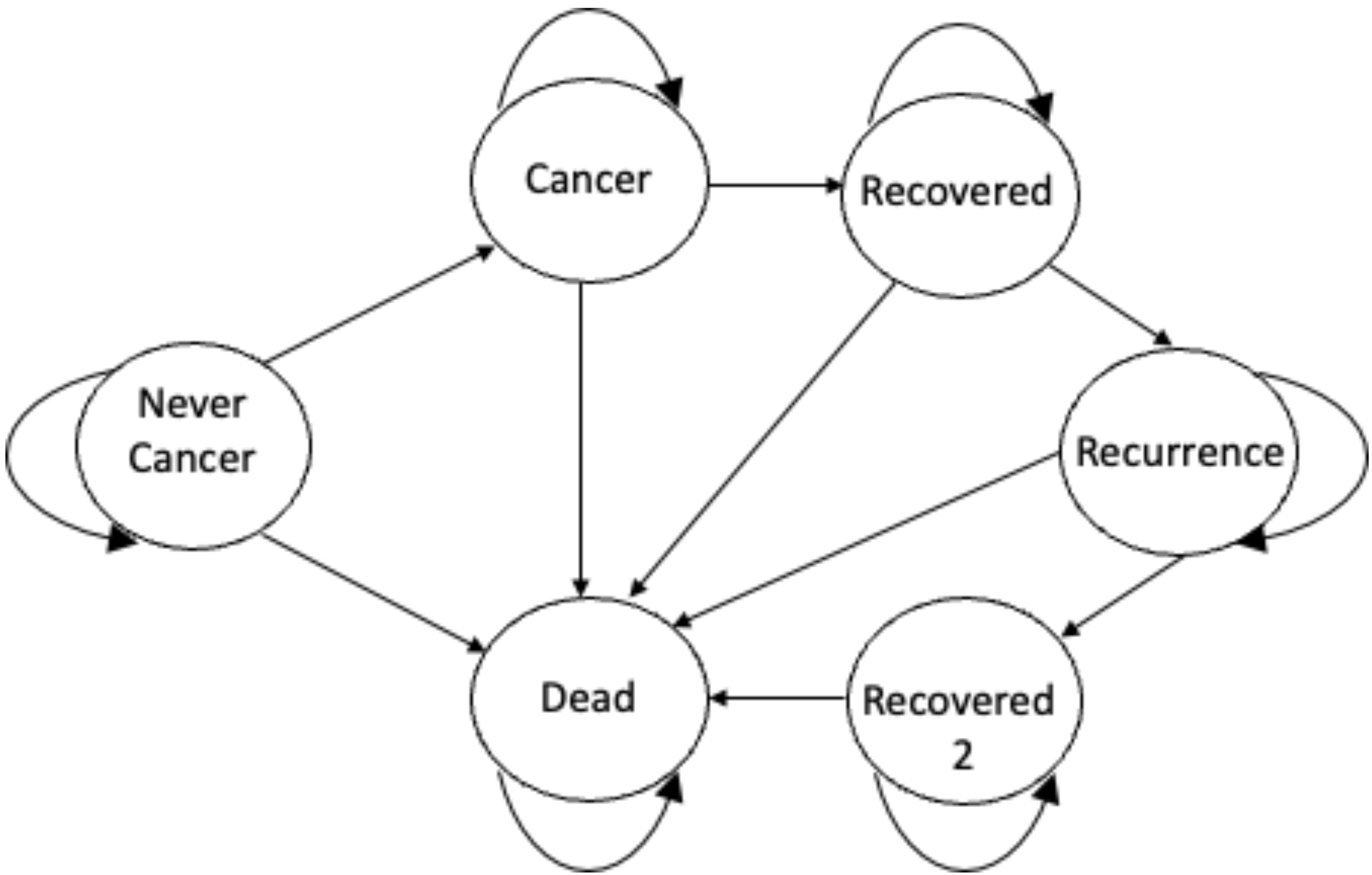
Markovian assumption

- "Memorylessness" assumption
- Probability of transition from one state to another depends only on the state a patient is in and the current cycle
- Does not depend on the length of time the patient has spent in the state
- Does not depend on other states the patient has visited
- If this assumption is violated, must create other states

A modified model



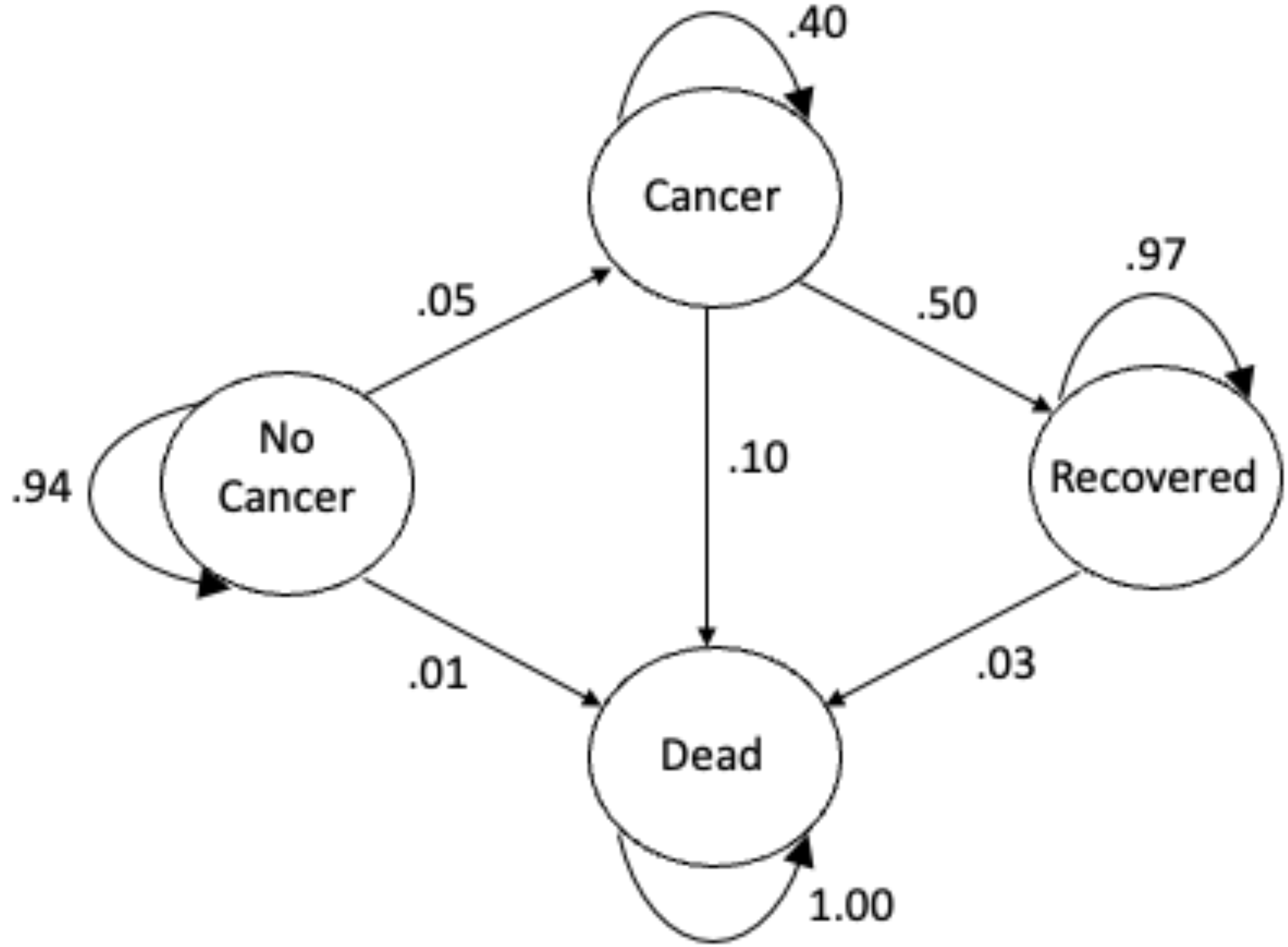
A further modification



Evaluating a Markov process

- Can calculate a matrix solution showing expected length of time in each state
- More often, **cohort simulation** is used
  - Explicitly shows number of individuals in each state at each timestep
  - Allows you to ‘look under the hood’
- Determine the cumulative length of time spent in each health state, multiplied by utility of that state

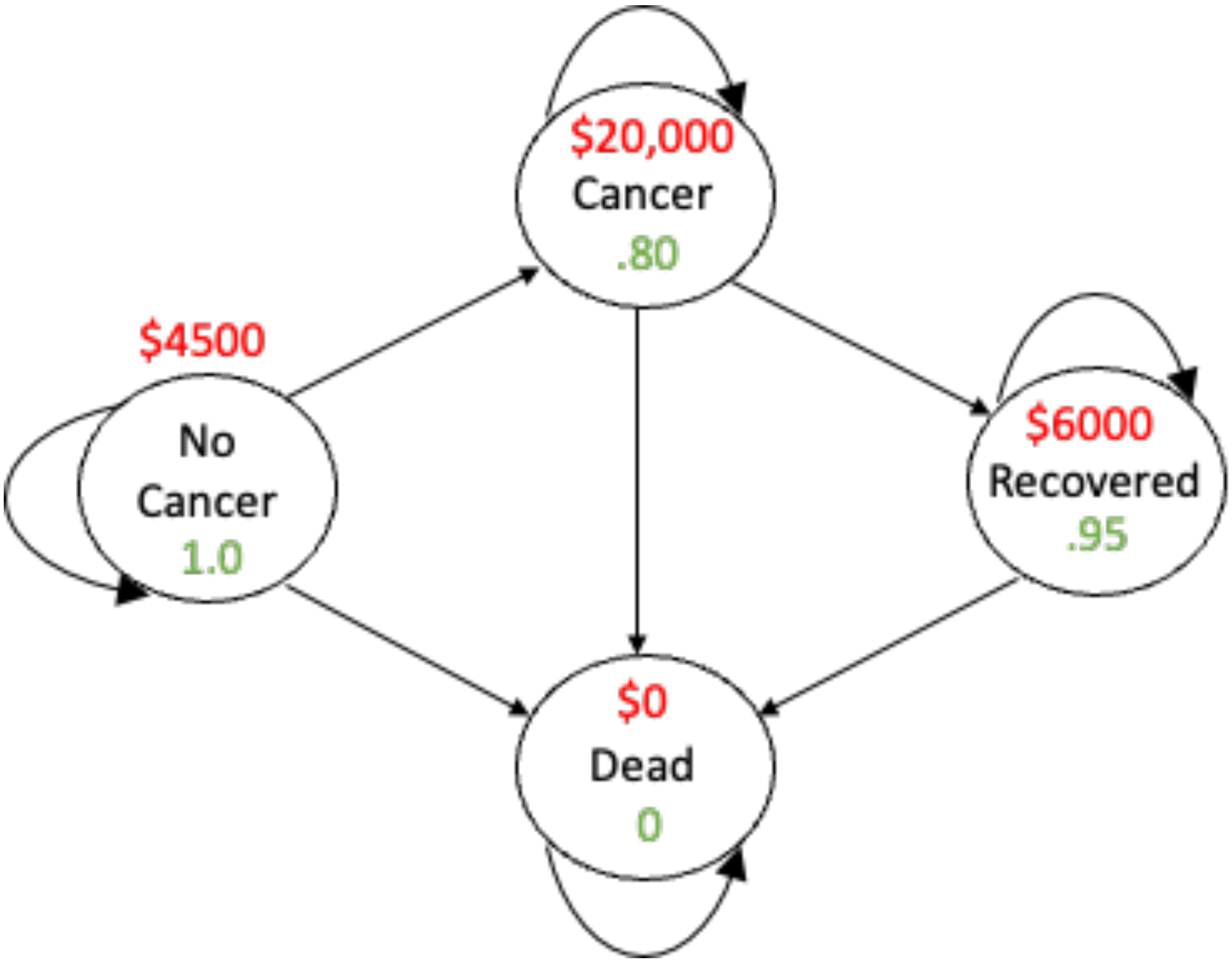
Evaluating the example Markov process



Calculating patient states

	No Cancer	Cancer	Recovered	Dead
Year 1	1000.0	0.0	0.0	0.0
Year 2	940.0	50.0	0.0	10.0
Year 3	883.6	67.0	25.0	24.4
Year 4	830.6	71.0	57.8	40.7
Year 5	780.7	69.9	91.5	57.8
Year 6	733.9	67.0	123.7	75.4
Year 7	689.9	63.5	153.5	93.1
Year 8	648.5	59.9	180.7	111.0
Year 9	609.6	56.4	205.2	128.9
Year 10	573.0	53.0	227.2	146.8

Valuing the health states



What is a policy question I could answer by extending/modifying this model?

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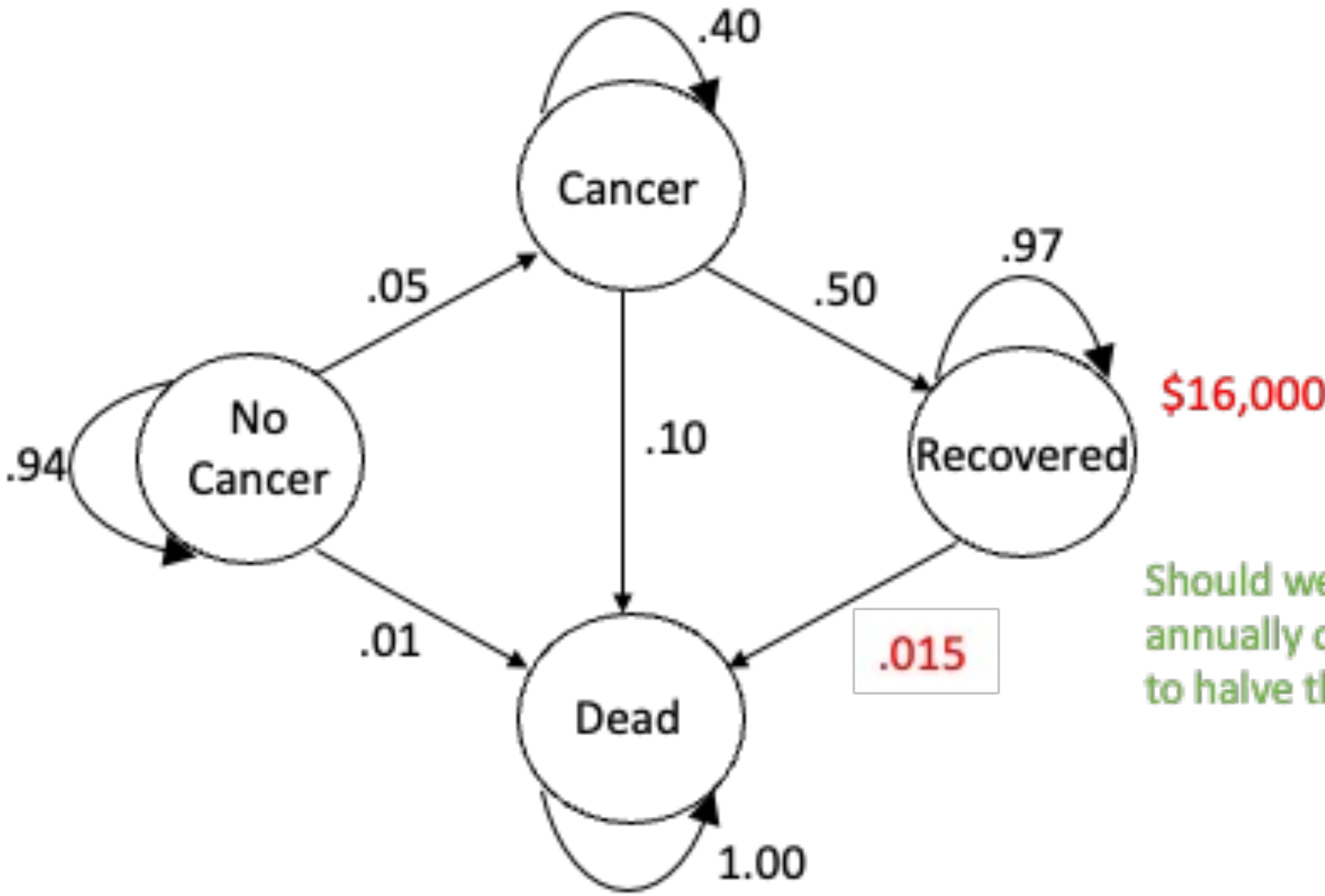
Calculating cost and health outcomes

	No Cancer	Cancer	Recovered	Dead	QALYs	Cost ($1000s)	Disc. QALYs	Disc. Cost
QALY	1.0	.80	.95	0				
Cost	$4500	$20,000	$6000	$0				
Year 1	1000.0	0.0	0.0	0.0	1000.0	4500.0	1000.0	4500.0
Year 2	940.0	50.0	0.0	10.0	980.0	5230.0	951.5	5077.7
Year 3	883.6	67.0	25.0	24.4	961.0	5466.2	905.8	5152.4
Year 4	830.6	71.0	57.8	40.7	942.2	5503.7	862.3	5036.7
Year 5	780.7	69.9	91.5	57.8	923.6	5460.8	820.6	4851.9
Year 6	733.9	67.0	123.7	75.4	905.0	5385.0	780.7	4645.2
Year 7	689.9	63.5	153.5	93.1	886.5	5295.5	742.4	4434.9
Year 8	648.5	59.9	180.7	111.0	868.0	5200.0	705.8	4228.0
Year 9	609.6	56.4	205.2	128.9	849.6	5101.8	670.7	4027.4
Year 10	573.0	53.0	227.2	146.8	831.3	5002.4	637.1	3833.9

Example policy question



Should we spend $10,000 annually on recovered patients to halve their death rate?

Cost and health outcomes with new policy

	No Cancer	Cancer	Recovered	Dead	Disc. QALYs	Disc. Cost ($1000s)	Δ Disc. QALYs	Δ Disc. Cost ($1000s)
Year 1	1000.0	0.0	0.0	0.0	1000.0	4500.0	0.0	0.0
Year 2	940.0	50.0	0.0	10.0	951.5	5077.7	0.0	0.0
Year 3	883.6	67.0	25.0	24.4	905.8	5388.1	0.0	235.6
Year 4	830.6	71.0	58.1	40.3	862.6	5570.7	0.3	534.0
Year 5	780.7	69.9	92.7	56.6	821.7	5682.5	1.0	830.6
Year 6	733.9	67.0	126.3	72.8	782.8	5748.2	2.1	1103.0
Year 7	689.9	63.5	157.9	88.7	745.9	5779.6	3.5	1344.7
Year 8	648.5	59.9	187.3	104.3	710.9	5783.4	5.1	1555.3
Year 9	609.6	56.4	214.4	119.6	677.6	5764.0	6.9	1736.6
Year 10	573.0	53.0	239.4	134.6	646.0	5724.9	8.9	1891.0
Total							27.9	9230.8

CE Ratio = $9230.8/27.9 = $330,800/QALY gained

Today

- Intro to Markov Models
- **Example: diagnosing Coronary Artery Disease**
- Guidance for building and analyzing Markov Models

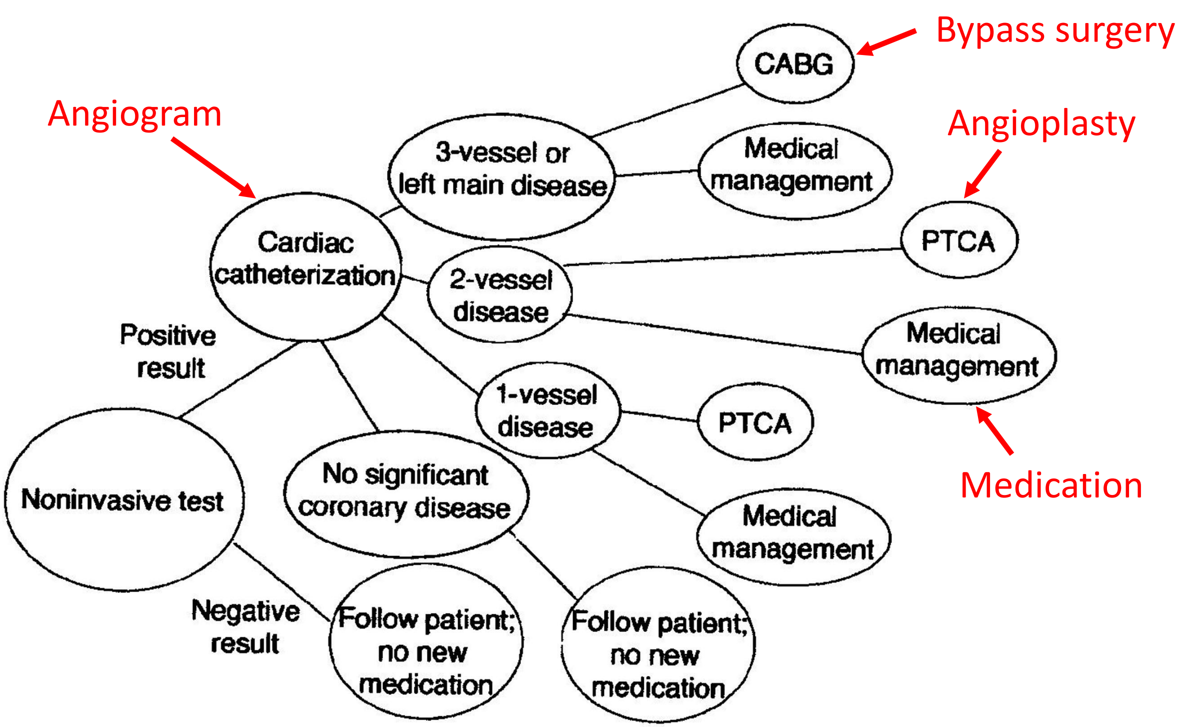
Diagnosing coronary artery disease

- What is the cost effectiveness of alternative test strategies for diagnosing CAD in intermediate-risk patients?
- Angiogram is “gold standard”
- Consider five non-invasive screening techniques to diagnose CAD (followed by angiogram if non-invasive test is positive)

Non-invasive screening tests

- Exercise electrocardiography (“treadmill test”)
- Planar thallium imaging
- Stress echocardiography (ultrasound)
- Single-photon emission computed tomography (SPECT)
- Positron emission tomography (PET scan)

Management of patients after screening



Overview of methods

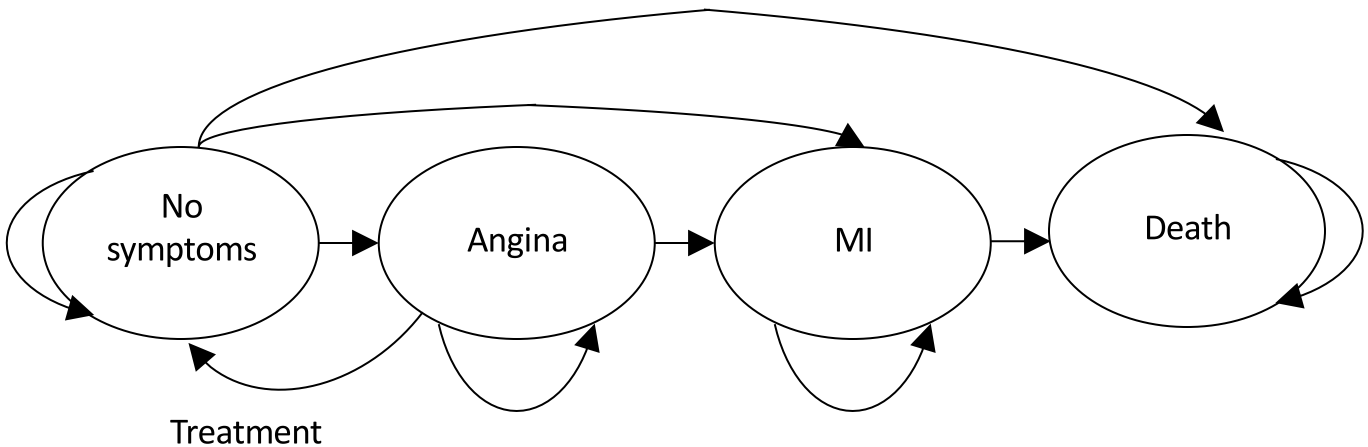
- Markov model of CAD in a cohort of patients
- Meta-analysis to estimate test sensitivity, specificity
- Evaluation of costs incurred and QALYs experienced for alternative testing strategies
- Societal perspective
- 30-year time horizon
- Discounting of costs, benefits at 3%

Patient population

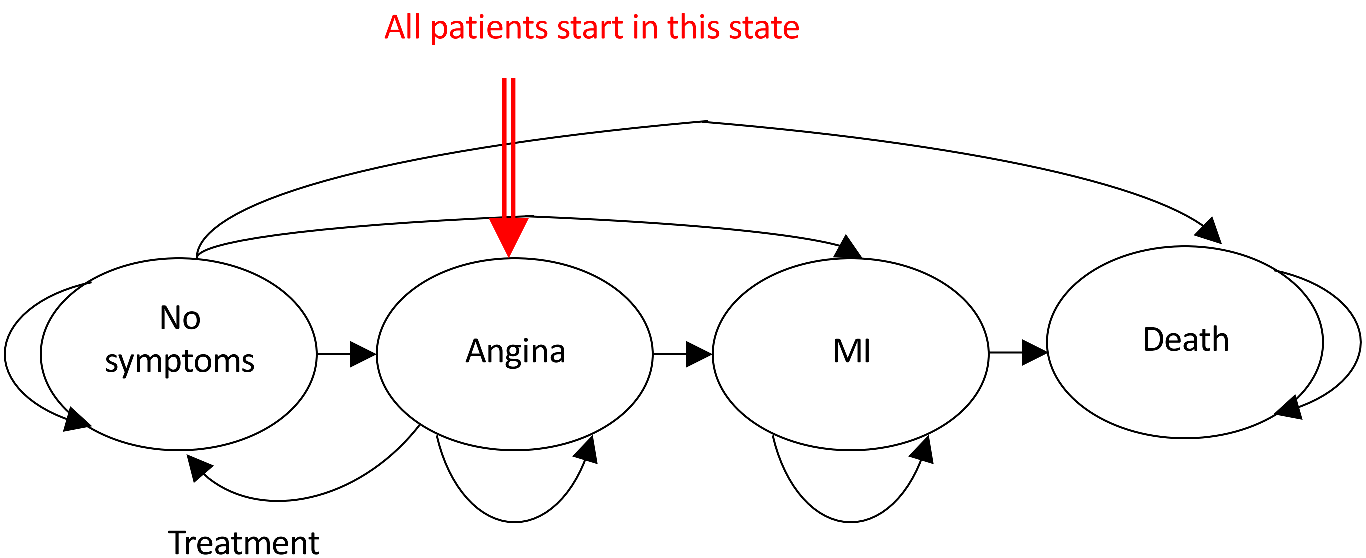
- Men and women aged 45, 55, 65, with a 25-75% chance of having CAD (“intermediate risk”)
  - History of chest pain
  - Age, sex, risk factors
- CAD = stenosis of 50% or more in left main artery, or 70% or more in one of the other arteries
- Base case: Men aged 55 with 50% risk of CAD

Markov model of CAD

(Time increment = 1 year)



Markov model of CAD



Meta-analysis

- A meta-analysis combines the results of several studies that address a set of related research hypotheses
- Meta-analysis is a way of increasing sample size for estimates of a given quantity
  - E.g., combine results of 132 different studies of the sensitivity of the treadmill test for diagnosing CAD
- How to perform a meta-analysis
  - Select studies
  - Decide what to measure
  - Create aggregate statistics

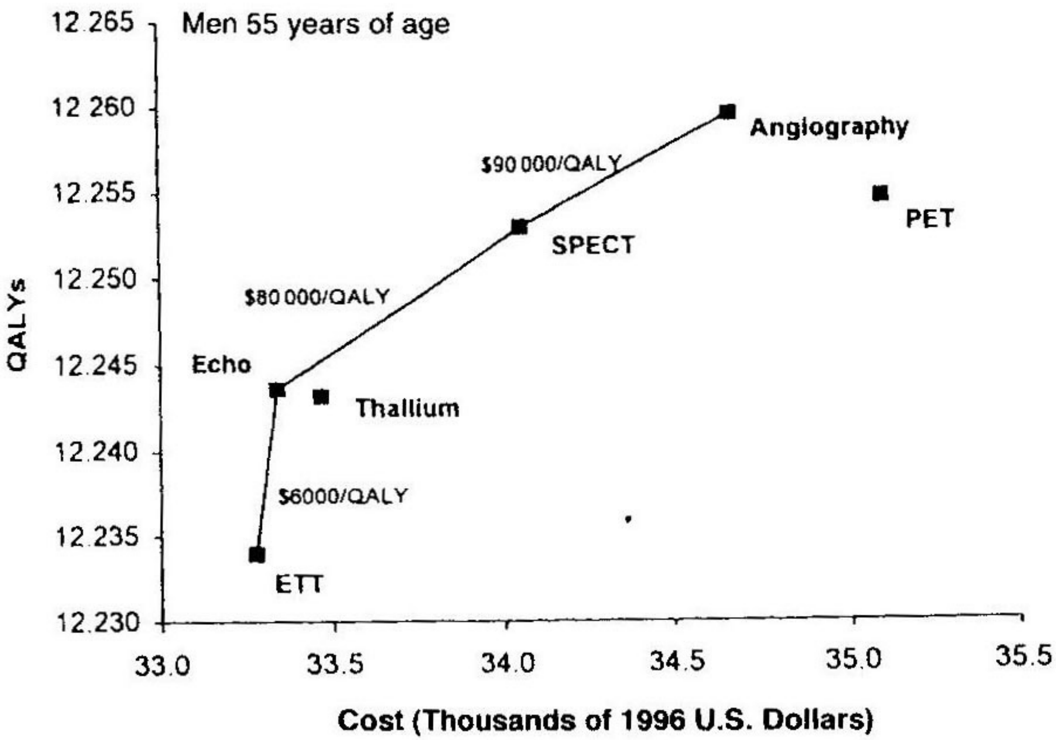
Test sensitivity, specificity, and cost

Test	Sensitivity Any CAD	Sensitivity Severe CAD	Speci-ficity	Cost
Treadmill test	.68	.86	.77	$110
Planar thallium imaging	.79	.93	.73	$221
Echocardiography	.76	.94	.88	$265
SPECT	.88	.98	.77	$475
PET scan	.91	??	.82	$1500

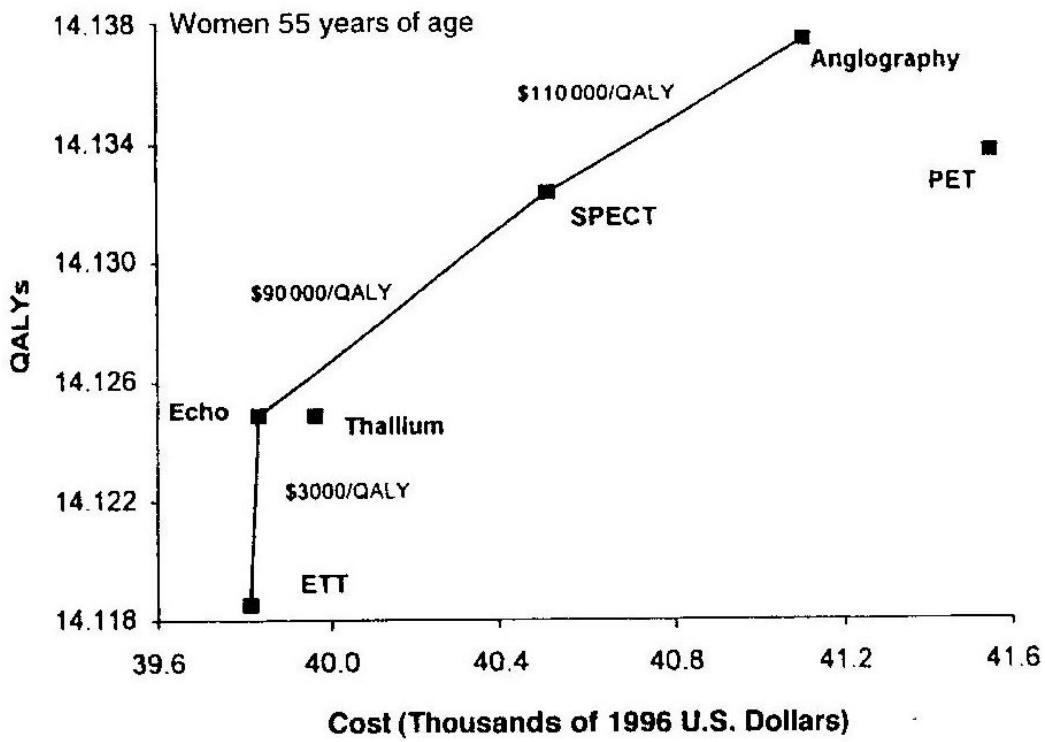
Treatments and cost

Treatment	Total Cost
Cardiac catheterization	$1,810
Single admission for MI	$7,415
PTCA	$11,685
CABG: 1- and 2-vessel	$32,390
CABG: 3-vessel and left main	$32,824

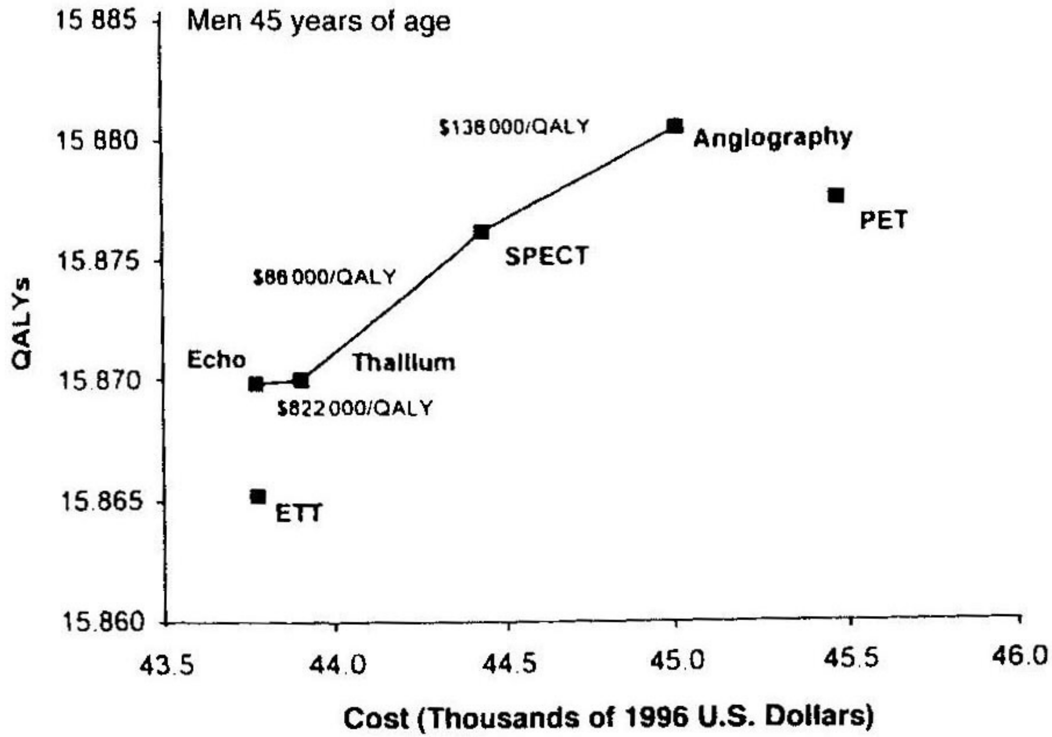
Incremental CE ratios: men age 55



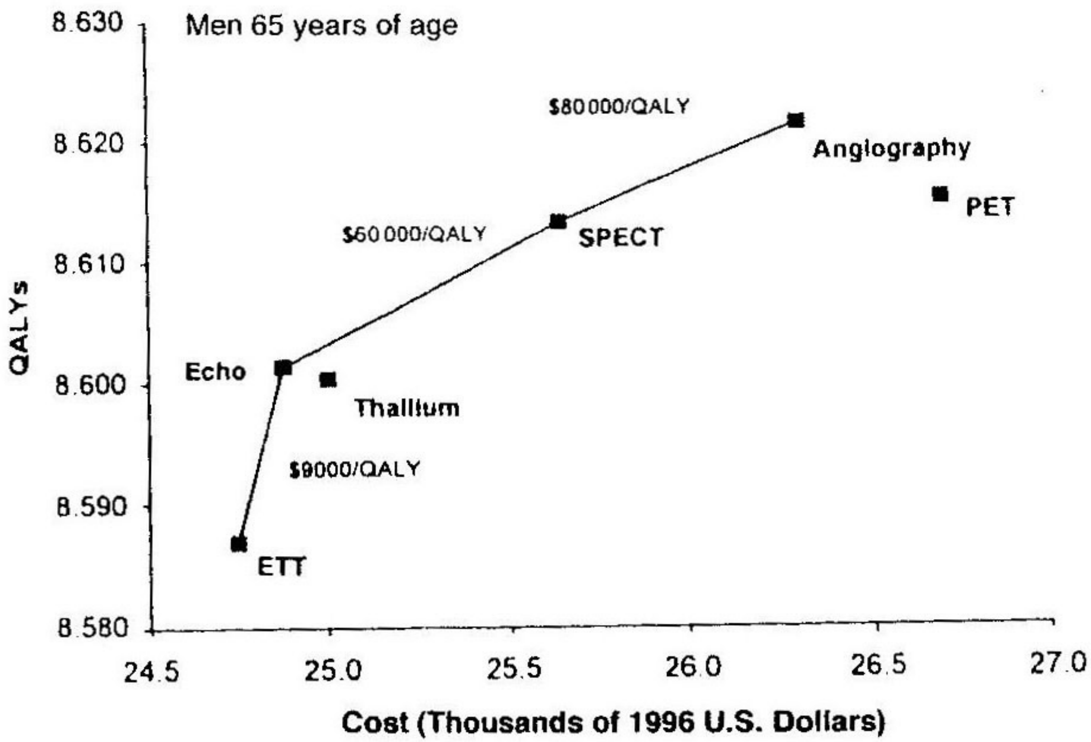
Incremental CE ratios: women age 55



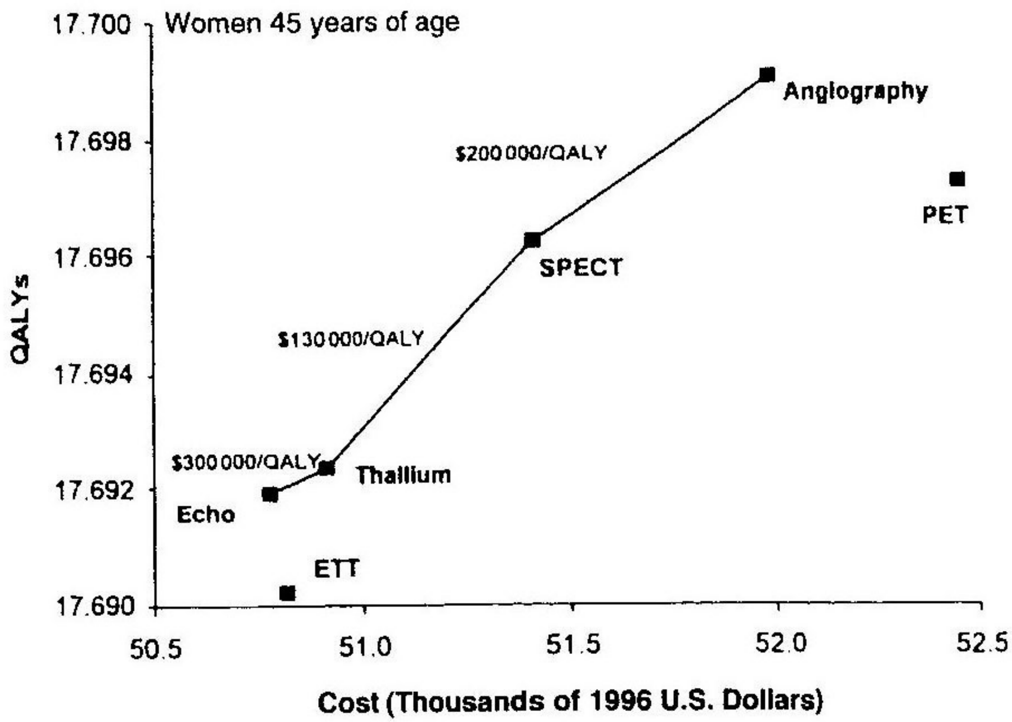
Incremental CE ratios: men age 45



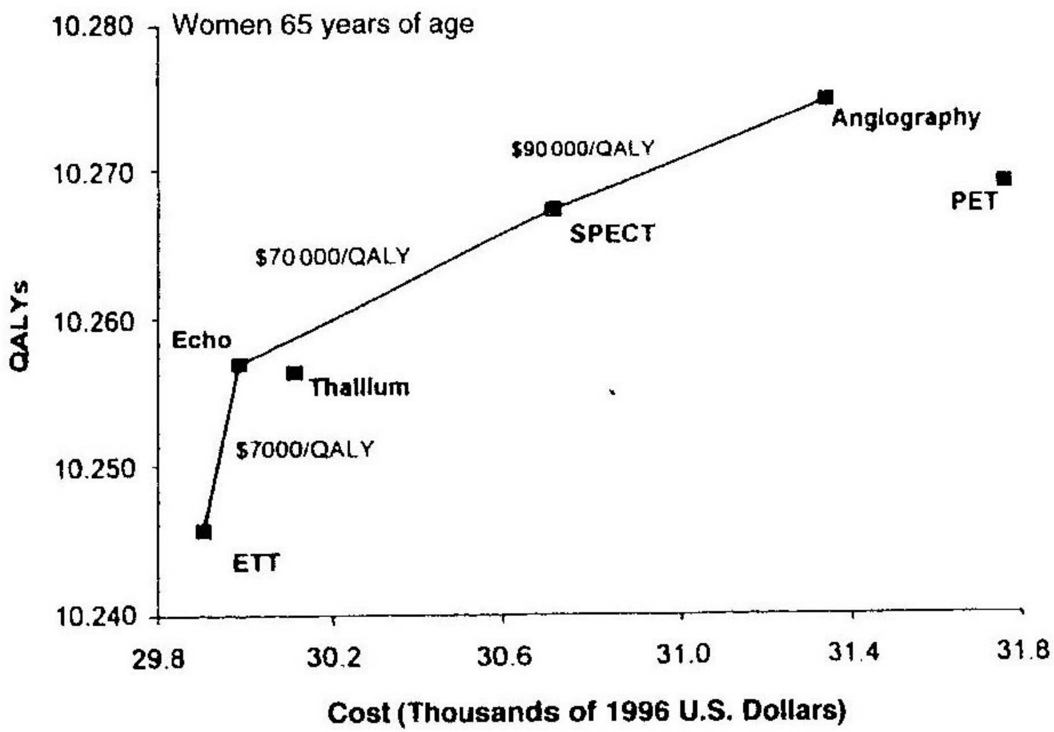
Incremental CE ratios: men age 65



Incremental CE ratios: women age 45



Incremental CE ratios: women age 65



Results: 55-year-old men

Test	Cost	LYs experienced	QALYs experienced
Angiography	$34,661	16.601	12.259
PET scan	$35,093	16.601	12.255
SPECT	$34,047	16.600	12.253
Echocardiography	$33,341	16.595	12.244
Planar th. imaging	$33,467	16.592	12.243
Treadmill	$33,281	16.581	12.234

Summary of incremental CE ratios ($1000's, compared to strategy in row above)

	Men			Women		
	45	55	65	45	55	65
ETT (Echo*)						
Echo (Thallium*)	822	6	9	300	3	7
SPECT	86	80	60	130	90	70
Angiogram	136	90	80	200	110	90

* For age 45 (both men and women)

Comparison to no-test strategy

- Patients are neither tested nor treated unless they experience MI
- Costs are incurred by patients who experience MI
- Not likely to be an acceptable strategy for a moderate-risk population
- CE of echocardiography compared to no testing:
  - \$31,000 – \$98,000/QALY gained
- SPECT and angiography can also be CE compared to no testing

Sensitivity analyses

- Patient age
  - Tests are more cost-effective for 65-year olds than for patients who are 55 or 45
- Disease prevalence
  - If high prevalence (75%), angiography looks favorable
  - If low prevalence (25%), echocardiography is favorable
- PET scan cost
  - PET scans not favorable even if cost is only $750

Sensitivity analyses (cont.)

- Indeterminacy rate of the tests
  - Treadmill test has base indeterminacy rate of 40%
  - Even if the rate is < 10%, echocardiography dominates
  - If the rate is zero, incremental CE of echo. is < $40,000
- Complications of angiography
  - Base case did not include non-fatal complications
  - Tripling the mortality rate does not change test rankings, but angiography becomes relatively more expensive per QALY gained

Discussion

- Important to use incremental CE ratios
- Best tests for intermediate-risk patients:
  - Echocardiography $\rightarrow$ SPECT $\rightarrow$ Angiography
- Should use local costs
- Do the noninvasive tests provide additional information for disease management?

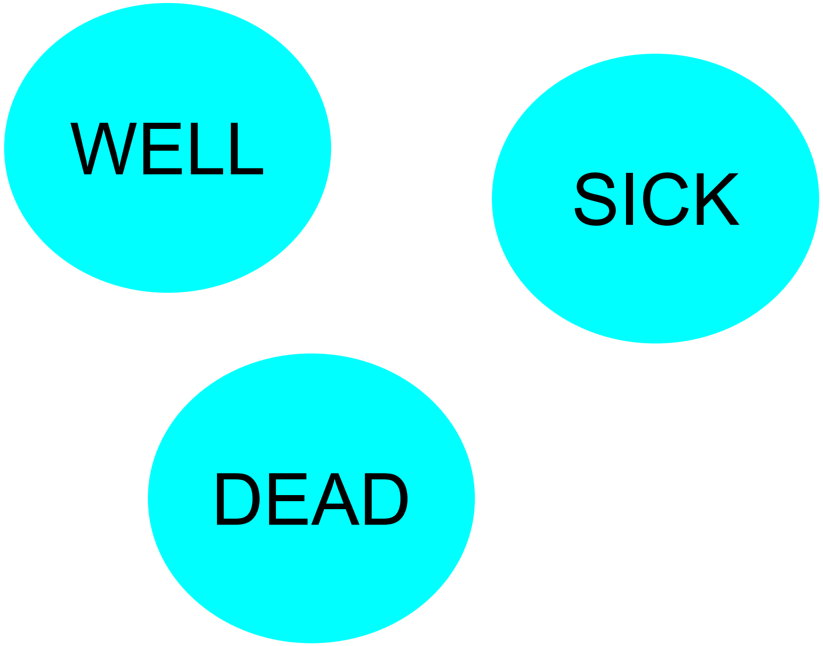
Today

- Intro to Markov Models
- Example: diagnosing Coronary Artery Disease
- **Guidance for building and analyzing Markov Models**

Building a Markov Model

1. **Determine health states**
2. Determine transitions
3. Choose cycle length
4. Estimate transition probabilities
5. Assign state utilities and/or costs
6. Calculate
7. Sensitivity analysis

Markov Health States



Health states must be

- Granular enough to allow you to model all relevant **differences** between your policies
- Simple enough to be tractable and allow you to parameterize your model

Building a Markov Model

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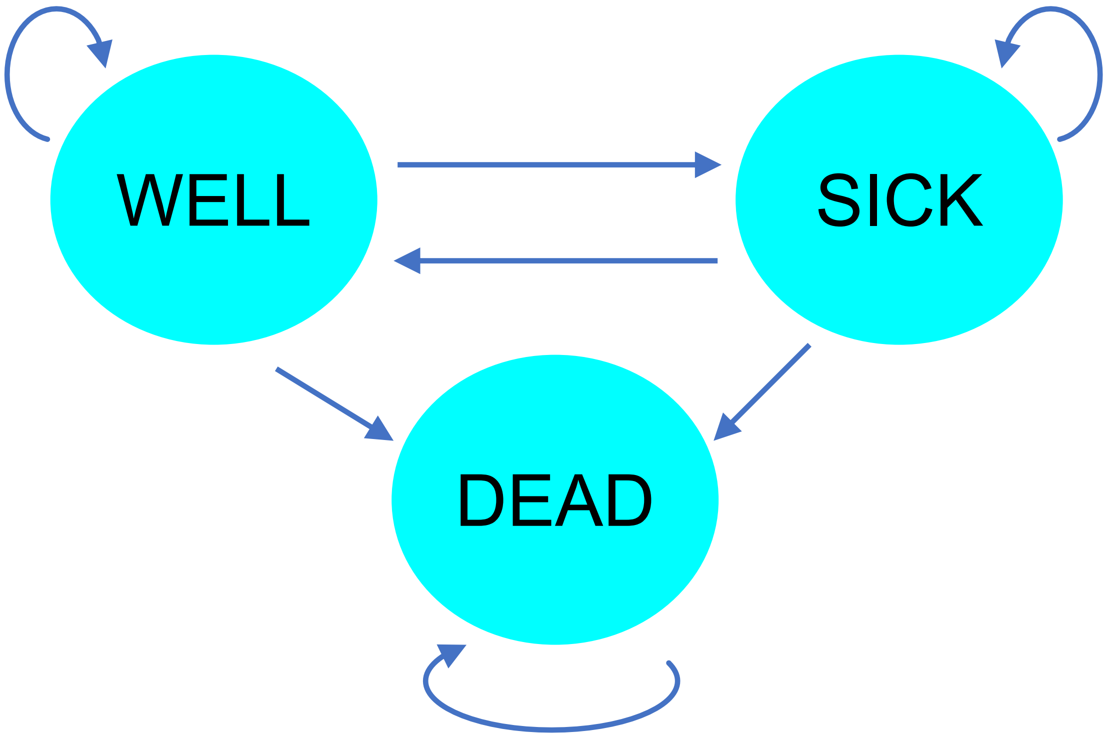
State Transition Diagram



- Transitions should reflect all possible transitions in real life in theory
- Sometimes you can make simplifying assumptions when it should have little effect on the difference between policy outcomes

  'We assumed that patients could only progress by one cancer stage per cycle (i.e. stage 1 cancer to stage 2). While it is possible to progress multiple stages in one month, it is very rare.'

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Cycle Length

- **Cycle:** A brief time interval during which patients within a cohort may make a transition into another health state or remain in the current health state

- Markov model assumes transitions can happen just once per cycle, so cycle must be sufficiently small for that to be a reasonable assumption

- Entire life of patient; relatively rare events → *yearly*
- Shorter time frame; frequent events; rapidly changing rate over time → *monthly, weekly, daily*

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Rates and probabilities

- A **rate** is the number of events in a population per ‘person-time at risk’
- A **transition probability** is the probability of the event happening in a single Markov cycle

Example: 100 patients followed for 3 years, and 60 die, on average at year 1.274

- **Rate of death:**

60 deaths / (40 pts X 3 yrs + 60 pts X 1.274 yrs) = 0.3054 per patient-year

- **3-year death probability (transition probability with 3-year cycle):**

60 deaths / 100 patients = 0.60 (3-year death probability)

What if your model uses a 1 year cycle? Or a 1 month cycle?

Menti quiz

Let’s investigate

Probability dead after 3 years, 1-year cycle length with transition probability of 0.2

Year	Alive	Dead
0	1	0
1	0.8	0.2
2	0.64	0.36
3	0.512	**0.488**

Probability dead after 3 years, 3-year cycle length with transition probability of 0.6

Year	Alive	Dead
0	1	0
3	0.4	**0.6**

An annual probability of death of 0.20 leads to too few deaths!

Cannot simply divide or multiply the transition probability to convert a transition probability to a new cycle length

Rate to probability conversions

$$p(t) = 1 - e^{-rt} \qquad\qquad r = -\frac{1}{t} ln(1-p)$$

p(t) is probability of transitioning in cycle length t; r is the rate

- Can convert a rate to a transition probability with cycle ***t*** using an equation on the left
- To change the cycle length of a transition probability:
  - **First:** convert it to a rate
  - **Second:** convert that rate back into a probability with new cycle length

Menti activity

Example: 100 patients followed for 3 years, and 60 die

- **Rate of death:**

60 deaths / (40 pts X 3 yrs + 60 pts X 1.274 yrs) = 0.3054 per patient-year

- **3-year death probability (transition probability with 3-year cycle):**

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What if your model uses a 1 year cycle?

$$p(t) = 1 - e^{-rt} \qquad r = -\frac{1}{t} ln(1-p)$$

p(t) is probability of transitioning in cycle length t; r is the rate

Solution

- **First:** convert 3-year probability to a rate

$$r = -\frac{1}{t} ln(1-p) = -\frac{1}{3} ln(1-0.60) = 0.3054 \text{ events per person-year}$$

- **Second:** convert that rate back into a probability with new cycle length

$$p(1) = 1 - e^{-rt} = 1 - e^{(-0.3054*1)} = 0.2632$$

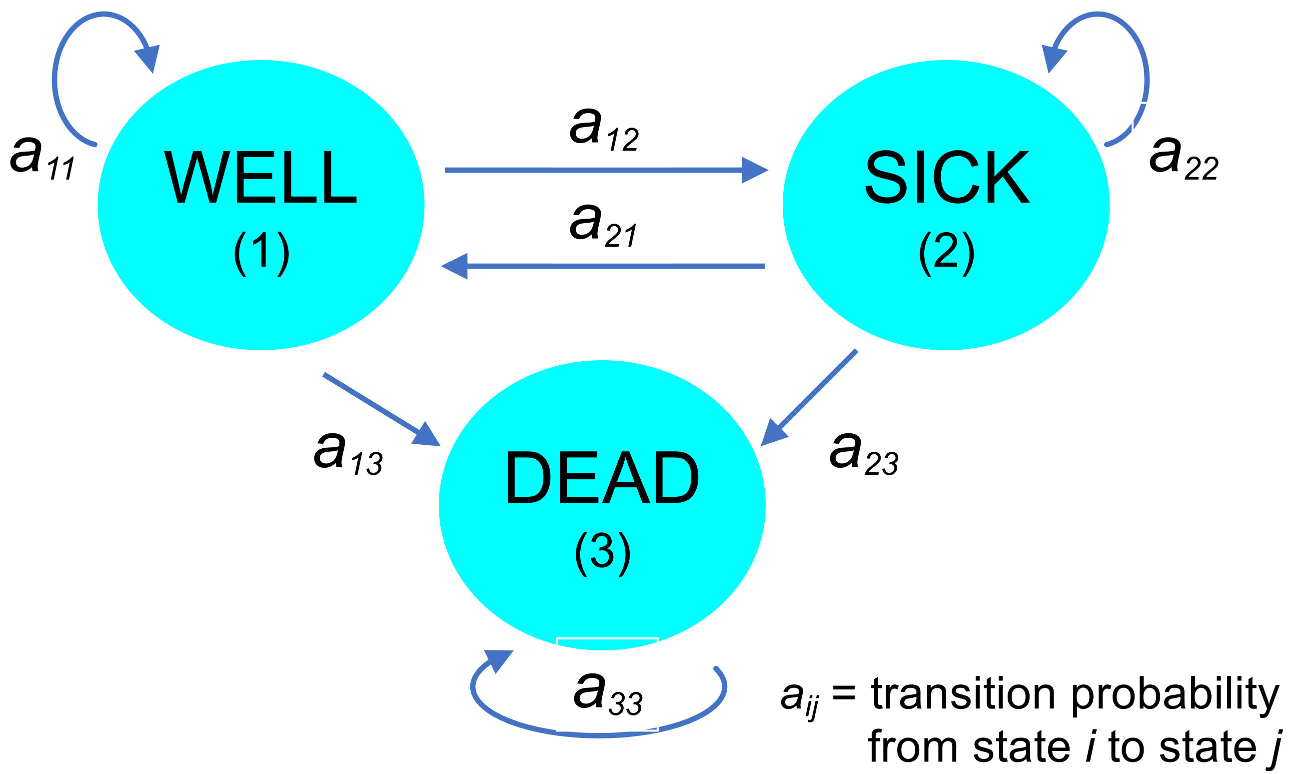
Probability dead after 3 years, 1-year cycle length with transition probability of **0.2632**

Year	Alive	Dead
0	1	0
1	0.737	0.263
2	0.543	0.457
3	0.4	**0.6**

Probability dead after 3 years, 3-year cycle length with transition probability of 0.6

Year	Alive	Dead
0	1	0
3	0.4	**0.6**

State Transition Diagram



Building a Markov Model

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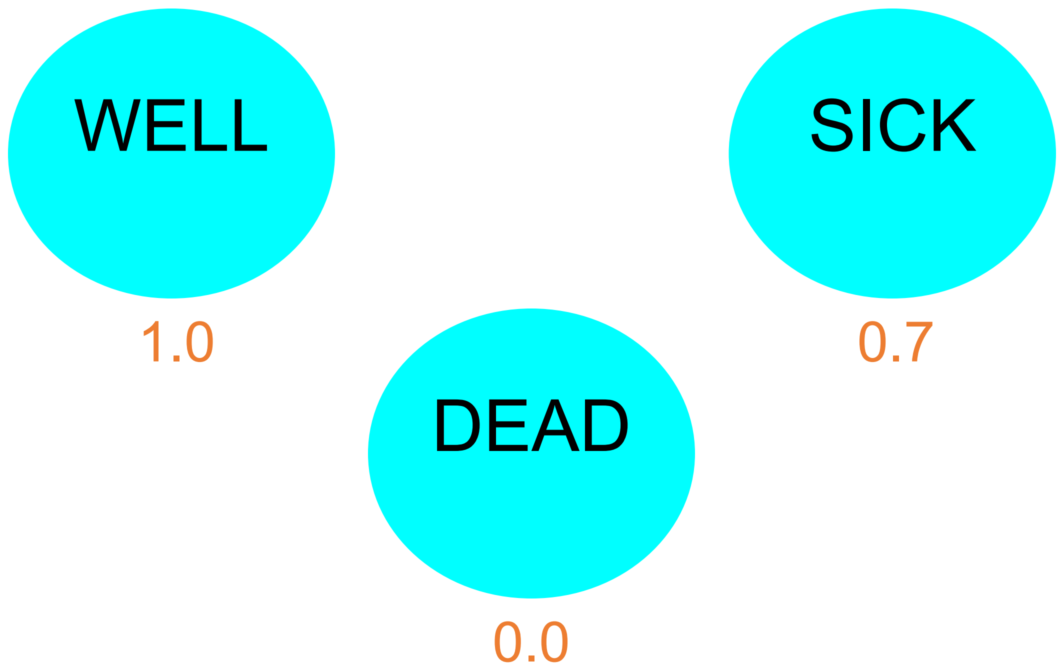
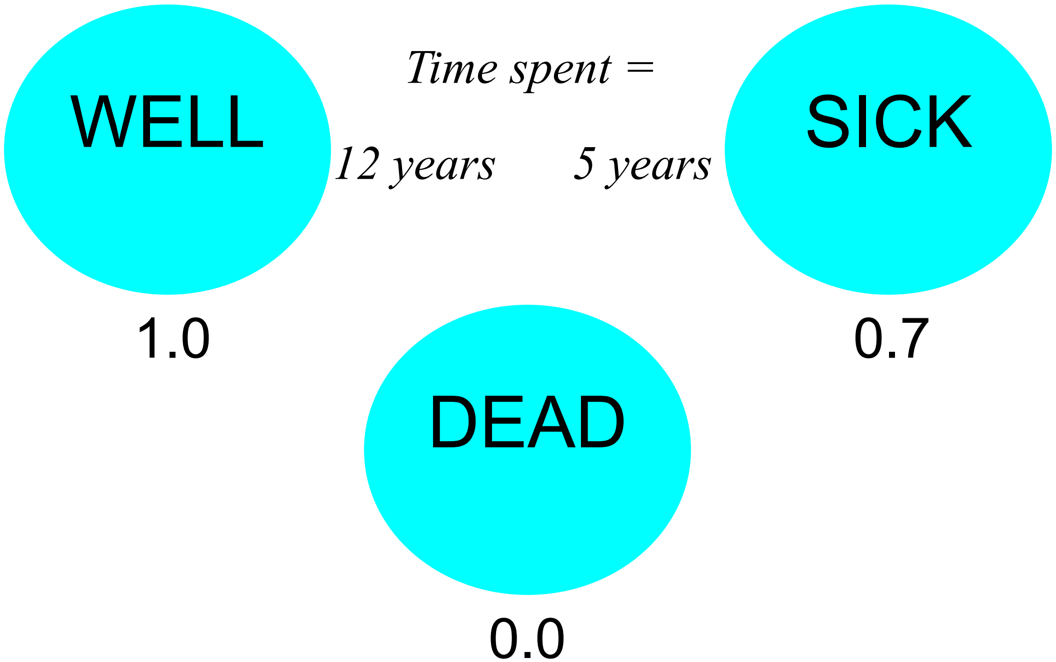
Quality of Life Adjustments



Total Utility Accrued = Σ (time spent in state x utility)

Quality of Life Adjustments



Quality Adjusted LE = (12*1.0)+(5*0.7) = 15.5 QALYs

Building a Markov Model

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Fundamental Matrix Solution

- Requires constant transition probabilities
- Does not require simulation
- Uses matrix algebra

Matrix Algebra Solution

Transition matrix:

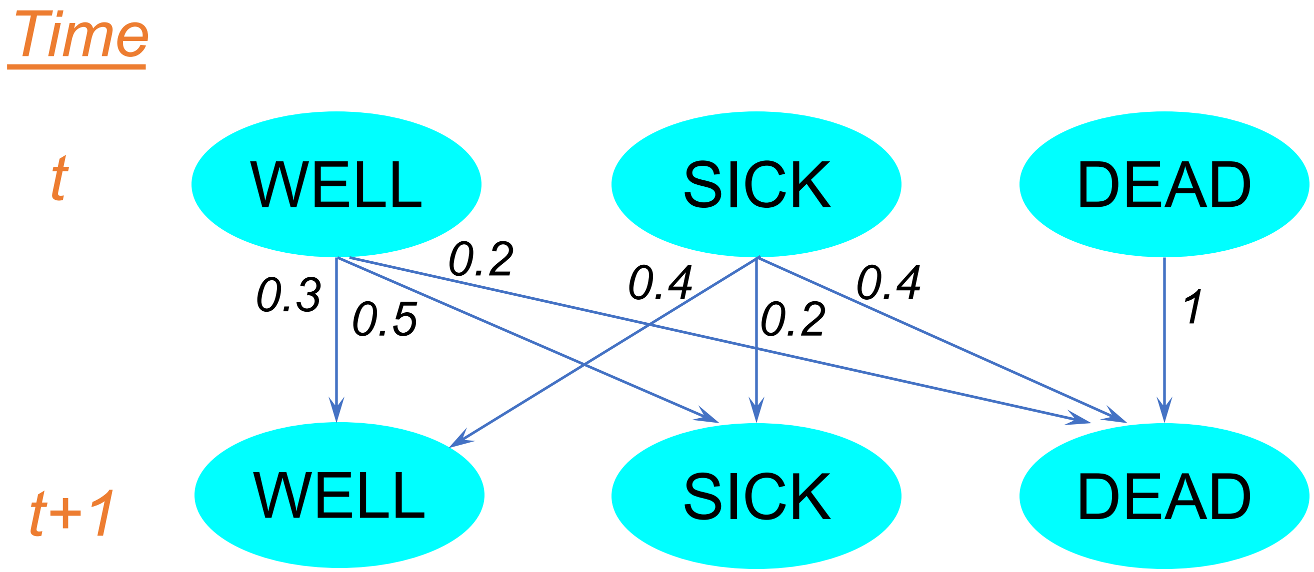
A =

	Well	Sick	Dead
Well	0.30	0.50	0.20
Sick	0.40	0.20	0.40
Dead	0	0	1

Initial state vector: $p^0 = [1\ 0\ 0]$

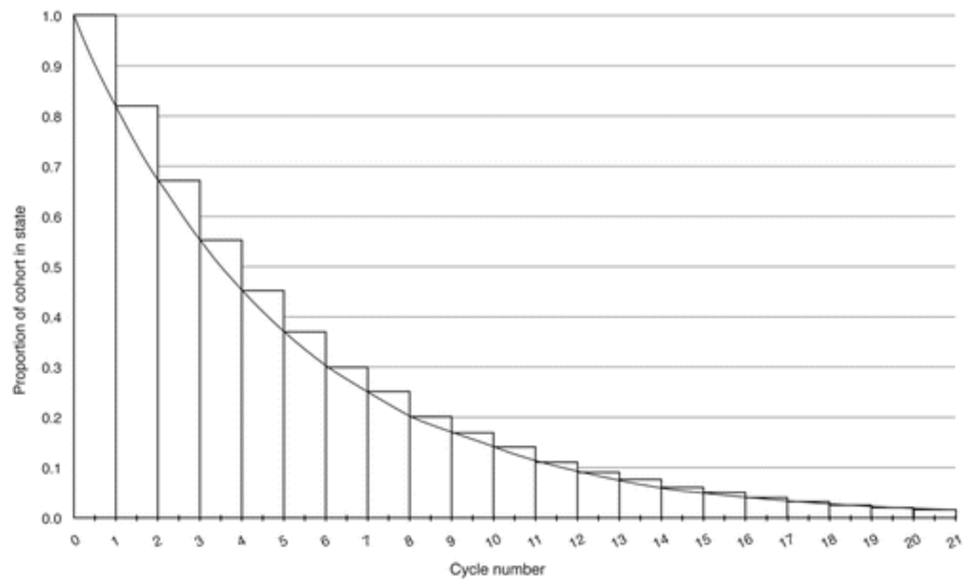
Calculation: $p^1 = p^0 \cdot A$

Three-State Markov Model



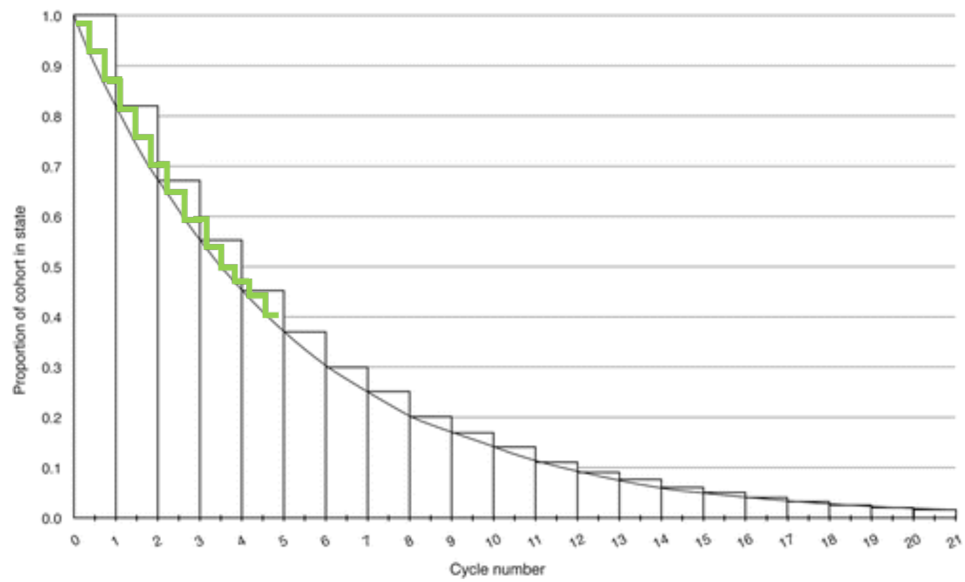
Fixed transition times

- Markov models assume transitions happen only at **end** of cycles
- In real life, events can happen at any time during the cycle
- This leads to **estimation error**

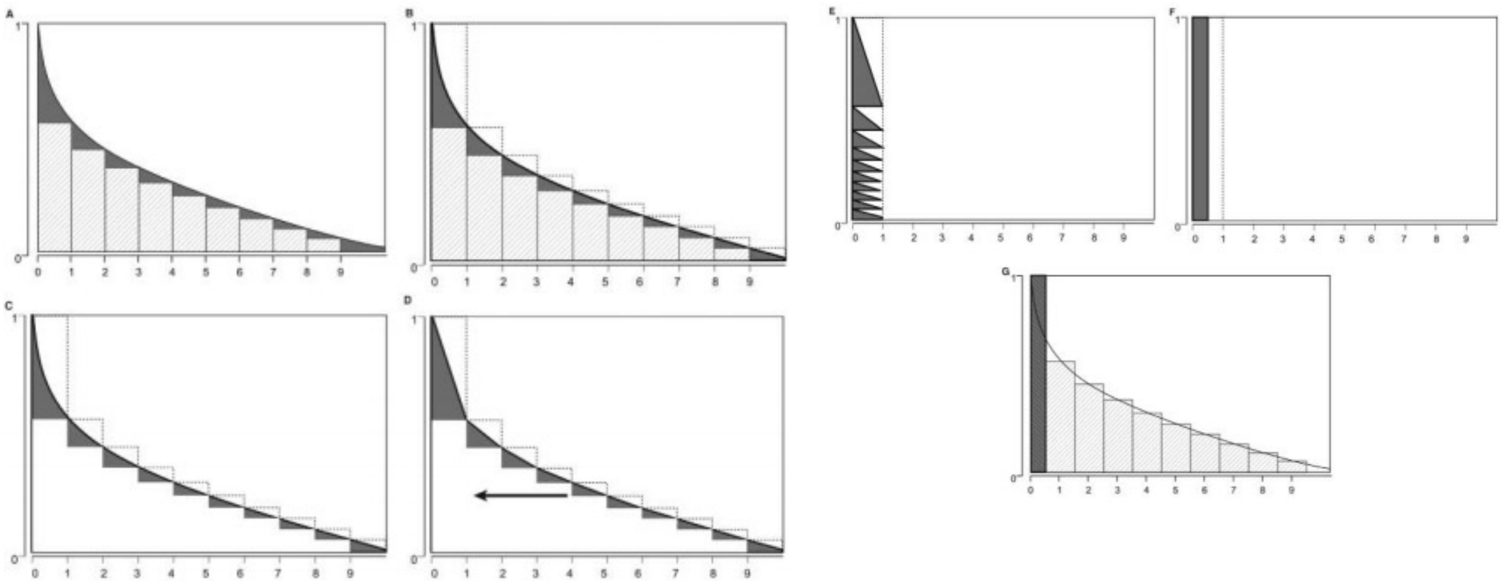


Solution #1: Shorter cycle lengths

- Shrinking the cycle length will improve estimation of the smooth function, reducing your estimation error



Solution #2 add half-cycle



- A common approach is to subtract a half-cycle's worth of utility or cost at the beginning
- However, this is imprecise due to time discounting

From Naimark, Krahn 2008 10.1177/0272989X08315241

Solution #3: Cycle tree method

- For individuals who transitions, assign half of their utility/cost per the **from** state and half of their utility/cost per the **to** state
- Example: Healthy to sick, 5% probability of death per cycle

Without cycle tree correction

Period	Healthy	Dead	Utility
0	10000	0	
1	9500	500	9500.0
2	9025	975	9025.0
3	8573.75	1426.25	8573.8
4	8145.063	1854.938	8145.1
		Tot	**35,244**

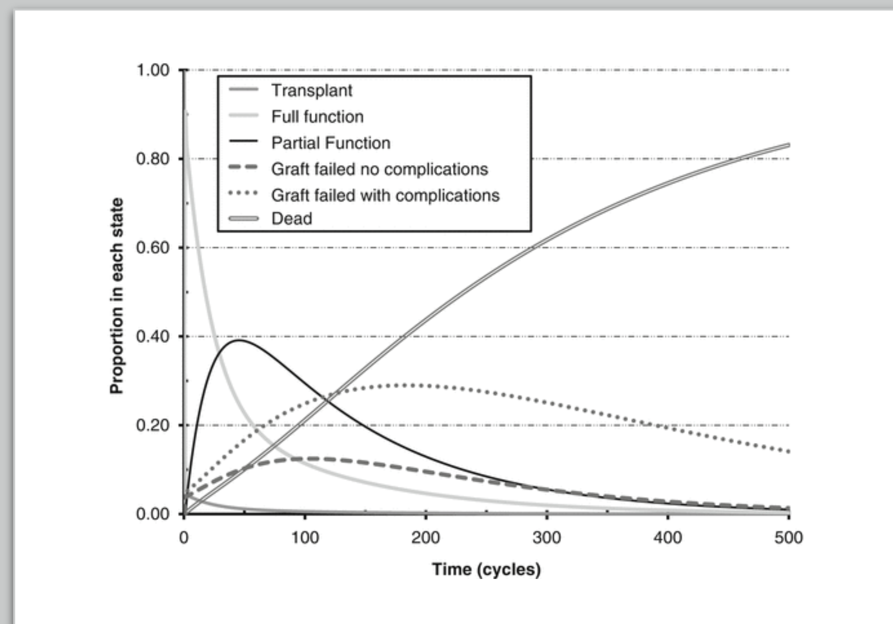
With cycle tree correction

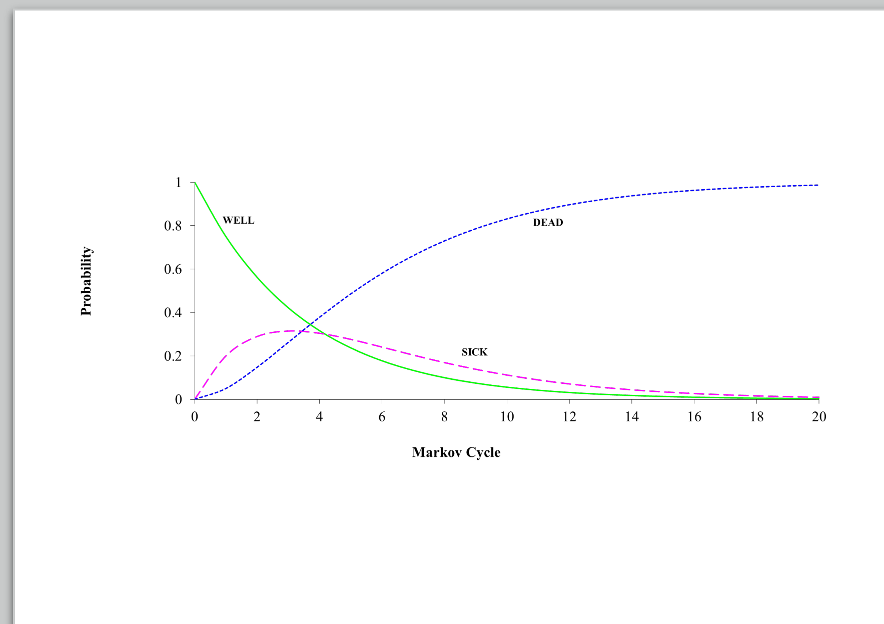
Period	Healthy	Dead	# stayed healthy	# transitioned healthy to dead	# stayed dead	Utility
0	10,000	-	-	-	-	
1	9,500	500	9,500	500	-	9,750
2	9,025	975	9,025	475	500	9,263
3	8,574	1,426	8,574	451	975	8,799
4	8,145	1,855	8,145	429	1,426	8,359
					Tot	**36,171**

From Naimark, Kabboul, Krahn 2013 10.1177/0272989X13501558

Markov Trace

Cycle	Well	Sick	Dead	Cycle Reward	Total Reward
0	1	0	0	0.5	0.5
1	0.30	0.50	0.20	0.80	1.30
2	0.29	0.25	0.46	0.54	1.84
3	0.19	0.20	0.62	0.38	2.22
↓					
N	0	0	1	0	3.1





Markov trace diagrams

Decision Trees + Markov Models

- Markov models can be “grafted” onto the ends of the branches of decision trees
- The averaged out value at a Markov node is the desired summary value of the Markov process (e.g., QALE)

Example:

Typical Diagnostic Test Strategy

Test

- Test +
  pPos
  - Disease
    PPV
    → True Positive…
  - No Disease
    #
    → False Positive…
- Test -
  #
  - Disease
    $\boxed{\#}$
    → False Negative…
  - No Disease
    NPV
    → True Negative…

Attach Markov cycle tree

Example: Decision tree with ‘grafted’ Markov models

Figure 1. Decision Tree Model of Index Procedure and Follow-Up at Six Months

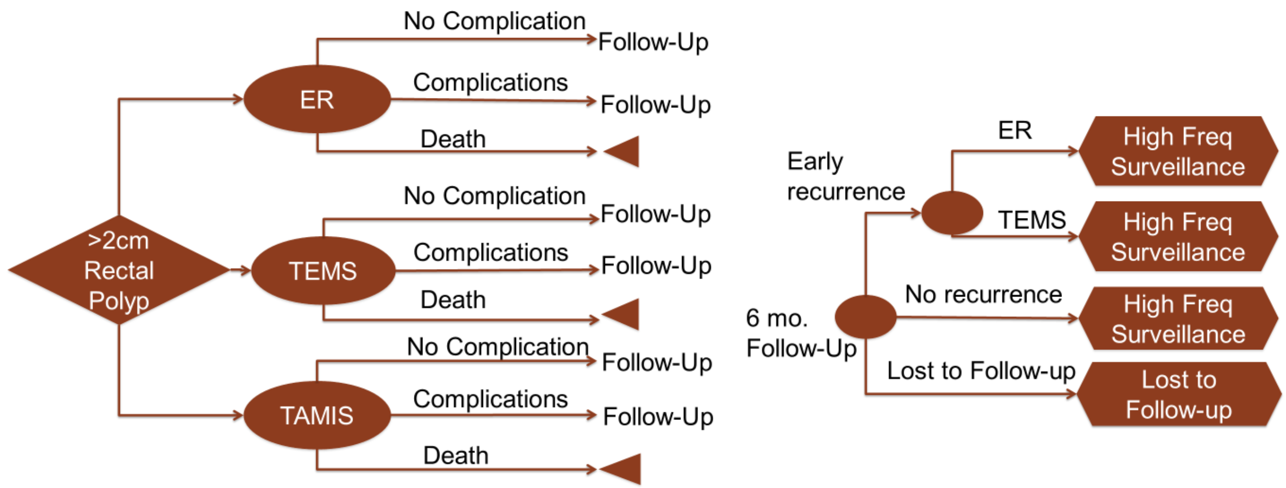
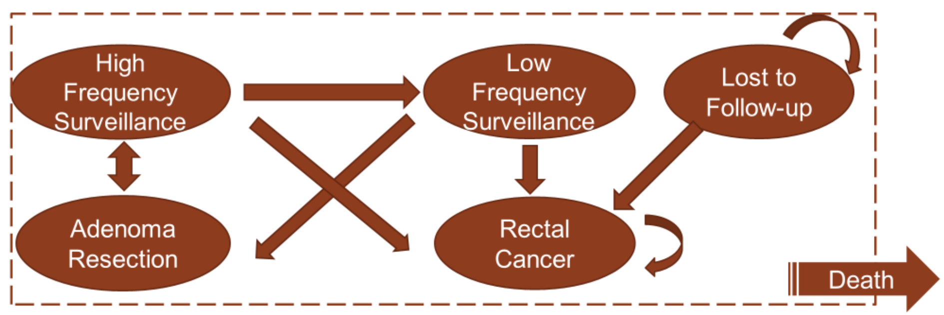


Figure 2. Markov Model of Lifetime Costs and QALYs



Issues in Markov Modeling

- Population heterogeneity (e.g., risk factors)
  - Separate sub-population models
- Transition probabilities depend on prior history
  - Expand state descriptions to reflect prior states
  - Choose different model type like a microsimulation (more next week!)

Extension: Add additional states to "build memory" into Markov models (semi-Markov processes)

- It is possible to add some 'memory' to a Markov model by adding states that are path-dependent:
  - e.g., the state of being in the second year of cancer remission
- Such states may be called "tunnel states"
- The probability of recurrence would be modeled as different from the state of "second year of remission" than from the state of "first year of remission", for example

Example: Transition probabilities depend on whether recurrence was local or regional (and on time since recurrence)

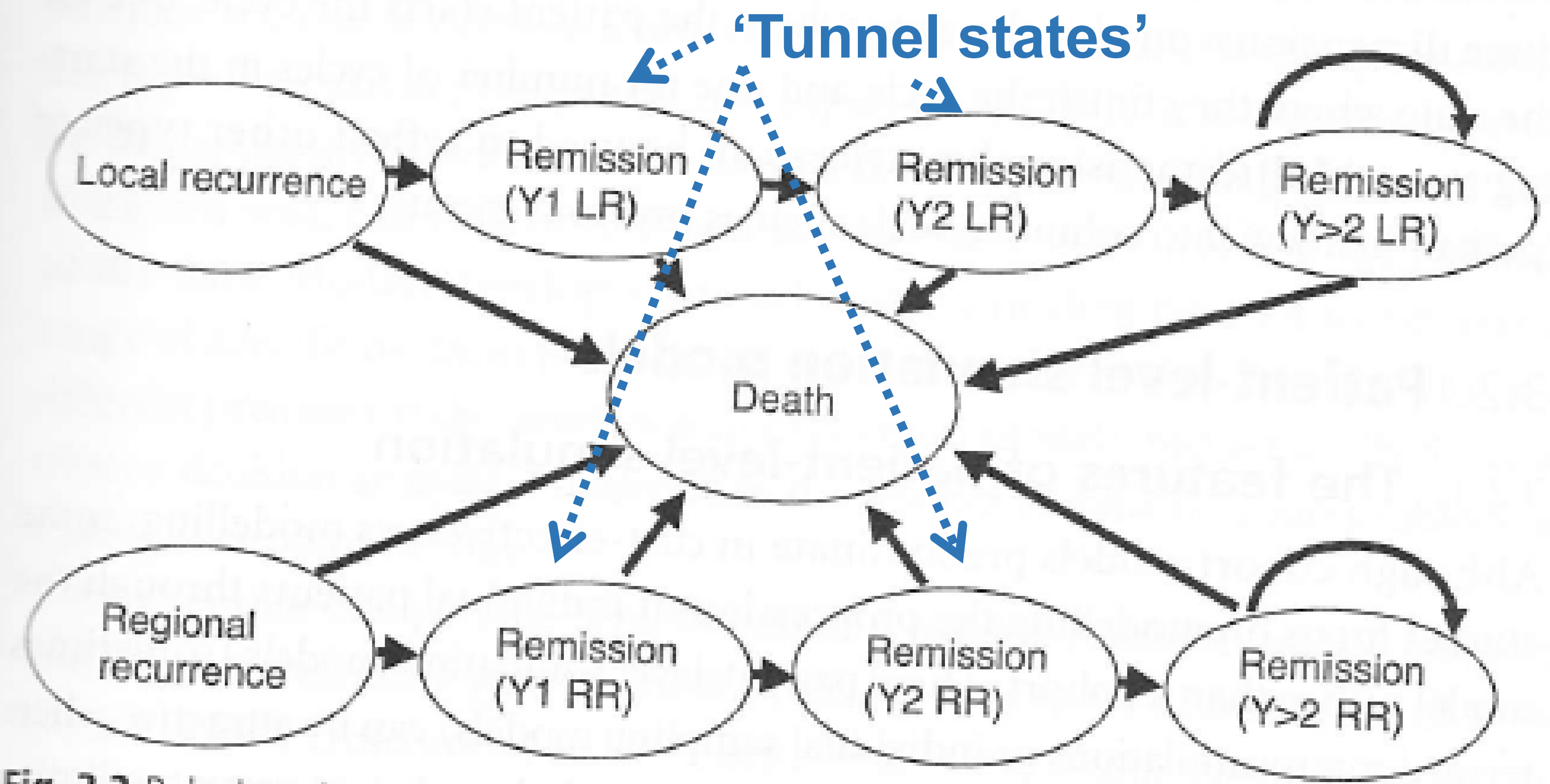


Fig. 3.3 Relaxing the Markov assumption by adding additional states to the model shown in Fig. 2.5.

Source: Briggs et al, Decision modelling for economic evaluation, 2006, page 57

Implementation

- Modeling extensive time-dependency may require many tunnel states
- Programming in a spreadsheet becomes very difficult
- Can use a language such as R – with 3-dimensional arrays:
  - One dimension for starting state
  - Another for ending state
  - Another for number of cycles in the starting state
- Tree Age is another common software that could be used

Strengths and limitations of Markov models

- Can provide a reasonable approximation to many health-related processes
- Are tractable, not-too-difficult to use
- But: Memory-less state transition probabilities that can only be partly overcome
- And, in some cases may be excessively unrealistic
- Discrete event simulation models offer an alternative – but greater flexibility means need more data to calibrate accurately