

Modeling in Medical Decision Analysis

Jeremy D. Goldhaber-Fiebert, PhD

Presented March 4, 2020

HEALTH
POLICY
STANFORD

CENTER FOR HEALTH POLICY/
CENTER FOR PRIMARY CARE AND OUTCOMES RESEARCH

Agenda

- Decision analysis
- Cost-effectiveness analysis
- Decision trees
- Sensitivity analysis
- Markov models
- Microsimulation

POLL SLIDE

- **Have you had a course in (*select all that apply*):**
 1. Medicine
 2. Epidemiology
 3. Probability and/or Statistics
 4. Computer Programming
 5. Decision Science/Economic Evaluation

WHAT IS A DECISION ANALYSIS?

What is a decision analysis?

- A quantitative method for considering decisions between multiple alternatives in situations of uncertainty

What is a decision analysis?

- A quantitative method for considering decisions between multiple alternatives in situations of uncertainty

Decisions between multiple alternatives:

- Allocate resources to one alternative (and not the others)
- There is no decision without alternatives => making a choice

What is a decision analysis?

- A quantitative method for considering decisions between multiple alternatives in situations of uncertainty

Quantitative method for considering decisions:

- Gather information
- Assess the consequences of each alternative
- Clarify the dynamics and trade-offs involved in selecting each
- Select an action to take that gives us the best expected outcome

We generally employ models to do this

The steps of a decision analysis

1. Enumerate all relevant alternatives
2. Identify important outcomes
3. Determine relevant uncertain factors
4. Encode probabilities for uncertain factors
5. Specify the value of each outcome
6. Combine these elements to analyze the decision

Decision trees and related models important for this

What is a decision analysis called when its important outcomes include costs?

1. Enumerate all relevant alternatives
2. Identify important outcomes
3. Determine relevant uncertain factors
4. Encode probabilities for uncertain factors
5. Specify the value of each outcome
6. Combine these elements to analyze the decision

Cost-effectiveness analysis (CEA): a type of decision analysis that includes costs as one of its outcomes

**WHAT IS A COST-EFFECTIVENESS
ANALYSIS?**

What is a cost-effectiveness analysis?

- In the context of health and medicine, a cost-effectiveness analysis (CEA) is a method for evaluating tradeoffs between health benefits and costs resulting from alternative courses of action
- **CEAs support decision makers; they are not a complete resource allocation procedure**

Cost-Effectiveness Ratio (CER):

How to compare two strategies in CEA

- **Numerator:** Difference between costs of the intervention (strategy) and costs of the

Incremental resources required by the intervention

Incremental health effects gained with the intervention

$$CER = \frac{C_i - C_{alt}}{E_i - E_{alt}}$$

Models for decision analysis and CEAs

- **Decision model:** a *schematic* representation of all of the clinically and policy relevant features of the decision problem
 - Includes the following in its structure:
 - Decision alternatives
 - Clinical and policy-relevant outcomes
 - Sequences of events
 - Enables us to integrate knowledge about the decision problem from many sources (i.e., probabilities, values)
 - Computes expected outcomes (i.e., averaging across uncertainties) for each decision alternative

Building decision-analytic model

1. Define the model's structure
2. Assign probabilities to all chance events in the structure
3. Assign values (i.e., utilities) to all outcomes encoded in the structure
4. Evaluate the expected utility of each decision alternative
5. Perform sensitivity analyses

Simple enough to be understood; complex enough to capture problem's elements convincingly (assumptions)

**“All models are wrong;
but some models are
useful”**

-- George Box and Norman Draper, 1987

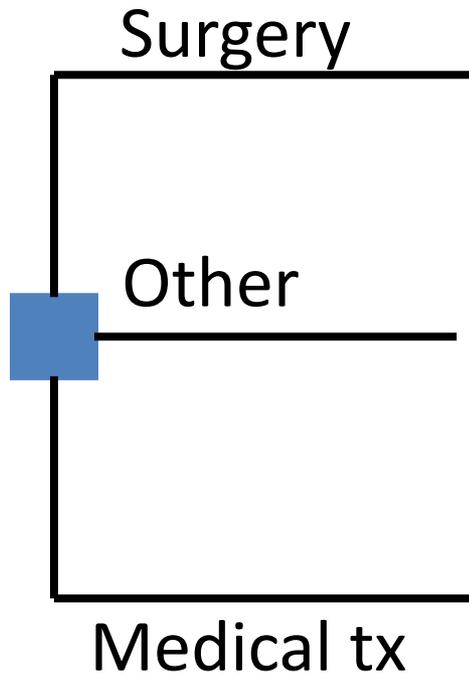
Building decision-analytic models

1. Define the model's structure
2. Assign probabilities to all chance events in the structure
3. Assign values (i.e., utilities) to all outcomes encoded in the structure
4. Evaluate the expected utility of each decision alternative
5. Perform sensitivity analyses

**WHAT ARE THE ELEMENTS OF A
DECISION TREE'S STRUCTURE?**

Decision node

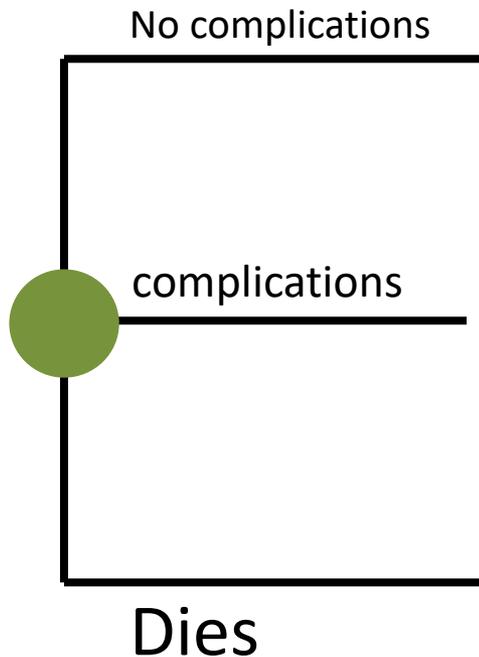
A place in the decision tree at which there is a choice between several alternatives



The example shows a choice between 2 alternatives, but a decision node can accommodate a choice between more alternatives ... provided alternatives are mutually exclusive.

Chance node

A place in the decision tree at which chance determines the outcome based on probability



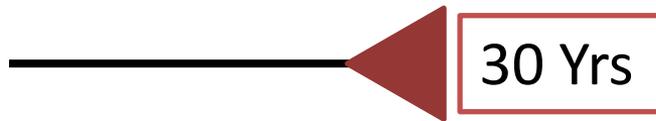
The example shows only 2 outcomes, but a chance node can accommodate more outcomes ... provided they are mutually exclusive AND collectively exhaustive.

What do mutually exclusive and collectively exhaustive mean?

- Mutually exclusive
 - Only one alternative can be chosen
 - Only one event can occur
- Collectively exhaustive
 - At least one event must occur
 - One of the possibilities must happen
 - Taken together, the possibilities make up the entire range of outcomes

Terminal node

Final outcome associated with each pathway of choices and chances



Final outcomes must be valued in relevant terms (cases of disease, Life years, Quality-adjusted life years, costs) so that they can be used for comparisons

Summary

- **Decision nodes:** enumerate a choice between alternatives for the decision maker
- **Chance nodes:** enumerate possible events determined by chance/probability
- **Terminal nodes:** describe outcomes associated with a given pathway (of choices and chances)

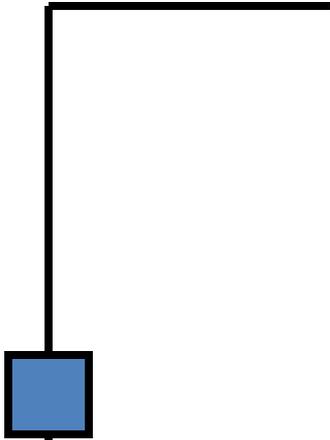
The entire structure of the decision tree can be described with only these elements

Example: decision tree

- Patient presents with symptoms
- Likely serious disease; unknown w/o treatment
- Two treatment alternative:
 - Surgery, which is potentially risky
 - Medical management, which has a low success rate
- With surgery, one must assess the extent of disease and decide between curative and palliative surgery
- ***Goal: maximize life expectancy for the patient***

The initial decision is between surgery and medical management

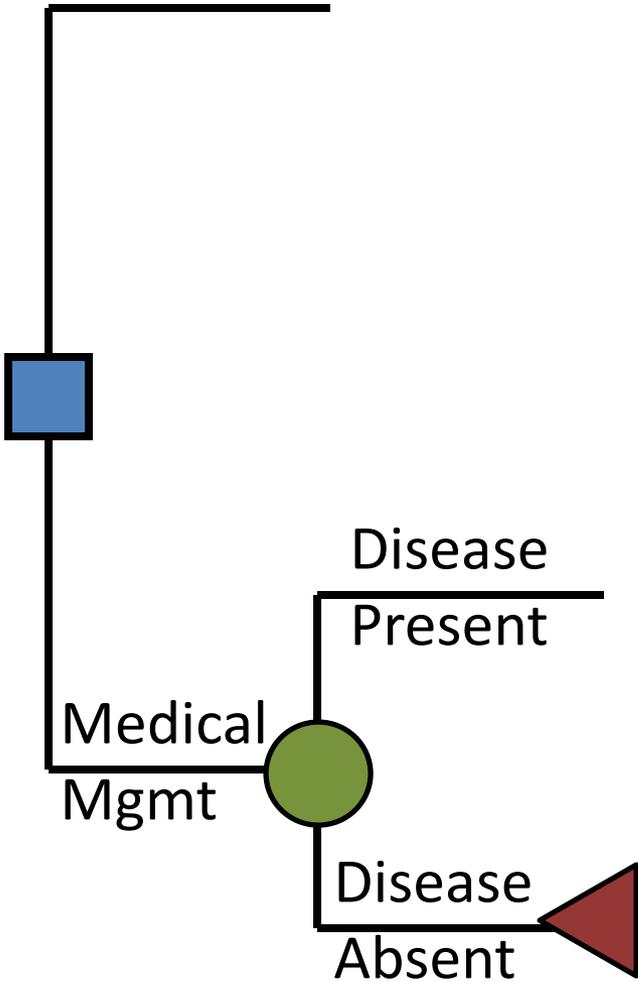
Surgery



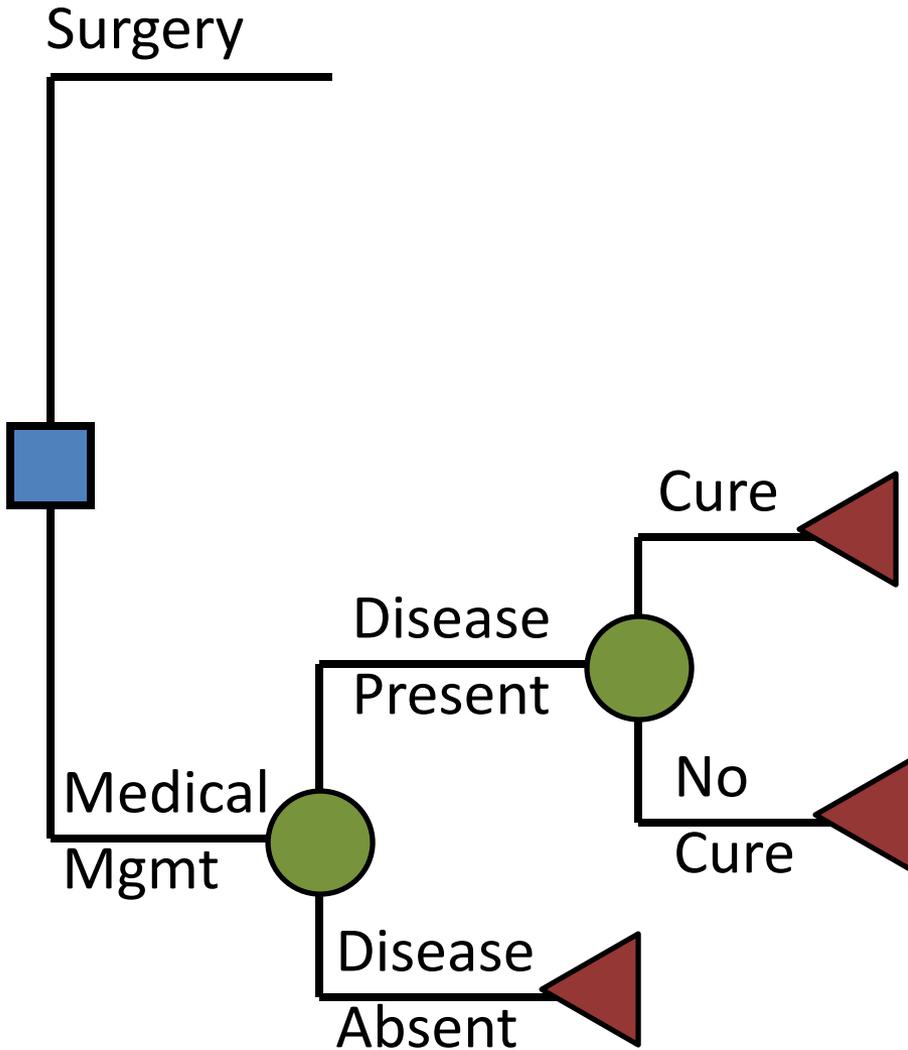
Medical
Mgmt

Treatment is initiated on patients w/ symptoms; some w/o disease

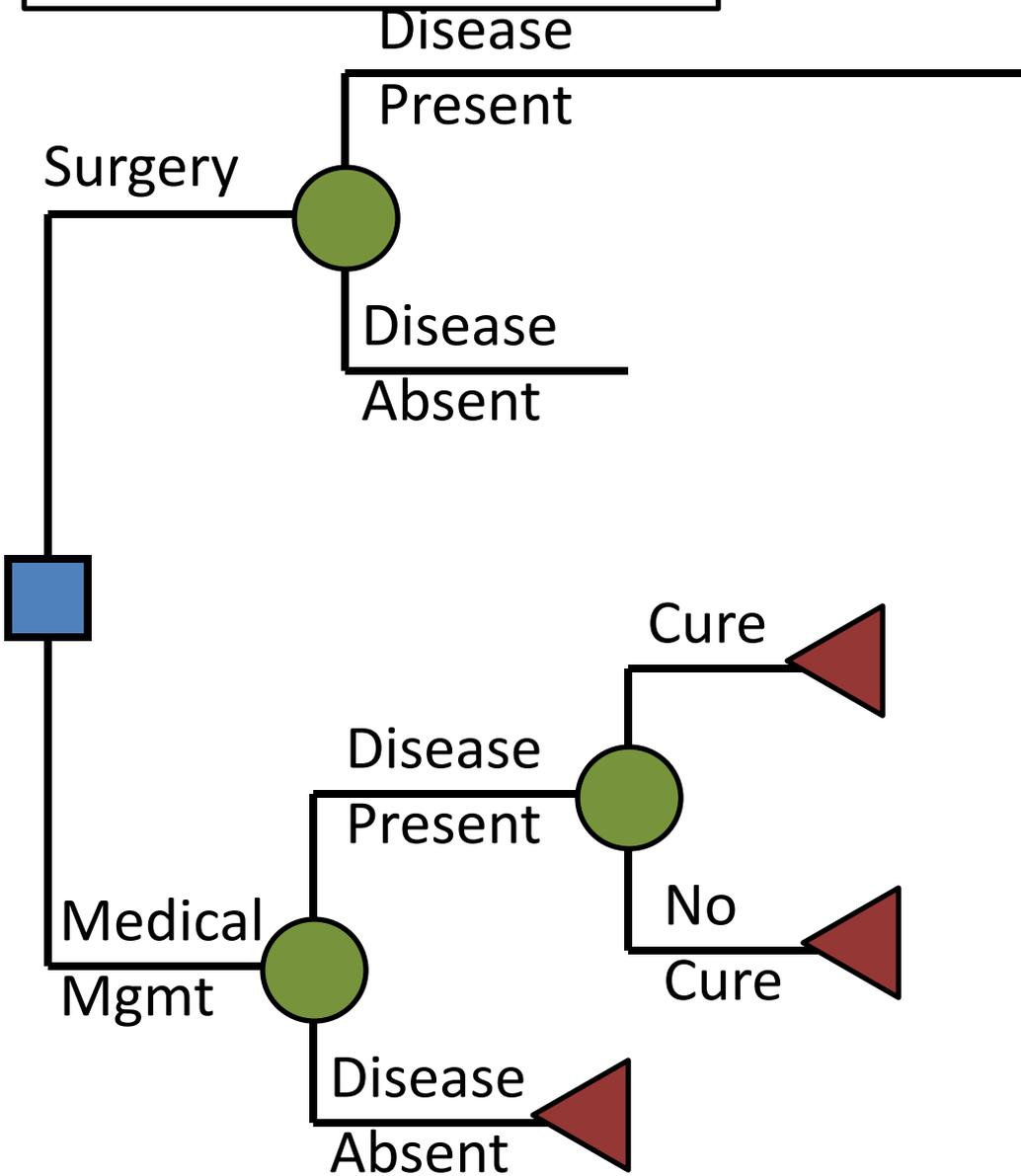
Surgery



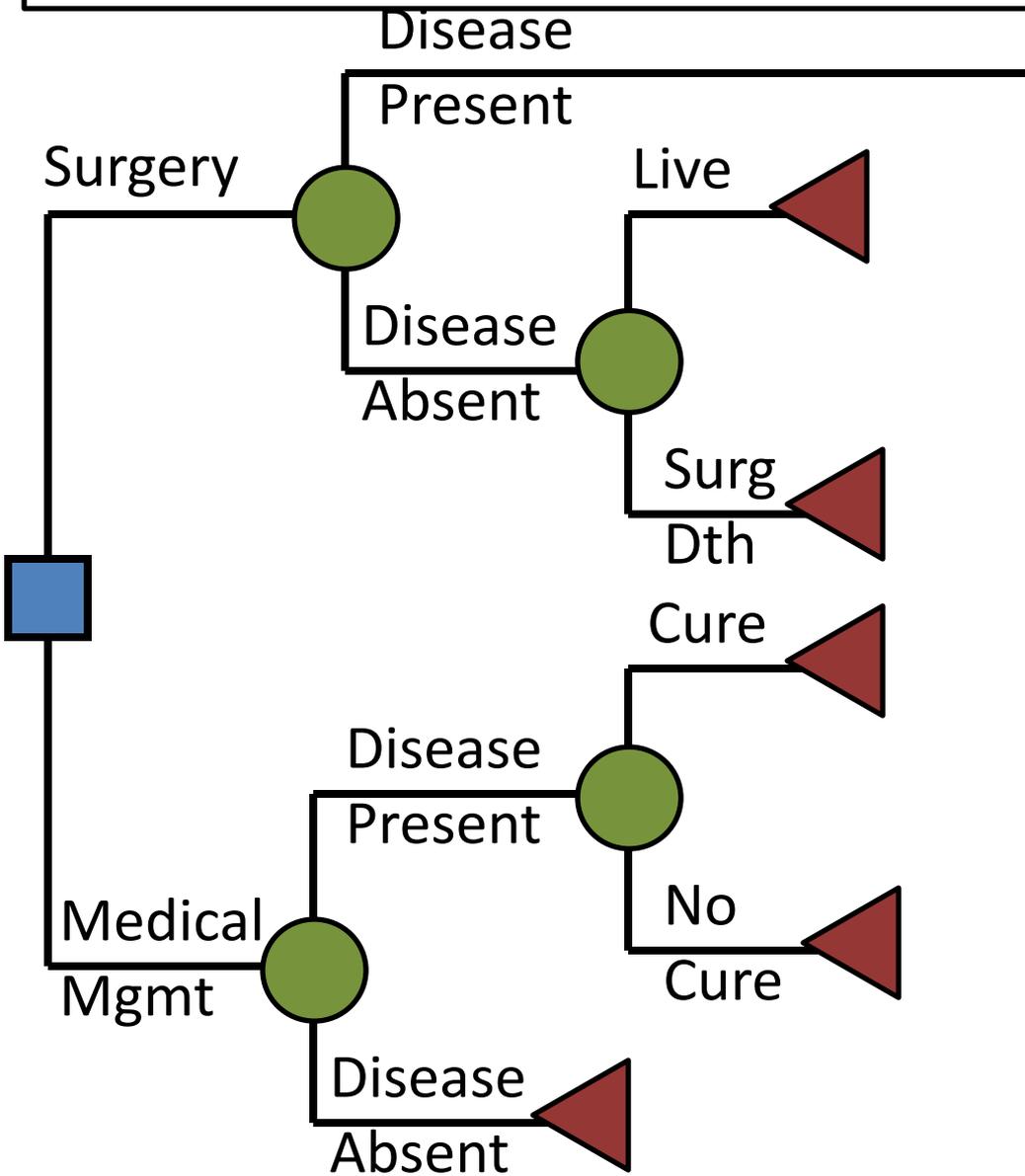
Those with disease have a chance to benefit from treatment



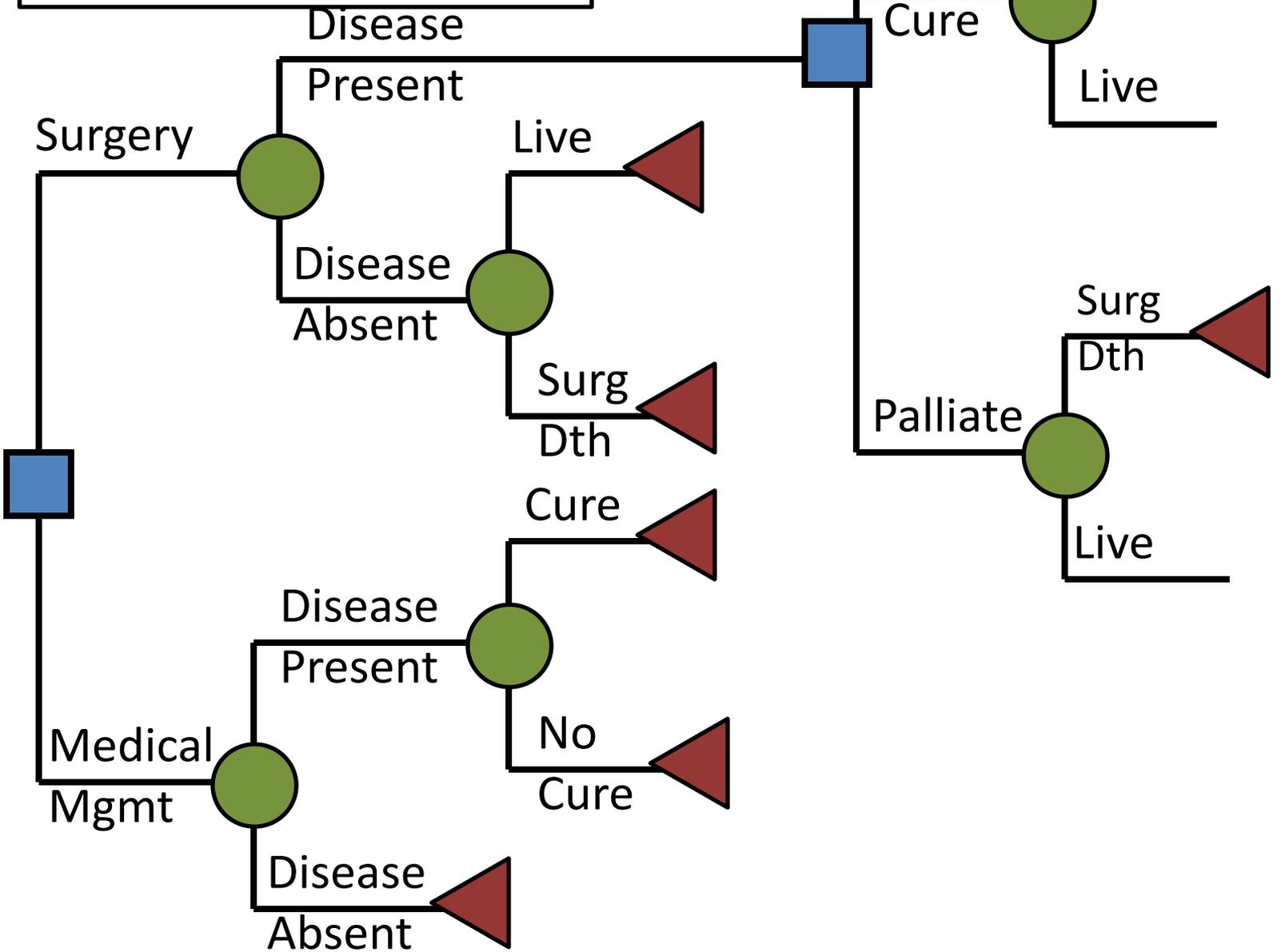
Likewise with surgery



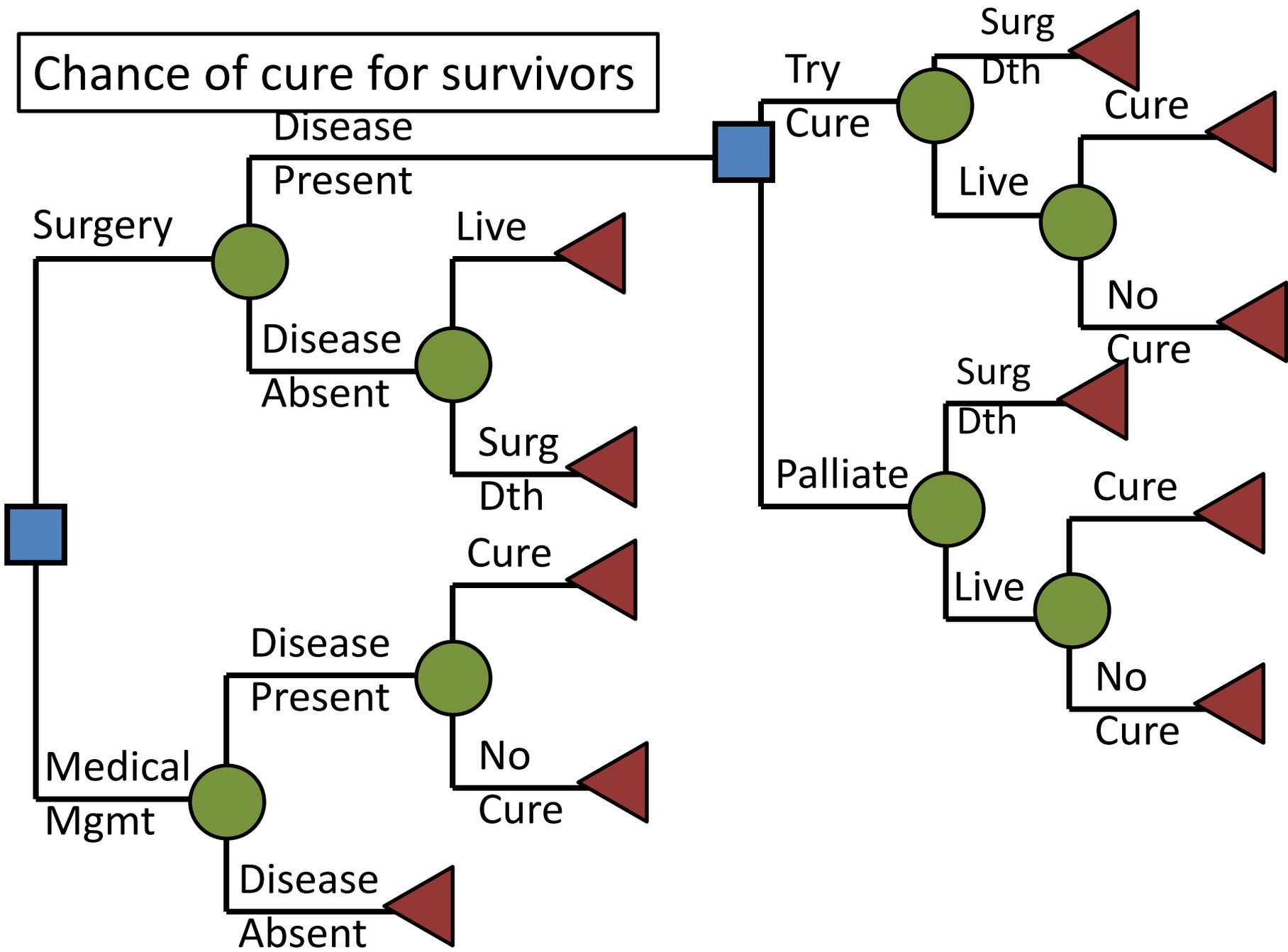
Surgery is risky even for those with no disease



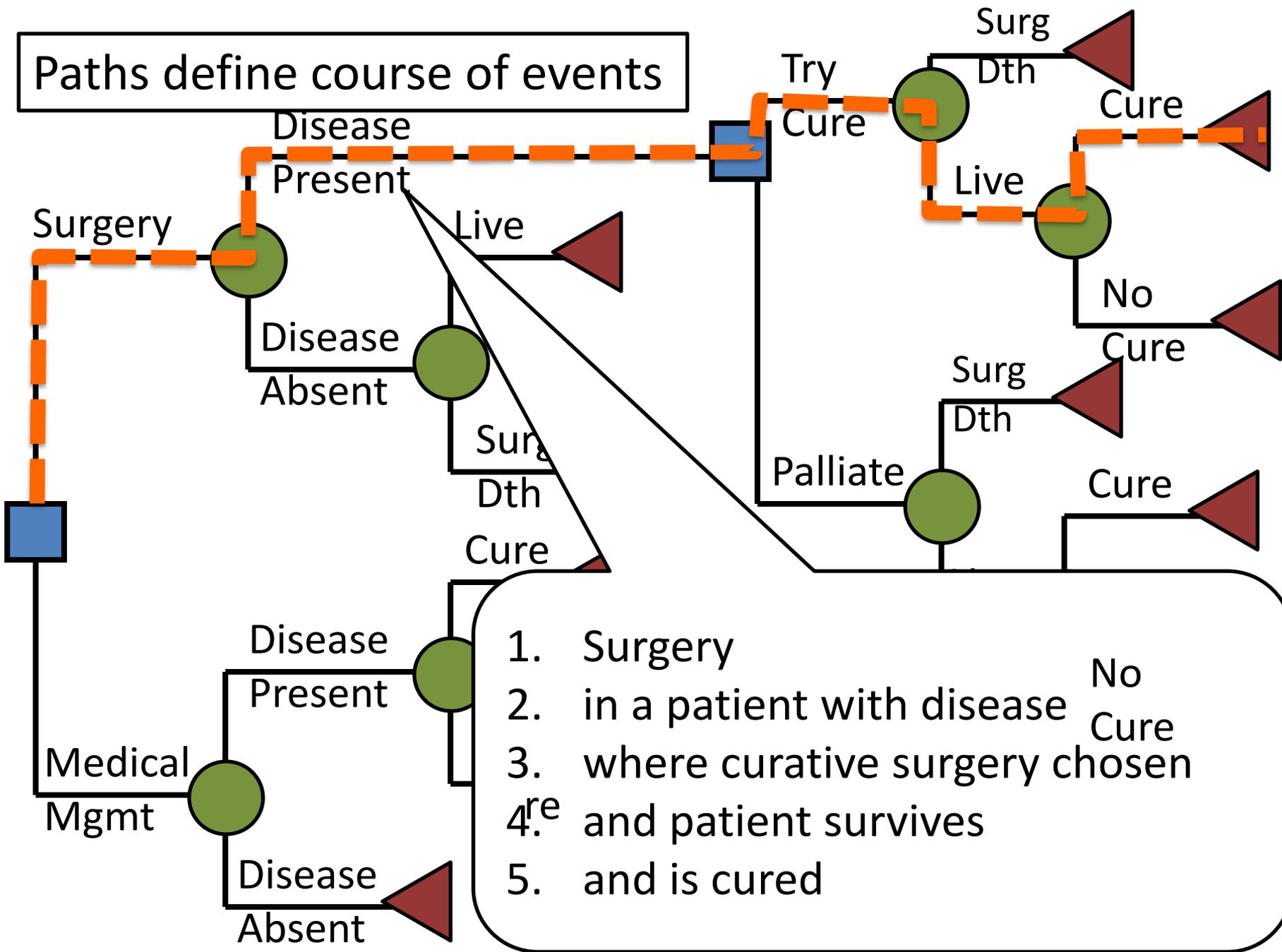
Surgical risks here too



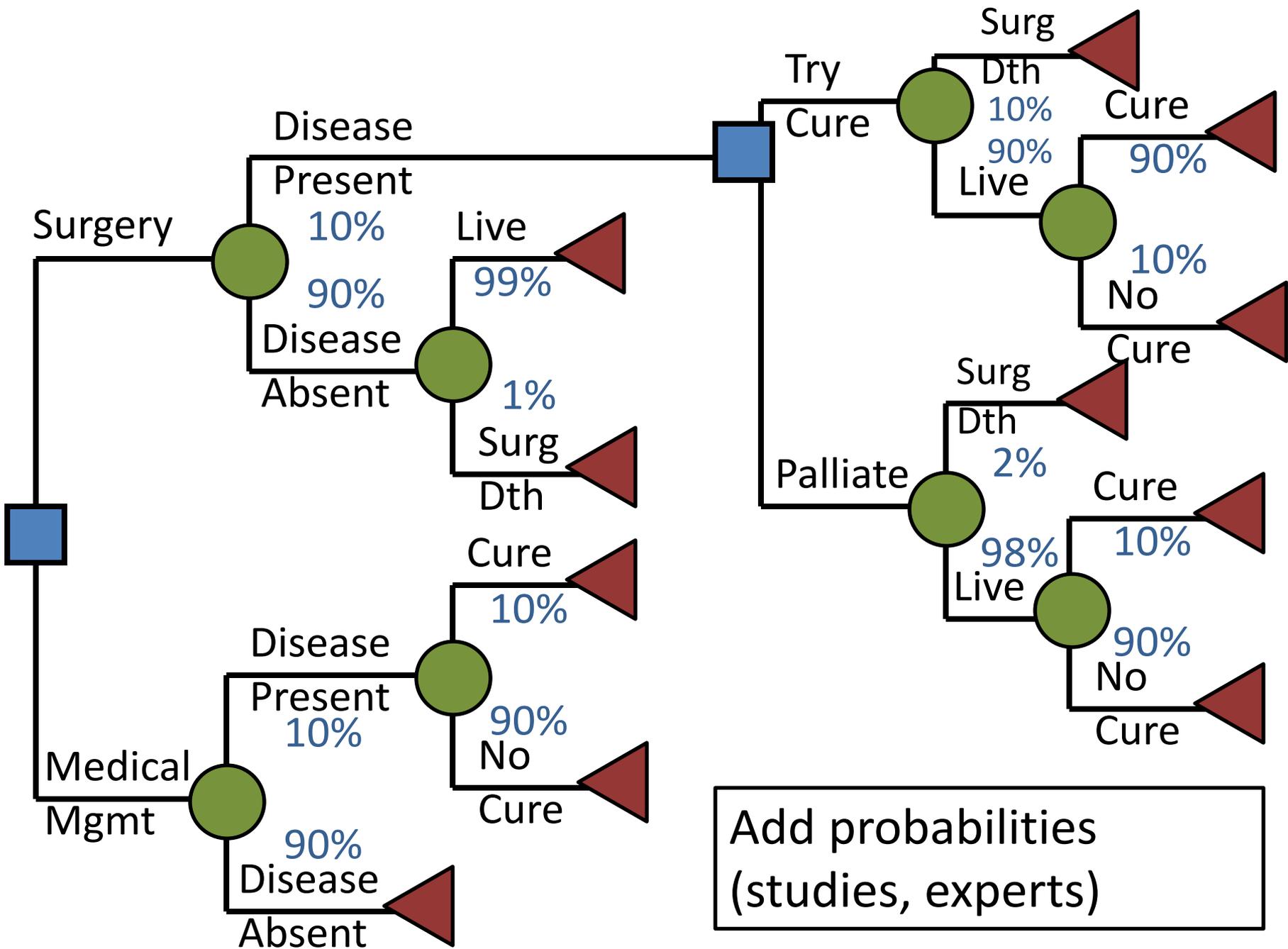
Chance of cure for survivors

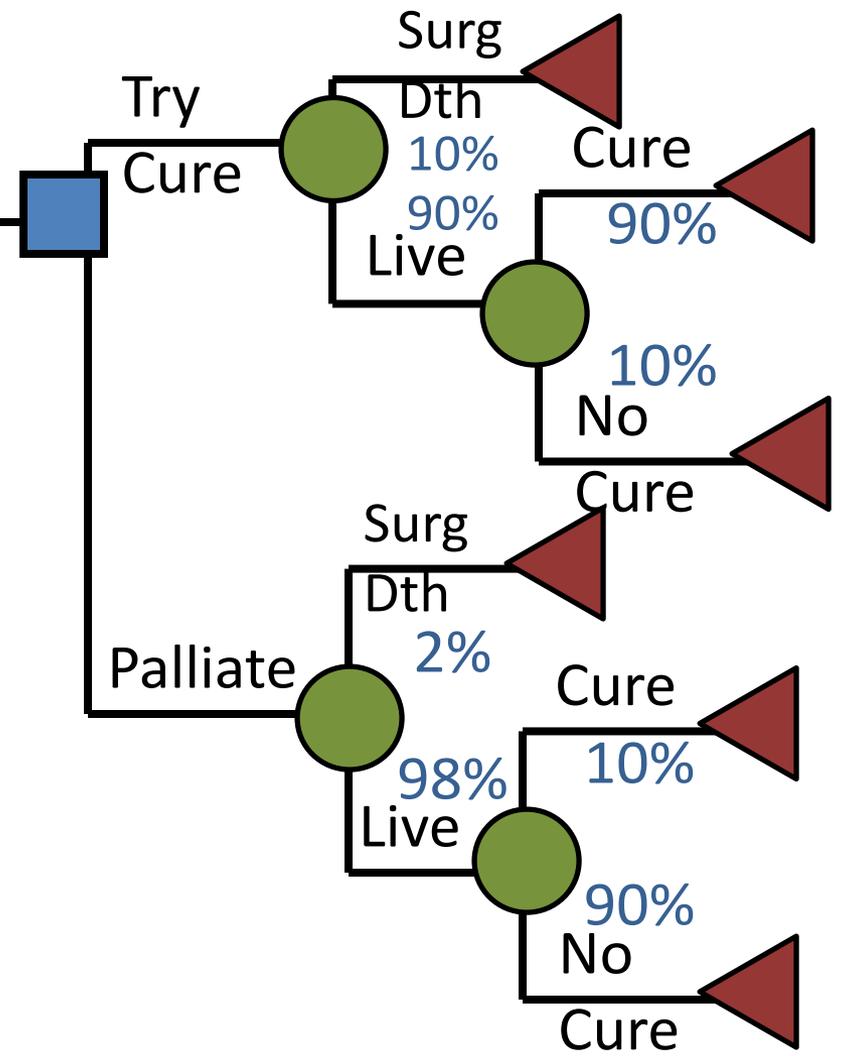
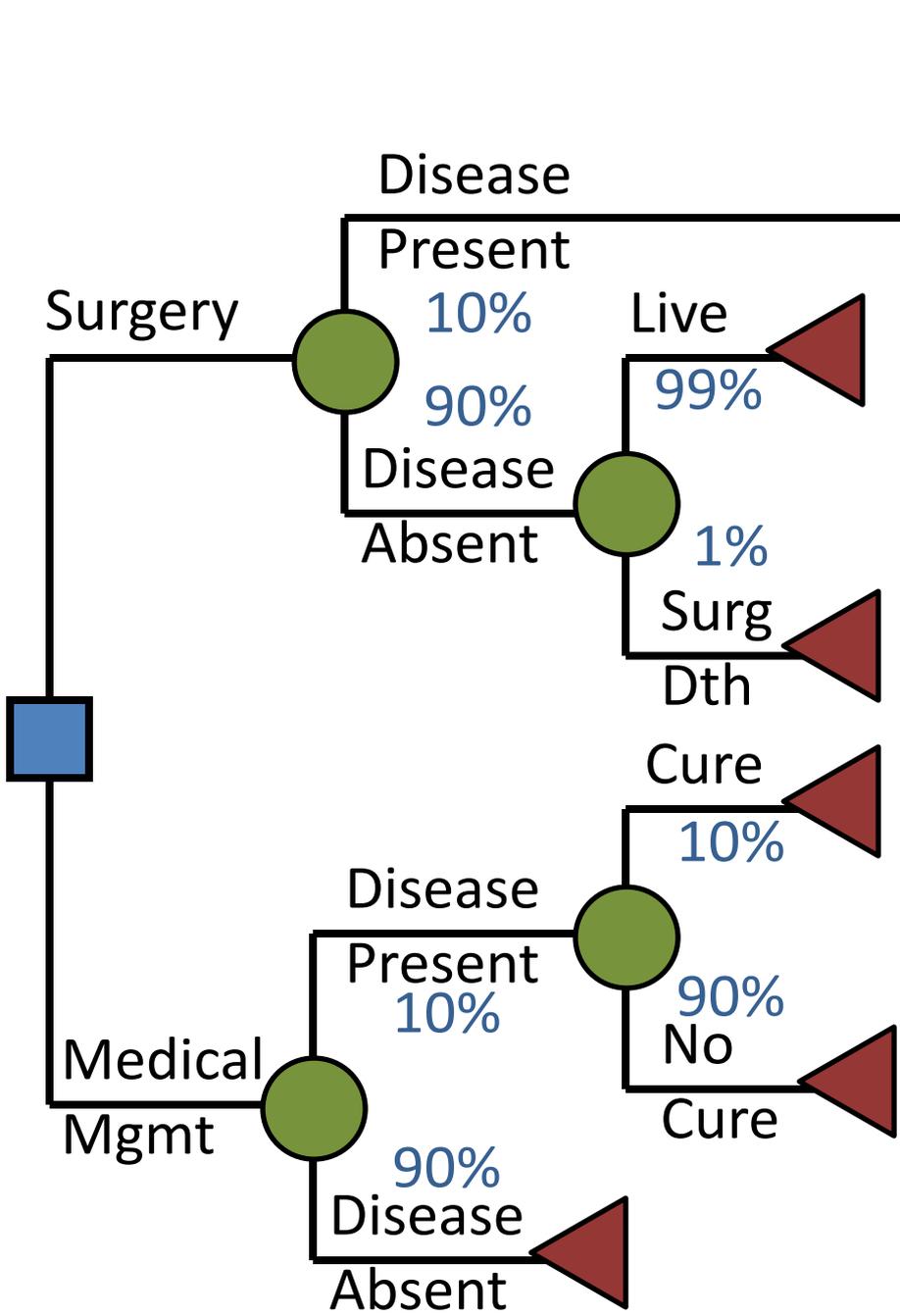


Paths define course of events

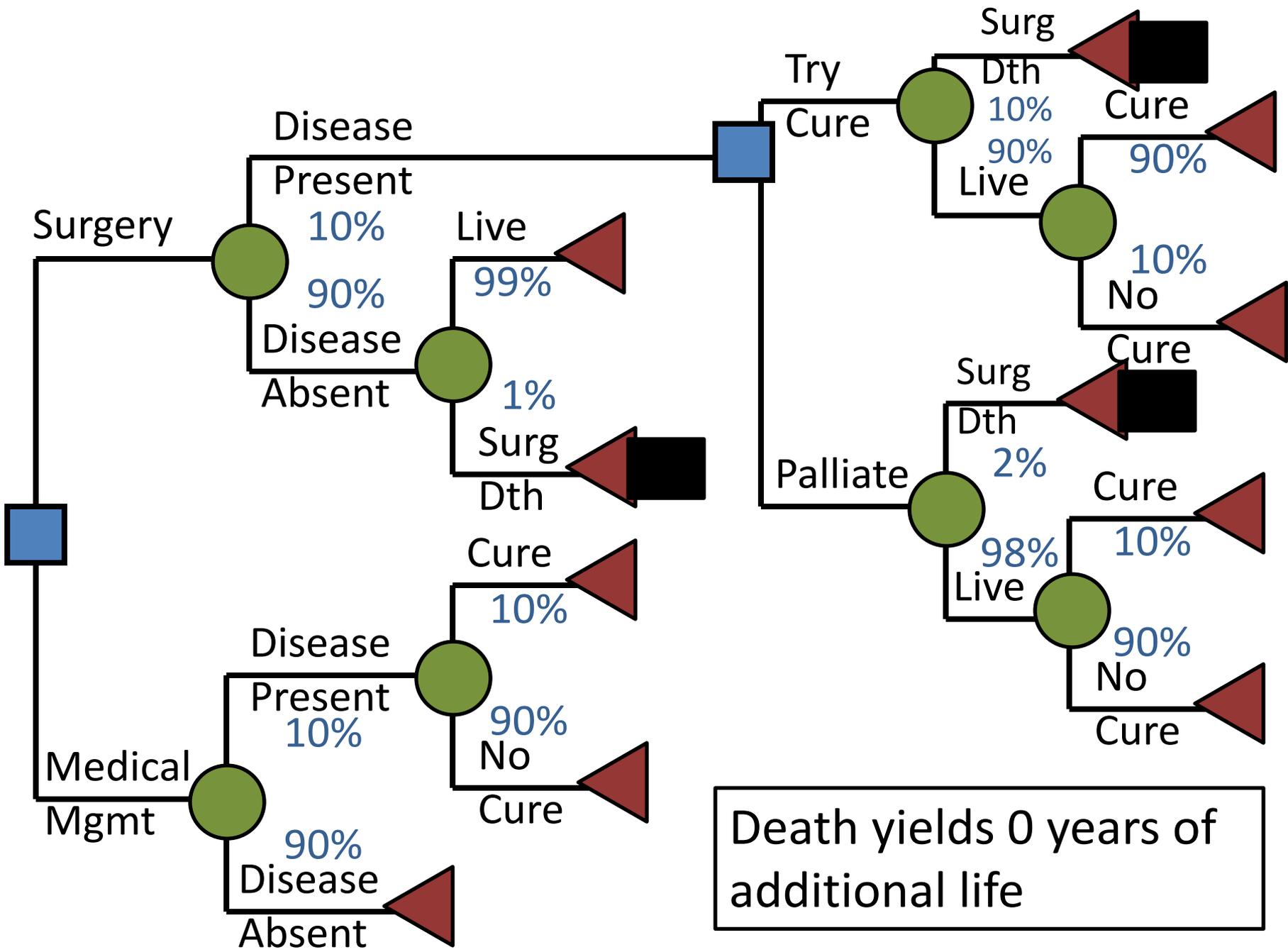


1. Surgery
2. in a patient with disease
3. where curative surgery chosen
- 4^{re}. and patient survives
5. and is cured

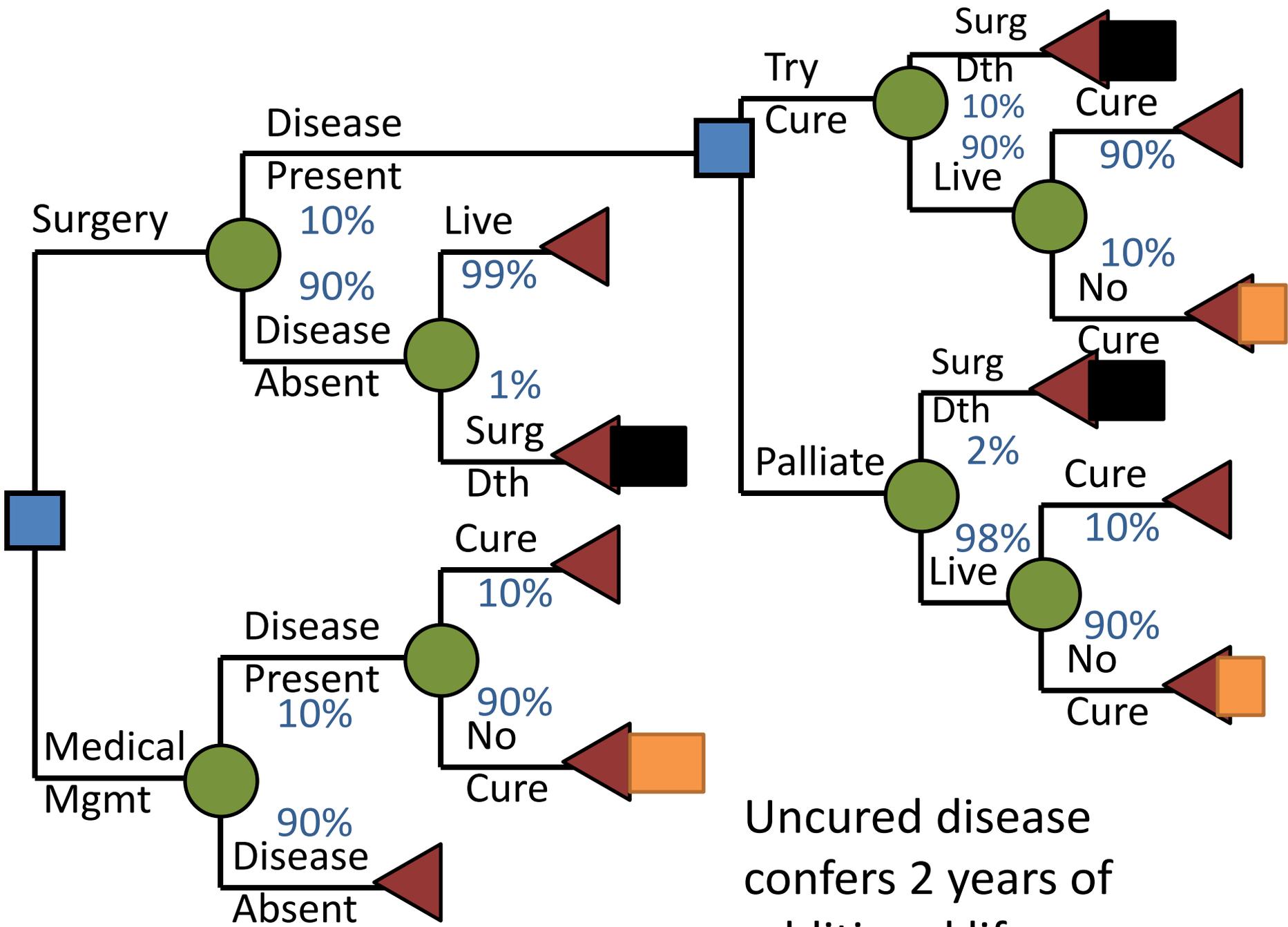




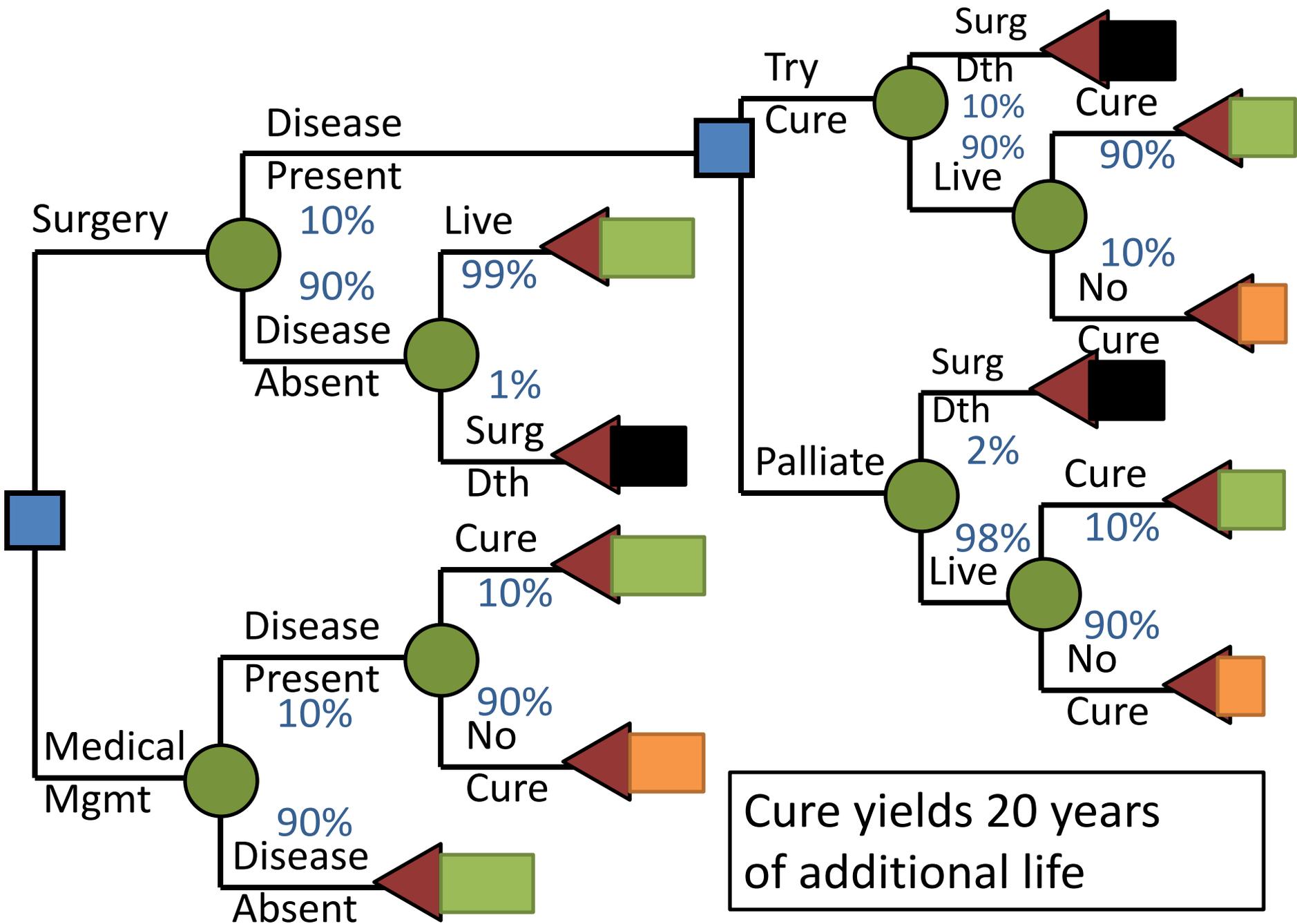
Now add outcomes



Death yields 0 years of additional life

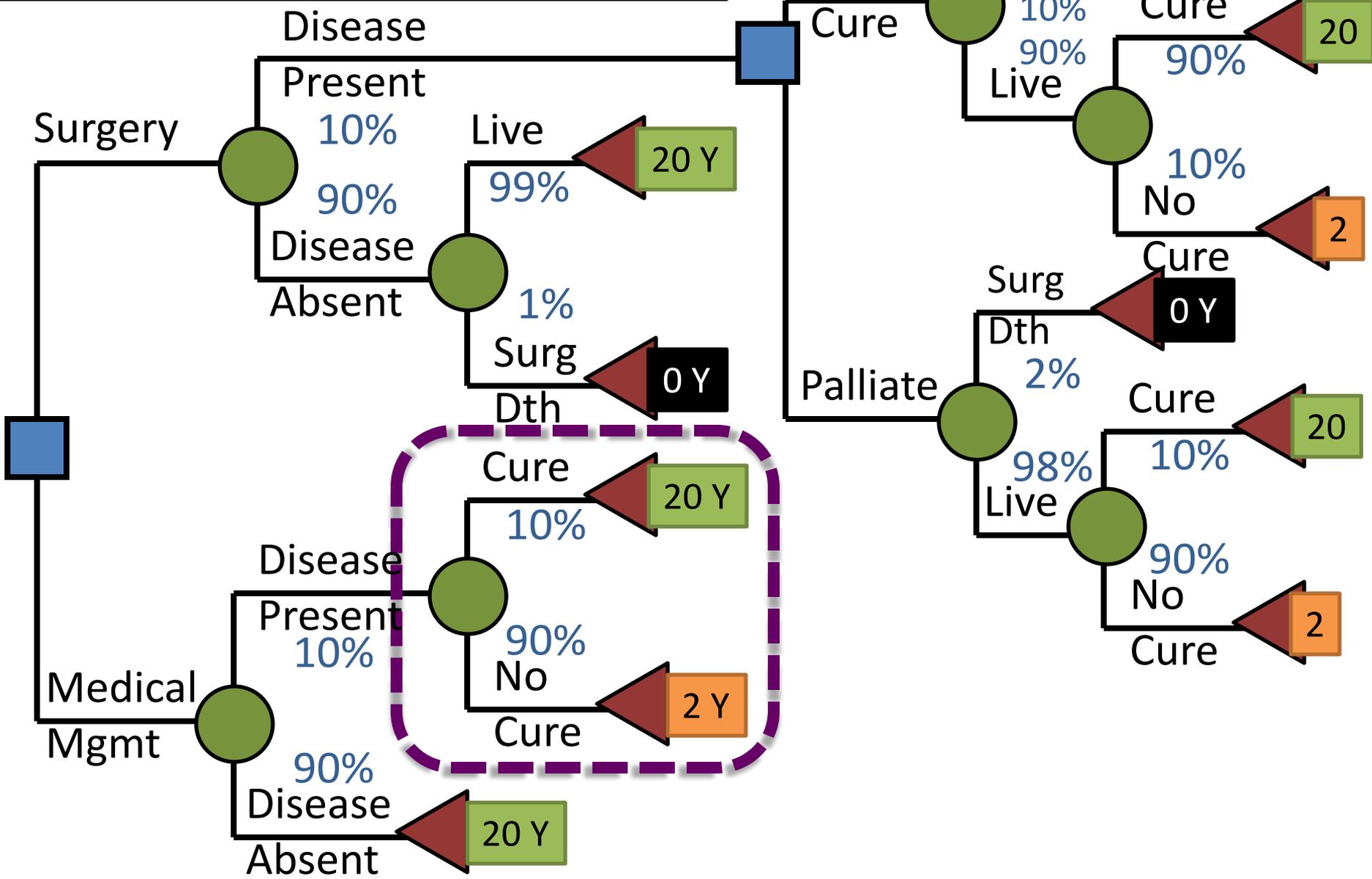


Uncured disease confers 2 years of additional life

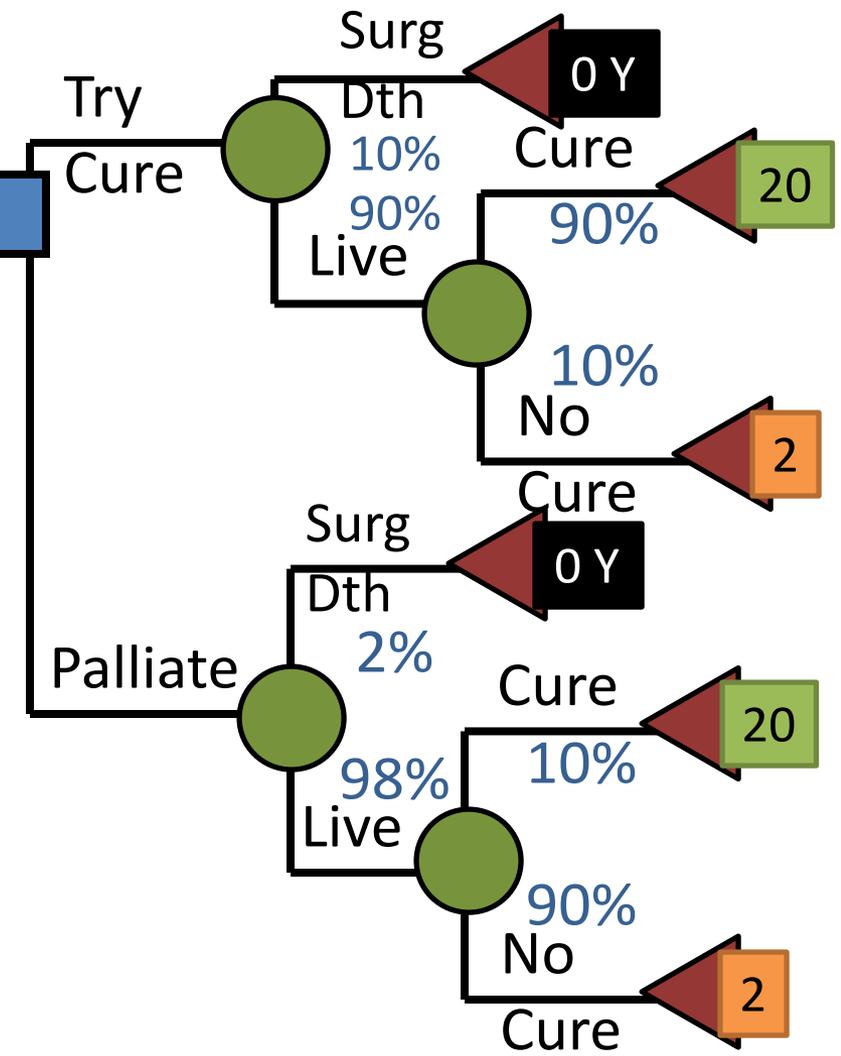
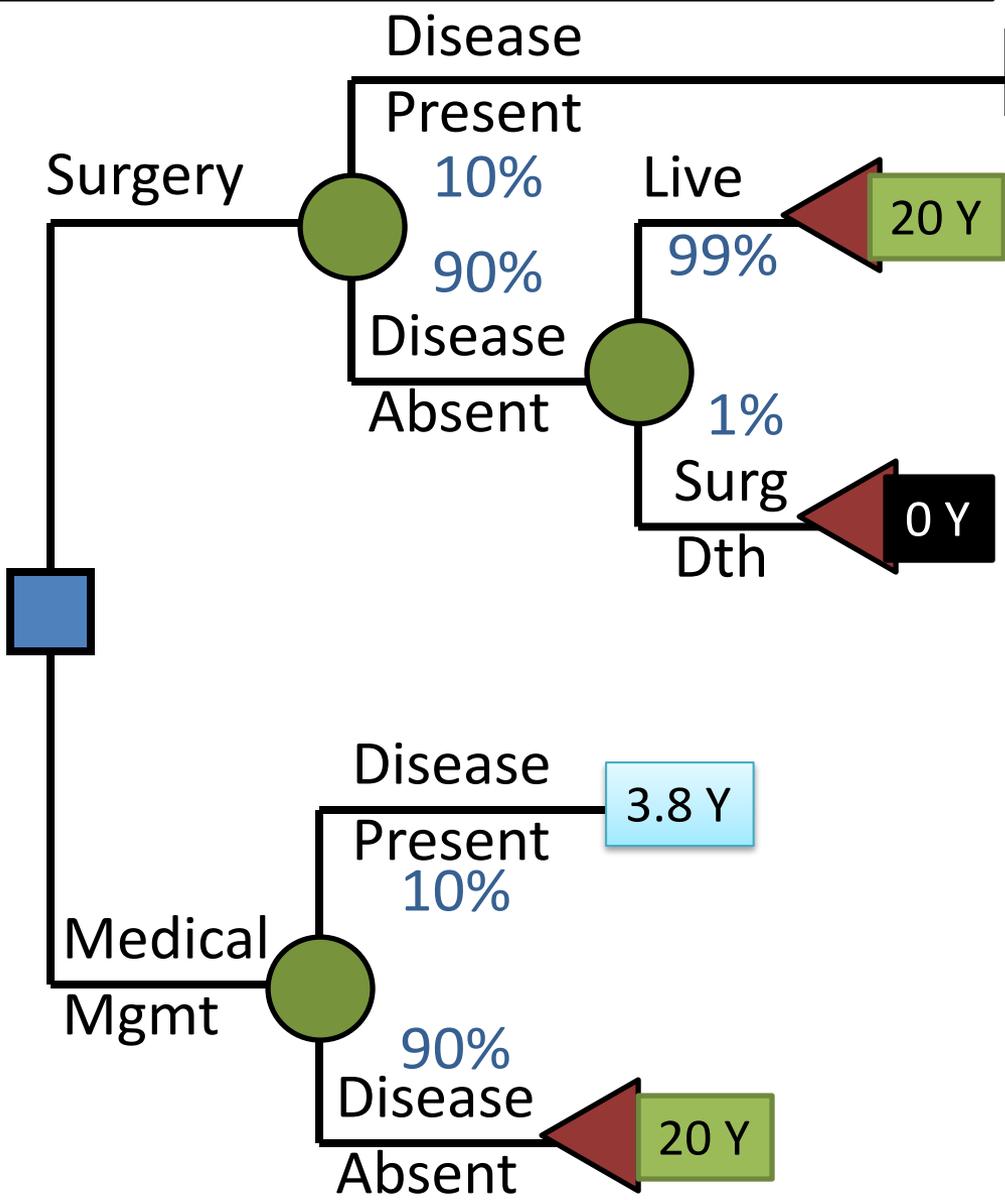


Cure yields 20 years of additional life

Now average out & fold back

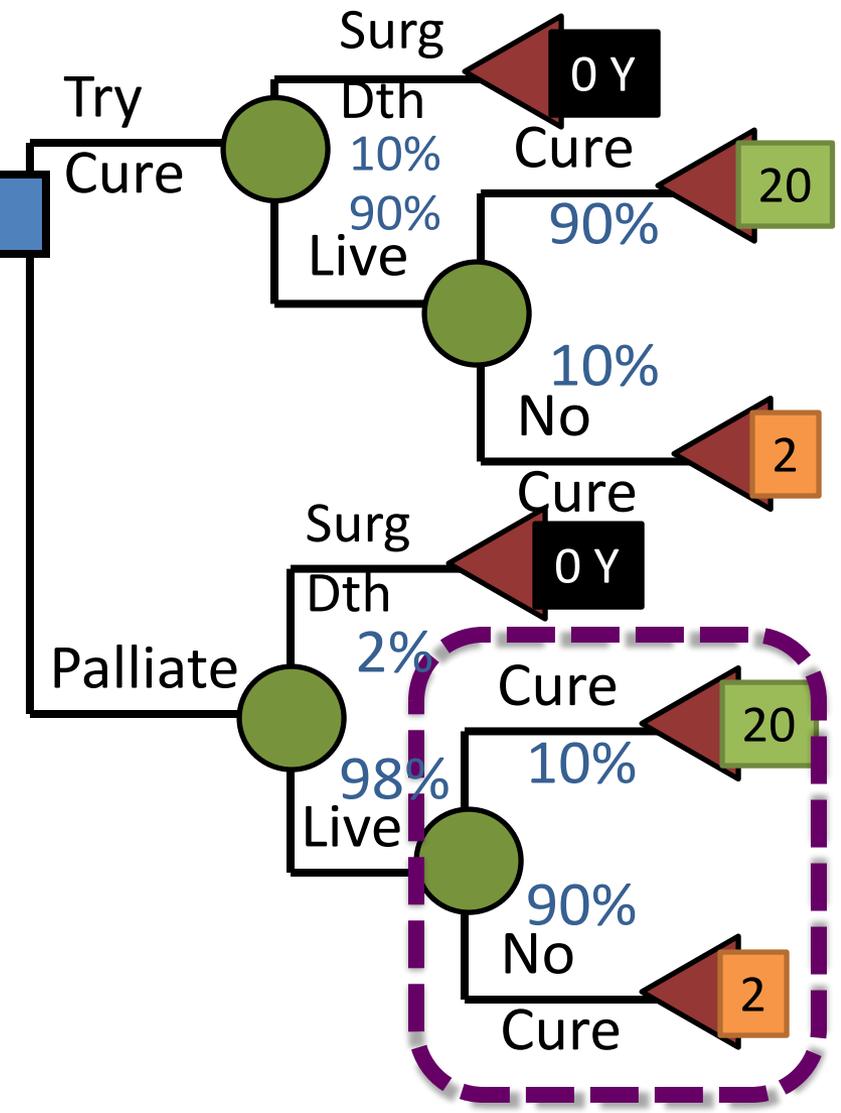
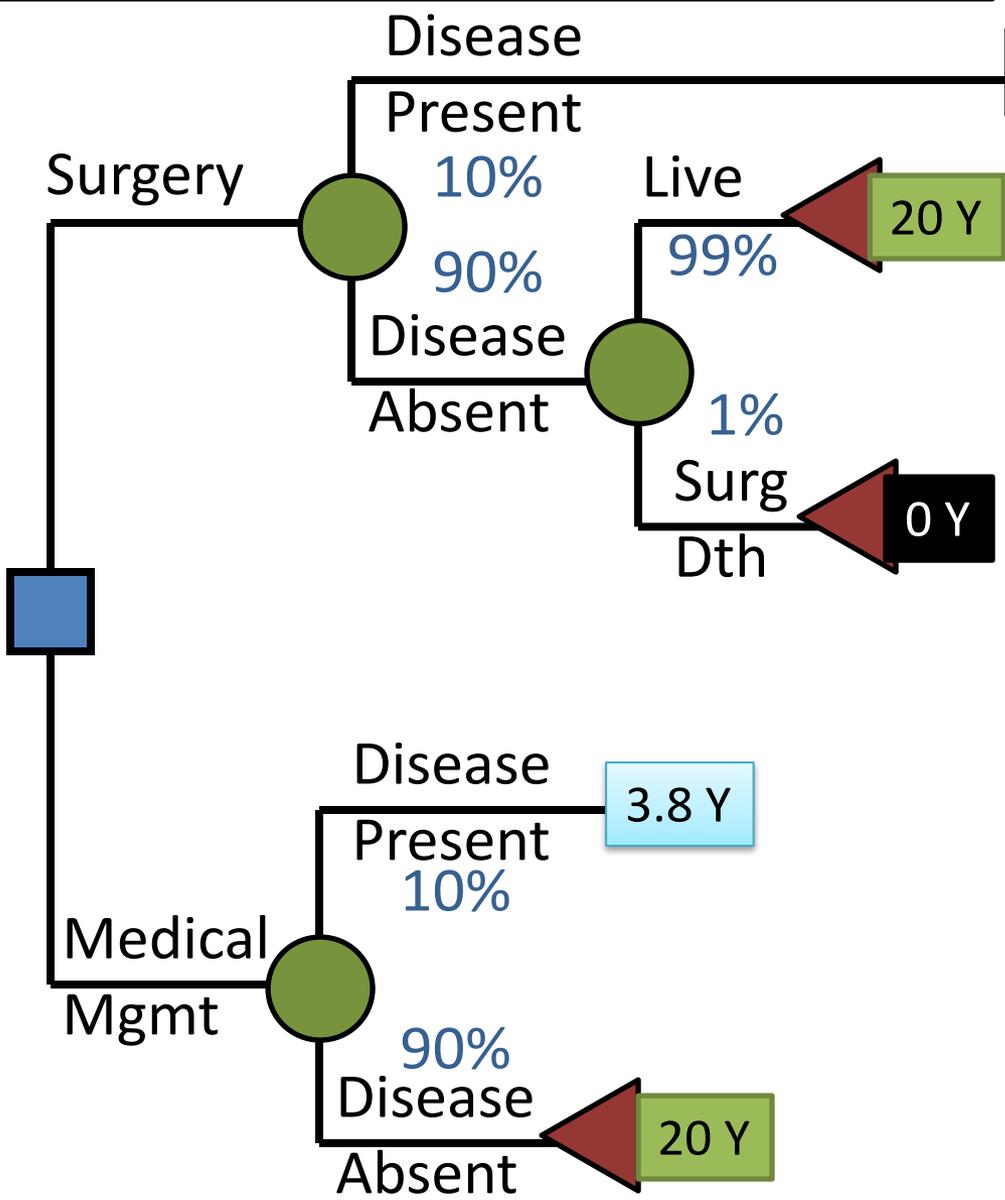


Now average out & fold back



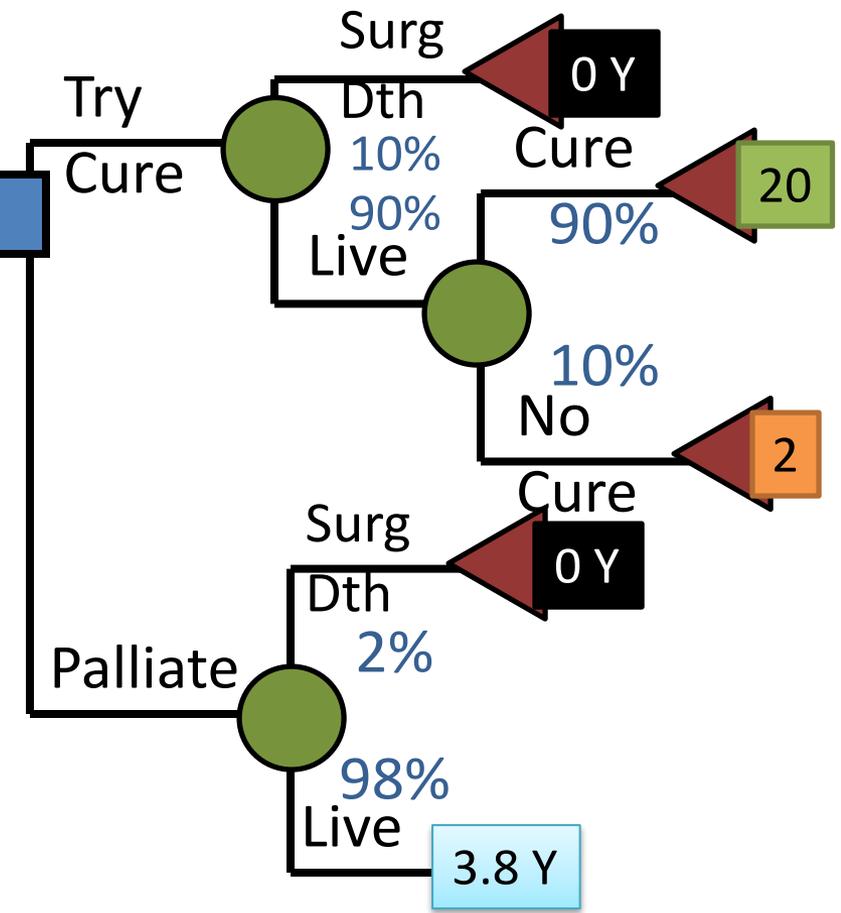
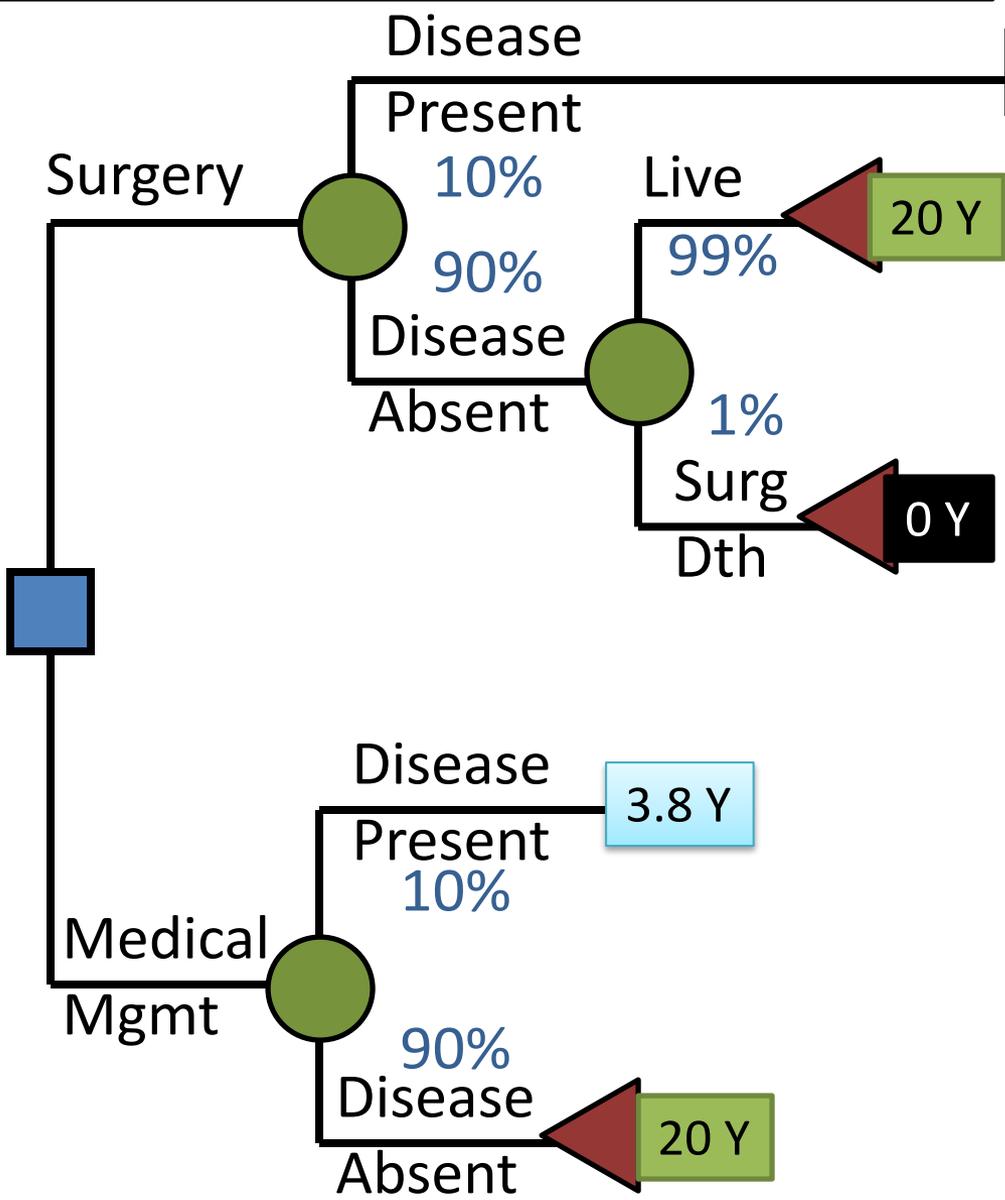
$$10\% * 20 + 90\% * 2 = 3.8 \text{ years (expected)}$$

Now average out & fold back



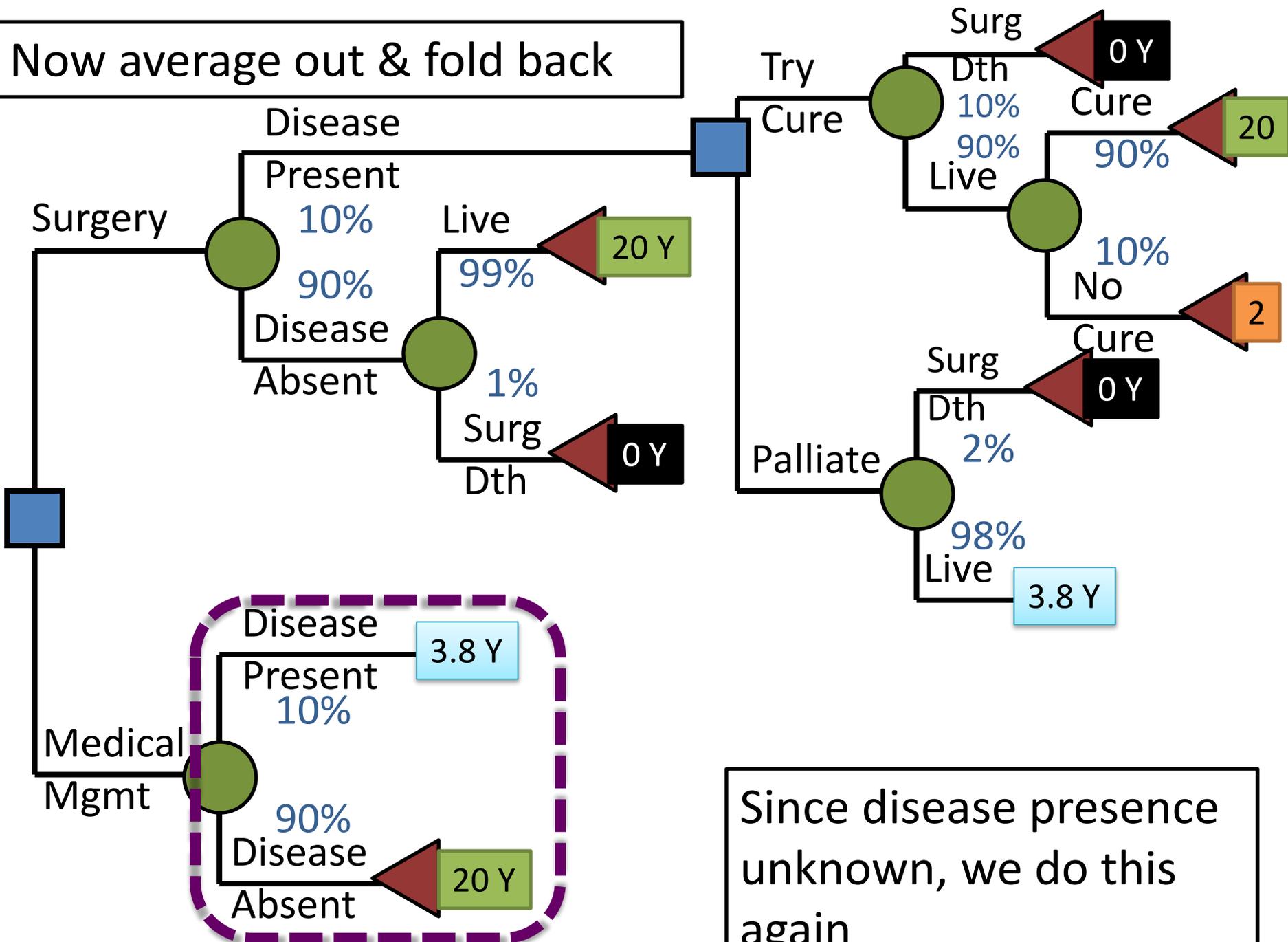
Same calculation here

Now average out & fold back



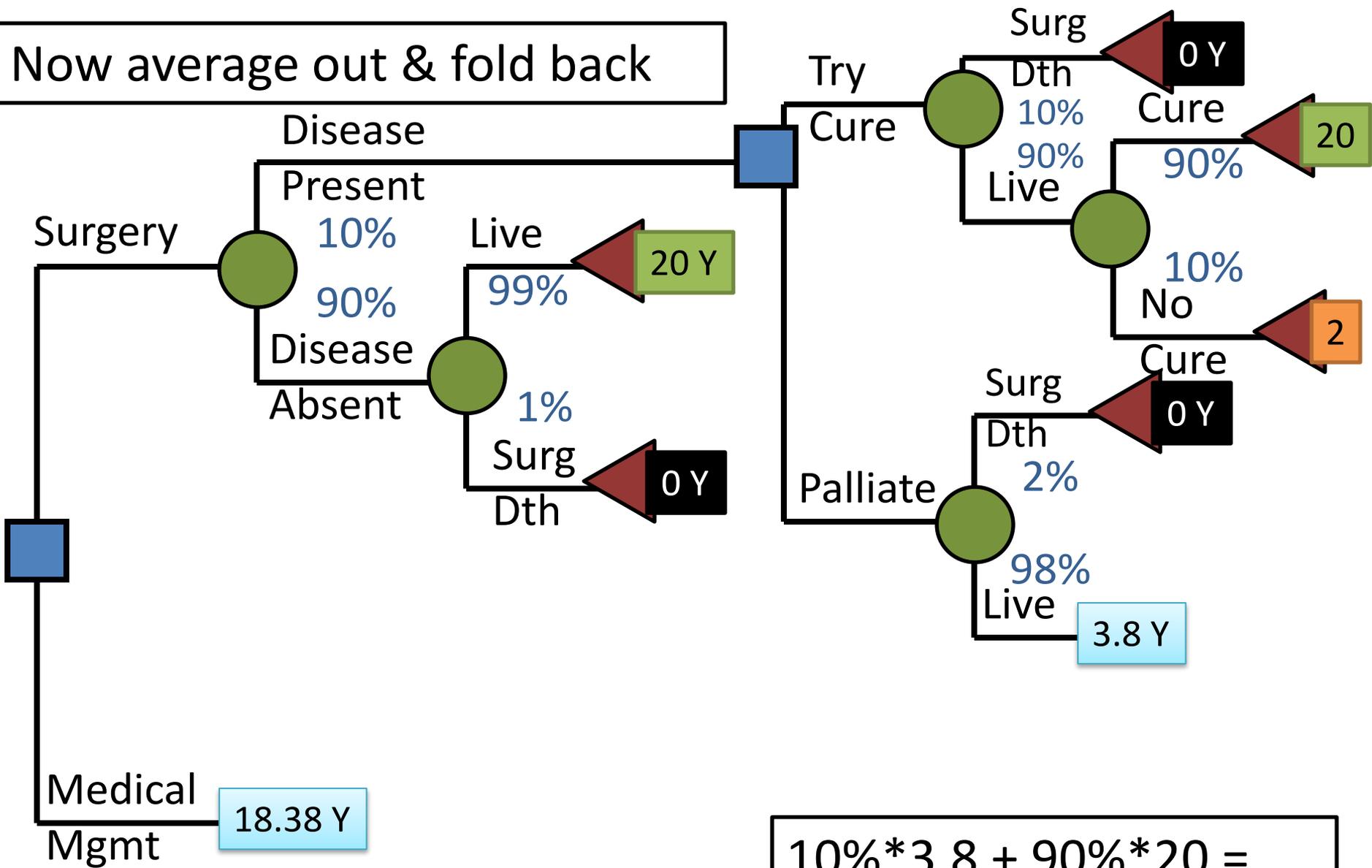
$$10\% * 20 + 90\% * 2 = 3.8 \text{ years (expected)}$$

Now average out & fold back



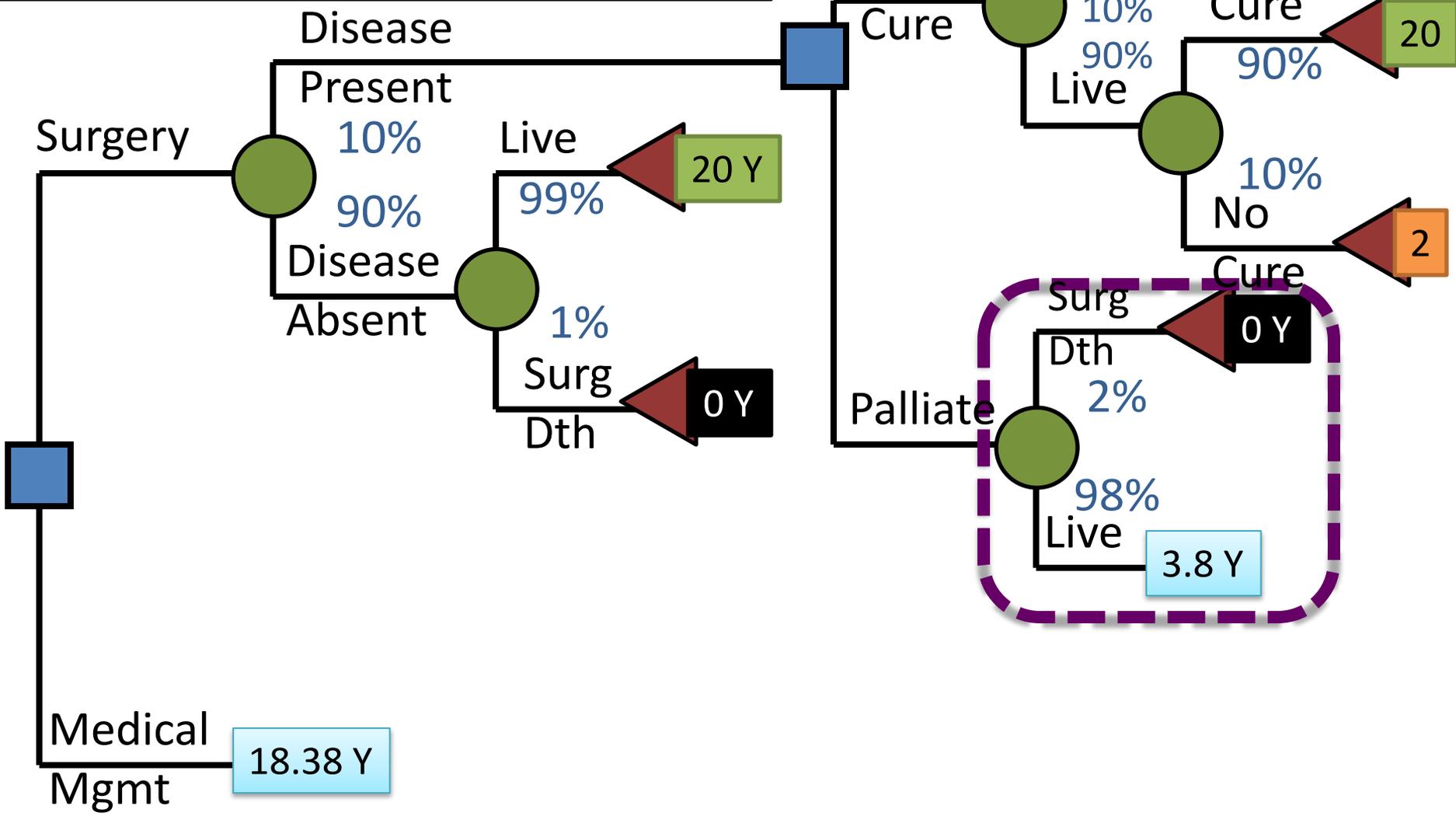
Since disease presence unknown, we do this again

Now average out & fold back

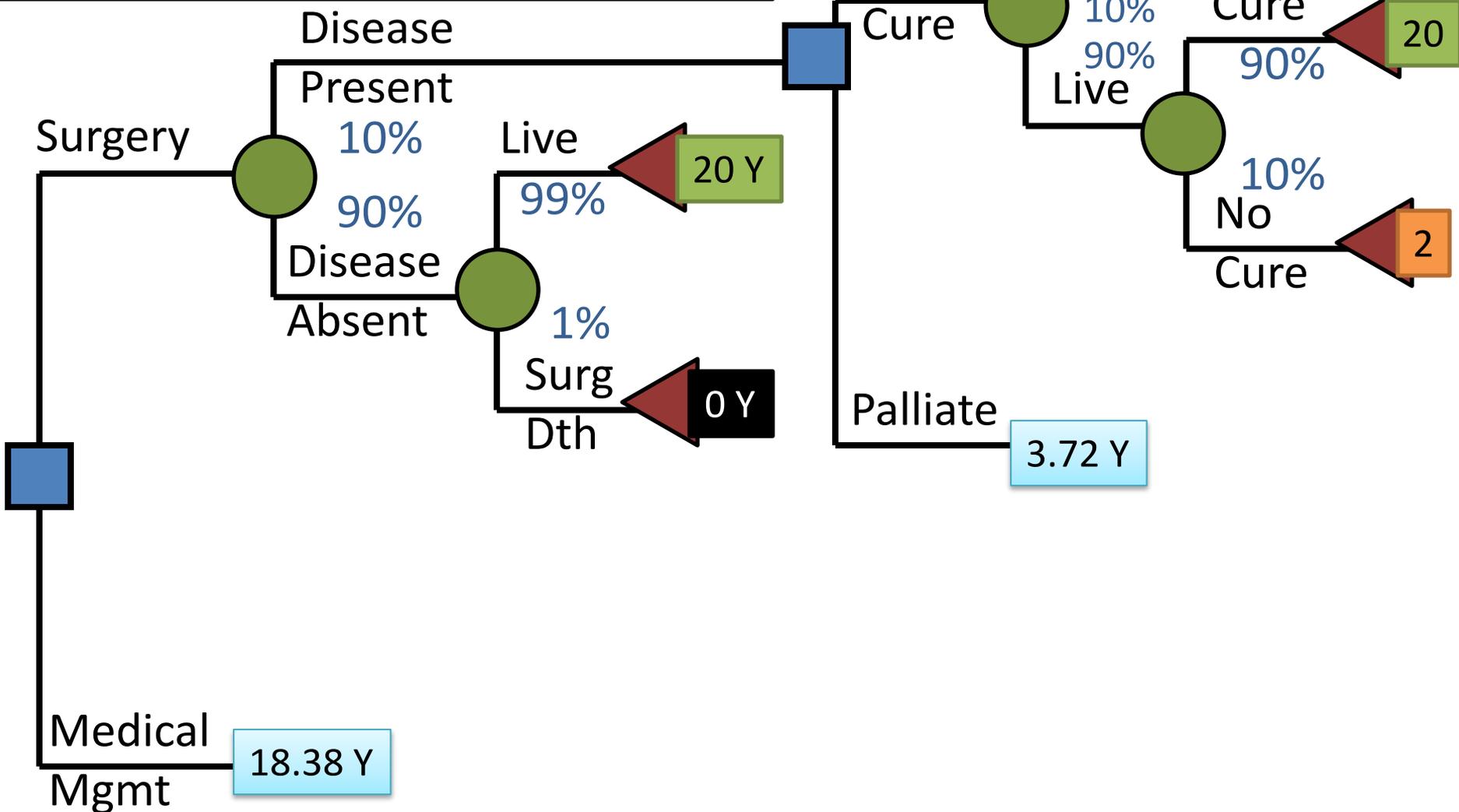


$$10\% * 3.8 + 90\% * 20 = 18.38 \text{ years}$$

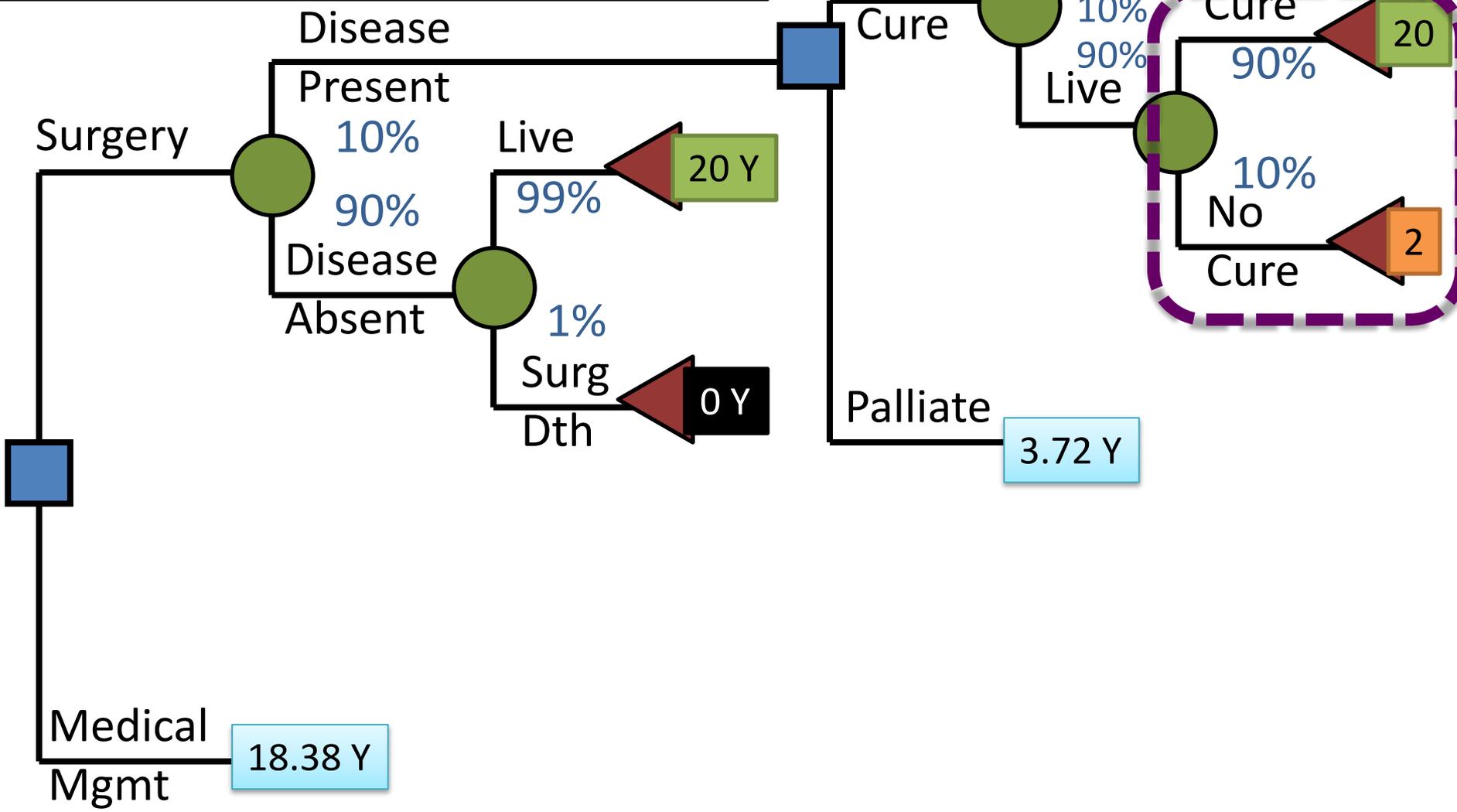
Now average out & fold back



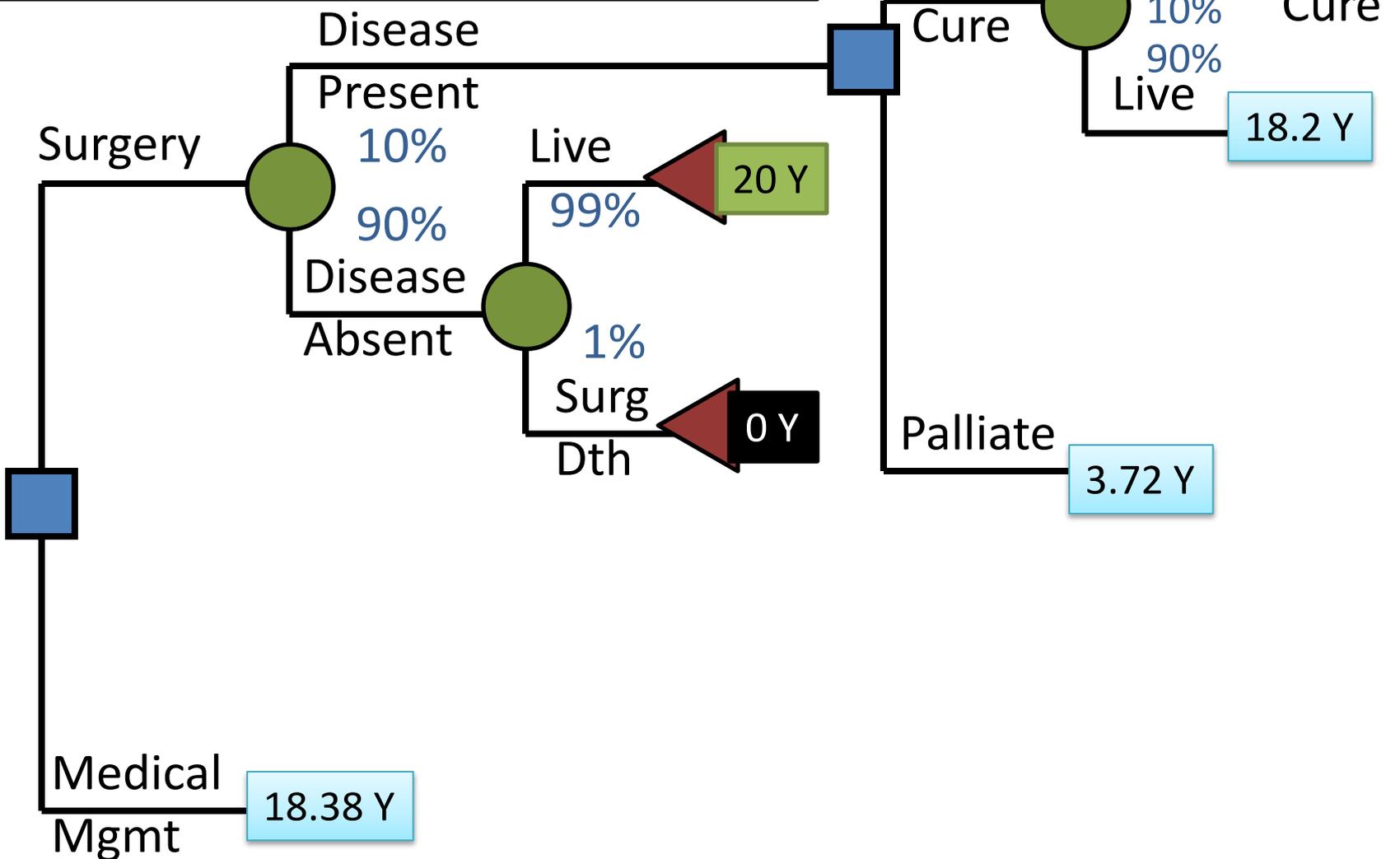
Now average out & fold back



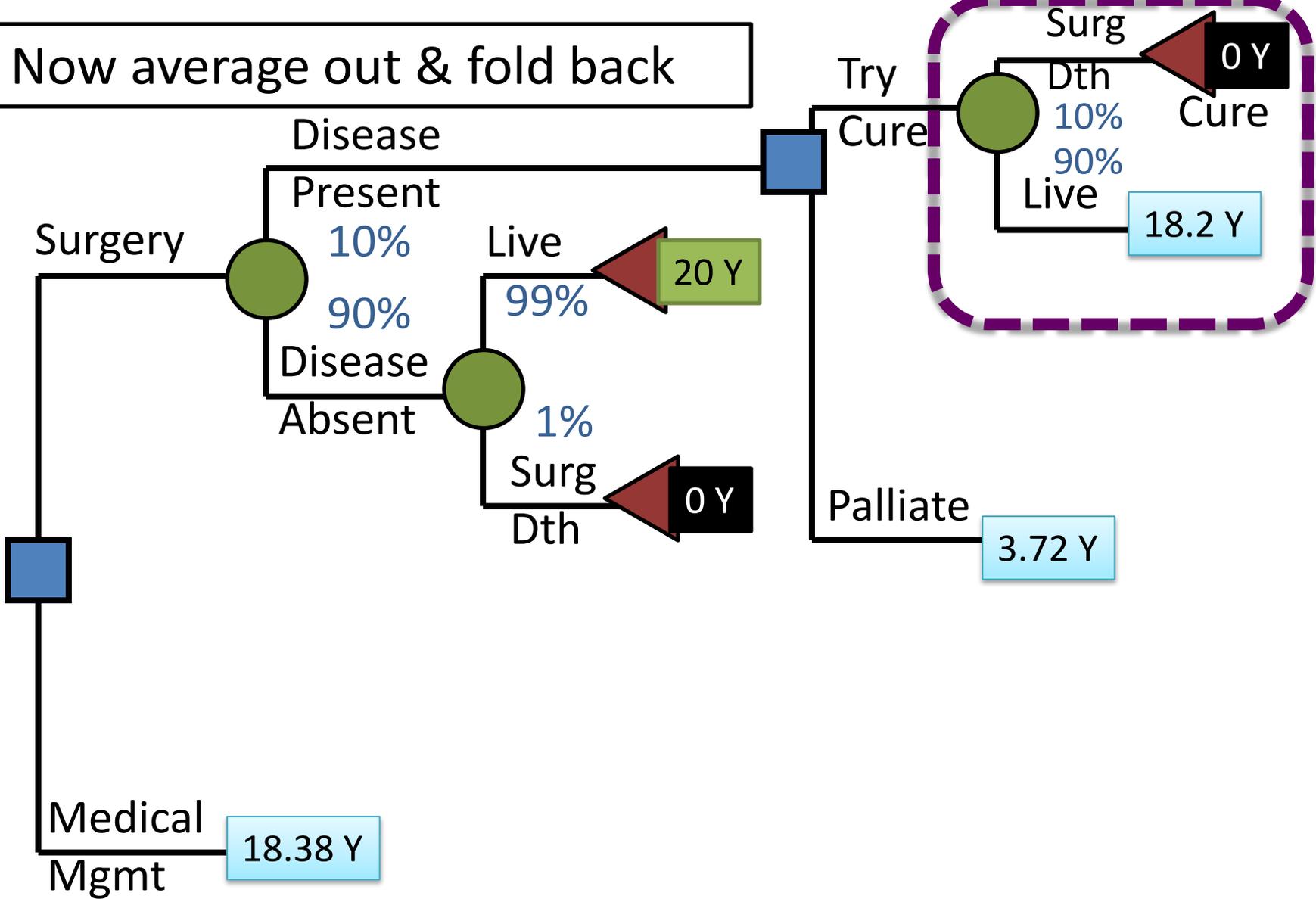
Now average out & fold back



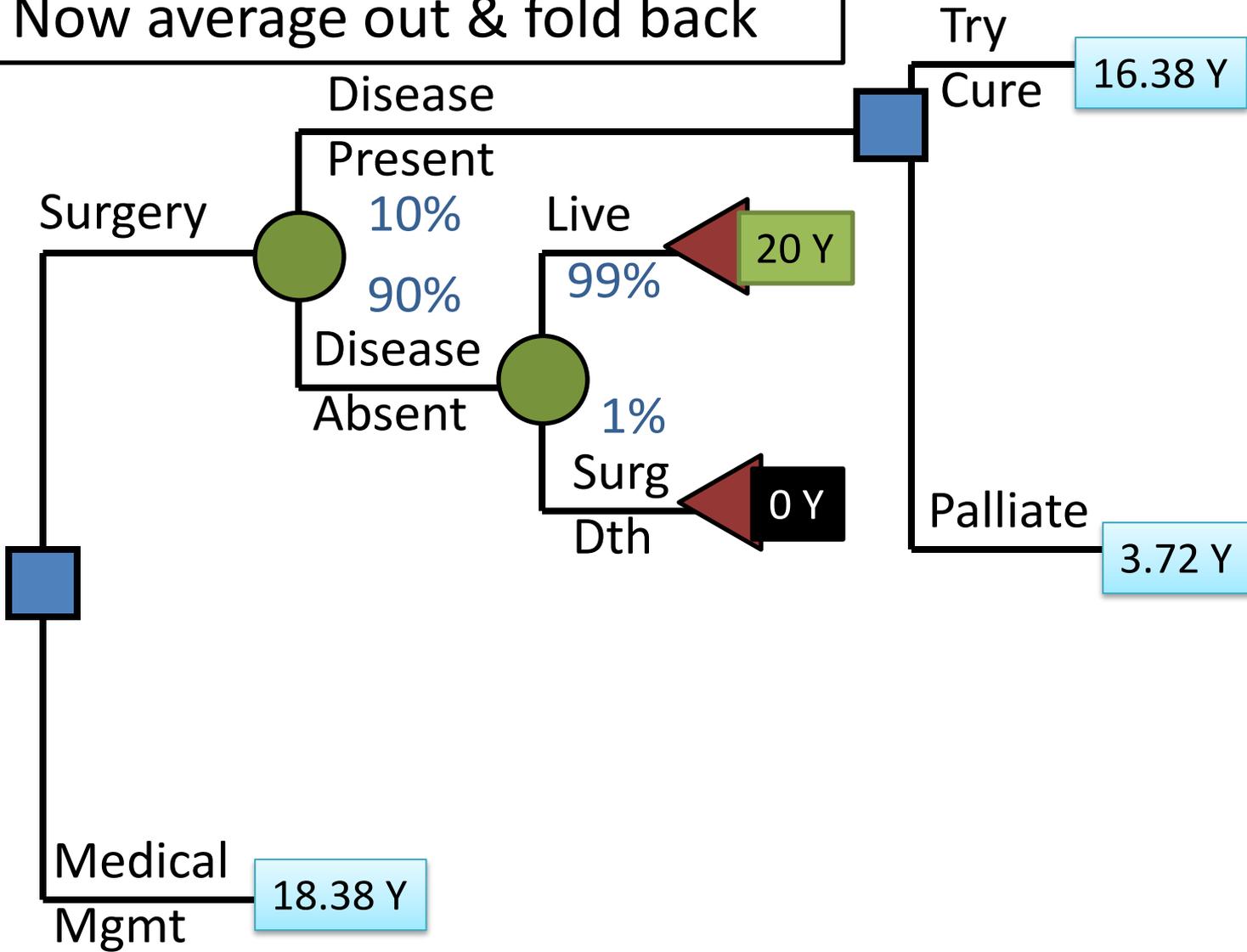
Now average out & fold back

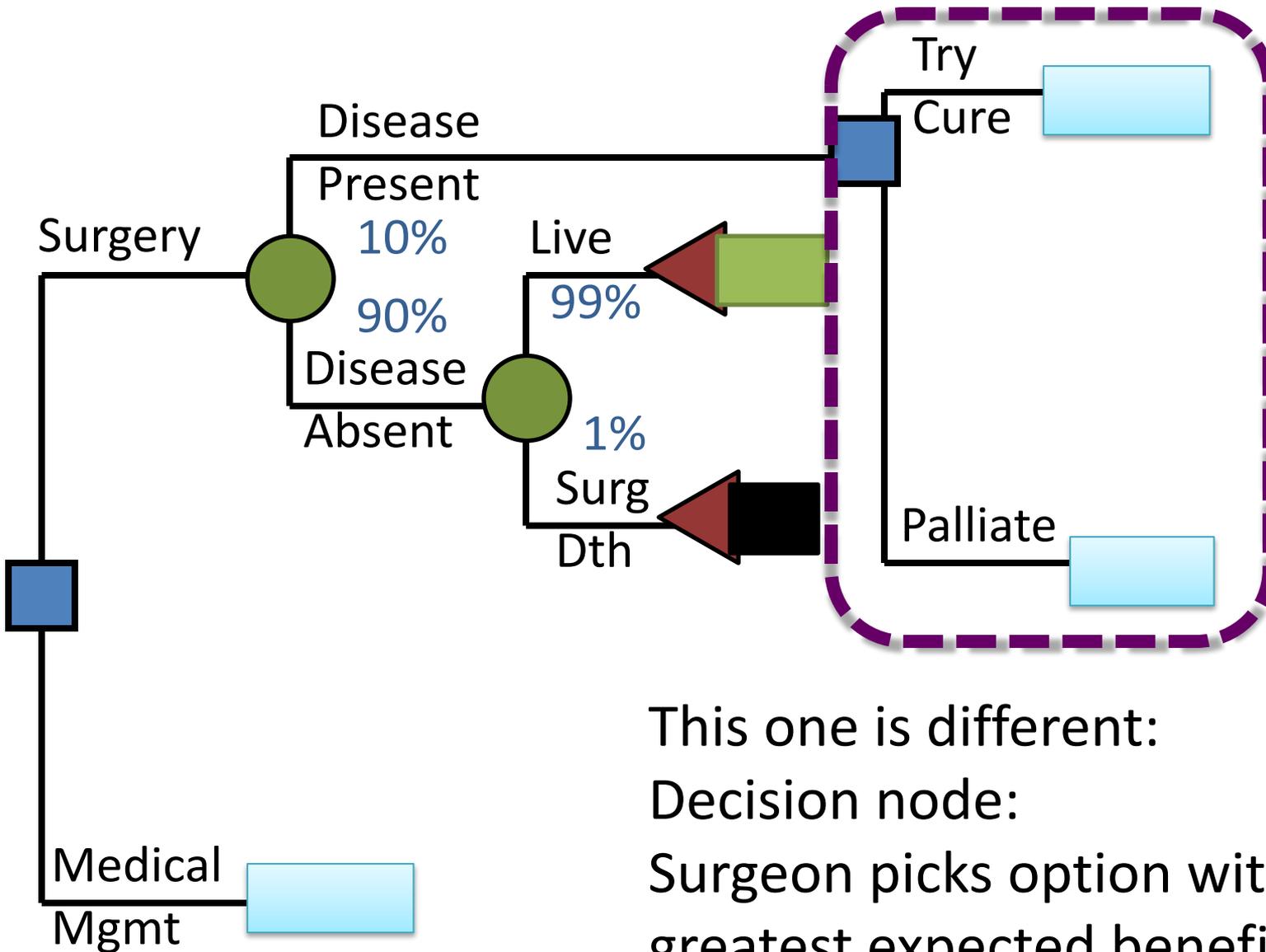


Now average out & fold back



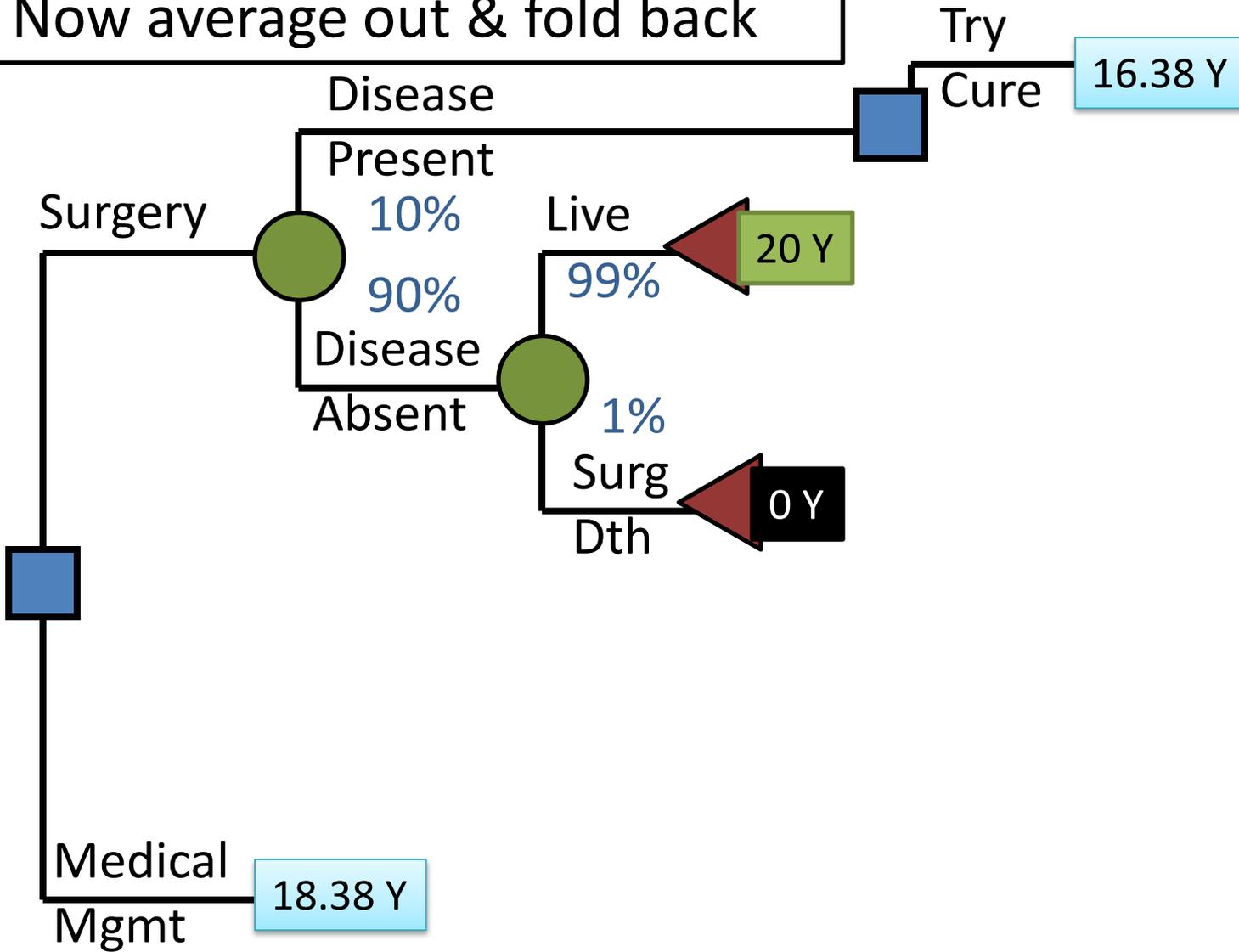
Now average out & fold back



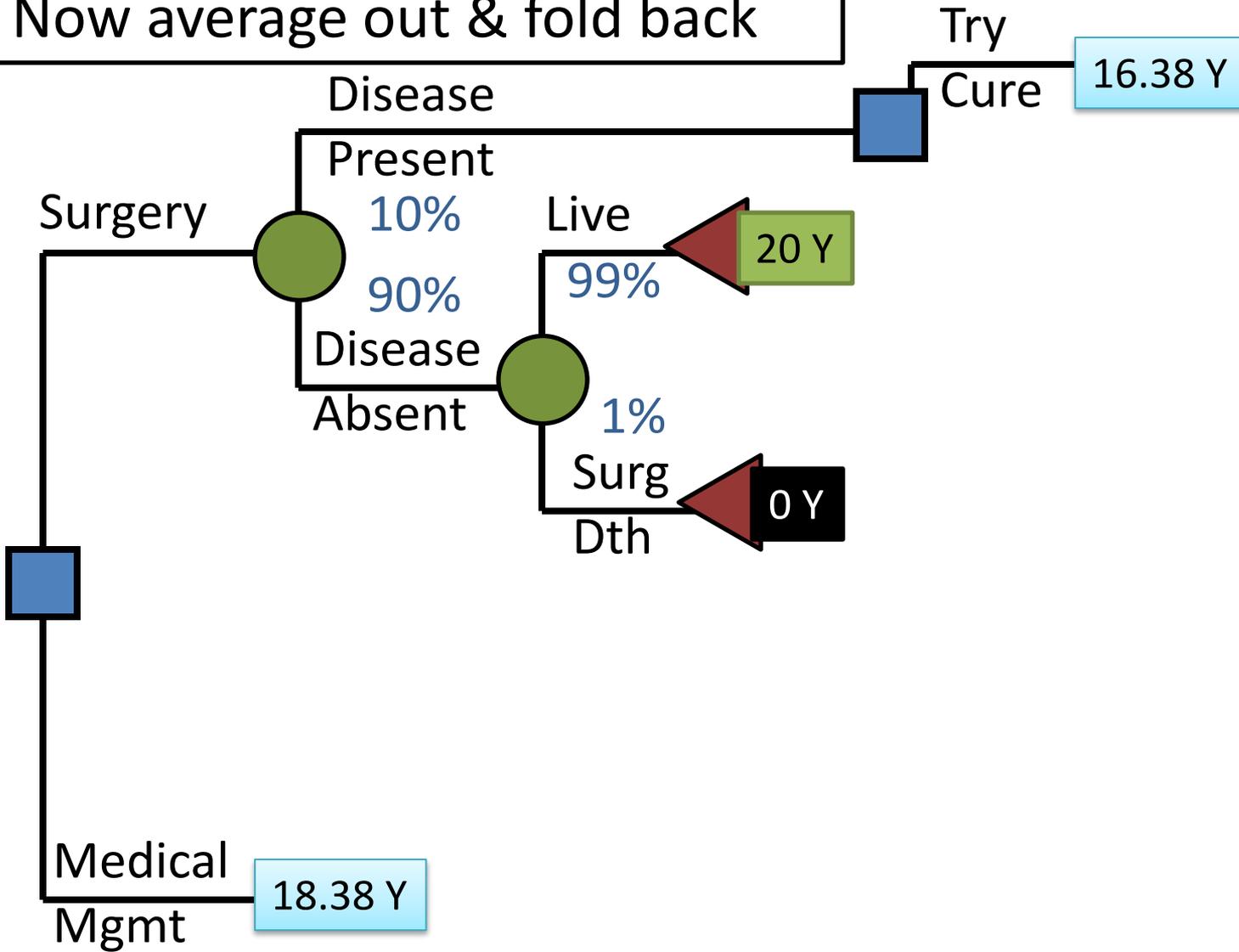


This one is different:
 Decision node:
 Surgeon picks option with
 greatest expected benefit:
 Try Cure (16.38 years) preferred
(called "folding back")

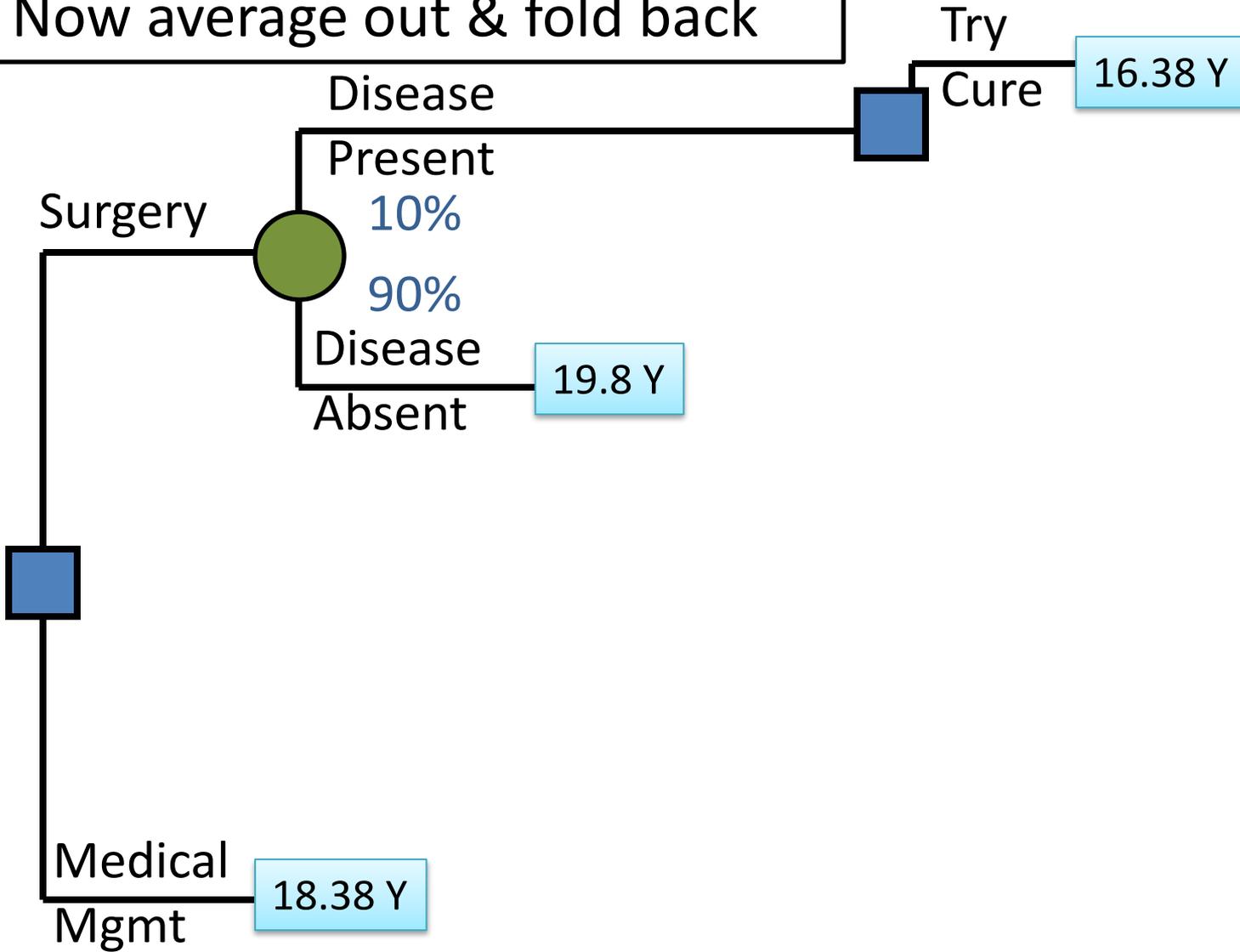
Now average out & fold back



Now average out & fold back



Now average out & fold back



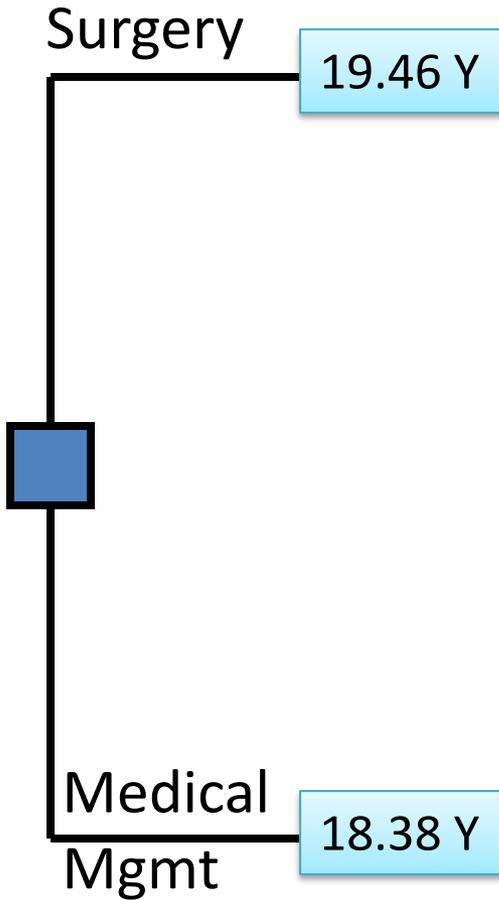
Surgery

19.46 Y



Medical
Mgmt

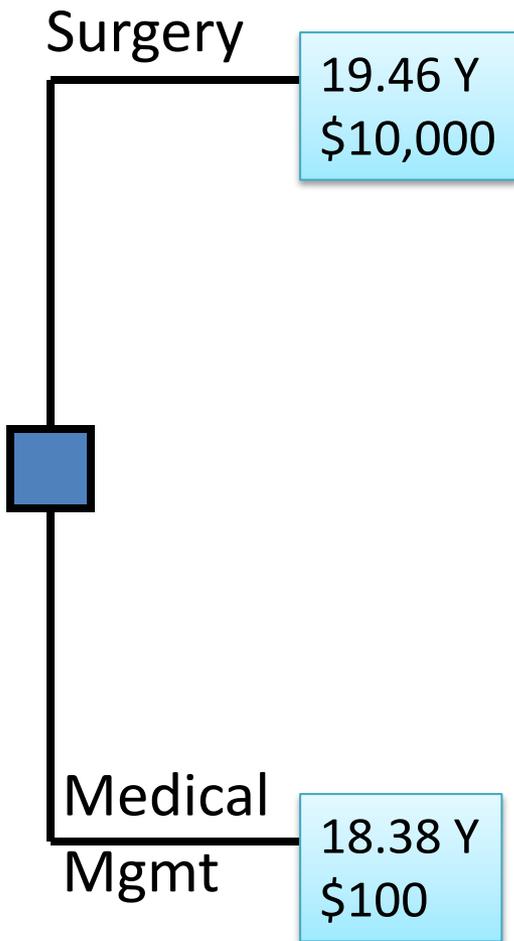
18.38 Y



Decision node again (overall)
Surgery is preferred to Medical Management because the incremental benefit of surgery is:

$$19.46 - 18.38 = \mathbf{1.08 \text{ years}}$$

Recommendation: Choose surgery (with “try cure” surgical option)



Use same approach for CEA but now with second set of outcomes

$$19.46 - 18.38 = \mathbf{1.08 \text{ years}}$$

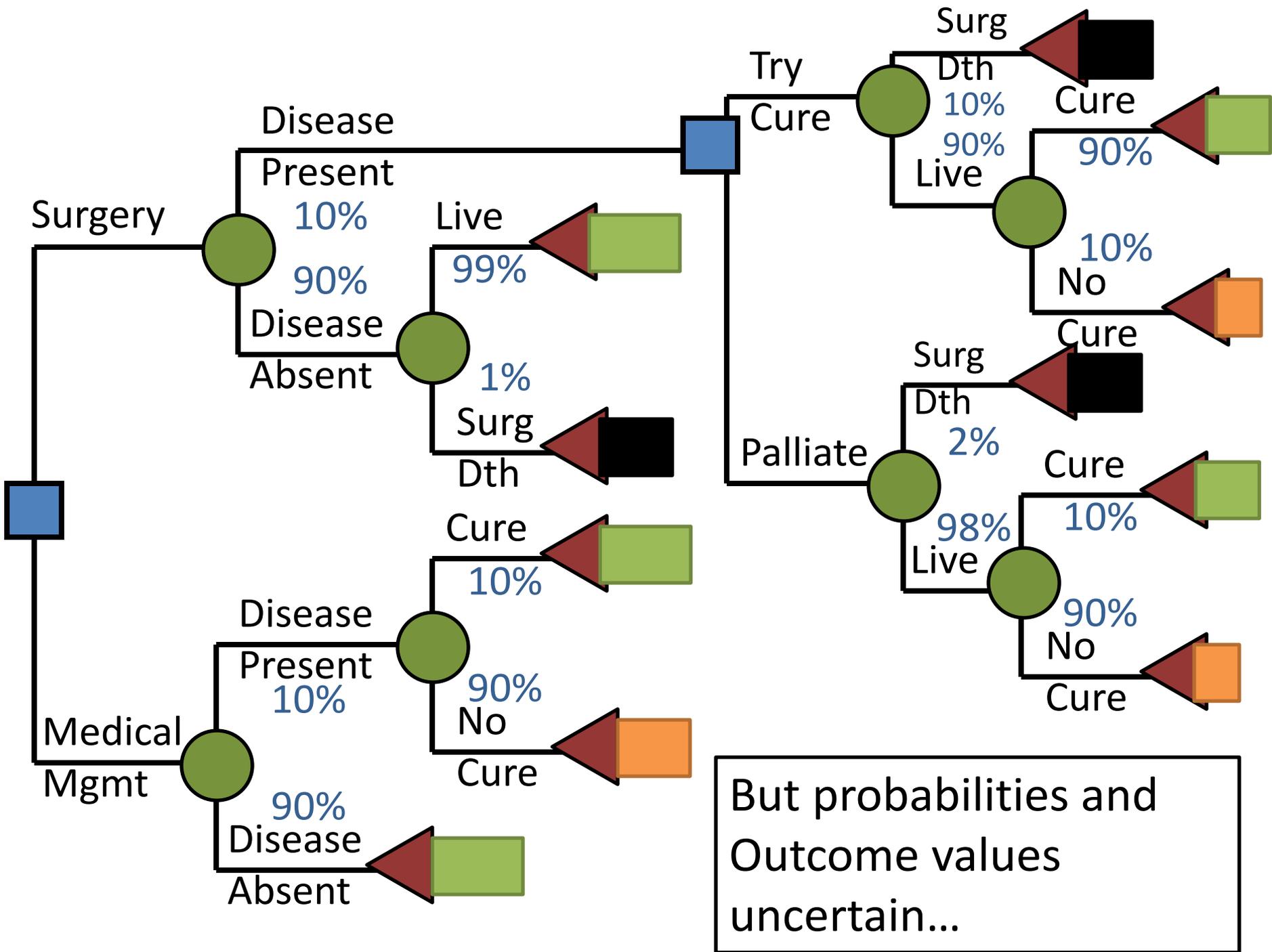
$$\$10,000 - \$100 = \mathbf{\$9,900}$$

$$\mathbf{\$9,900 / 1.08 =}$$

$$\mathbf{\$9,167 \text{ per life year gained}}$$

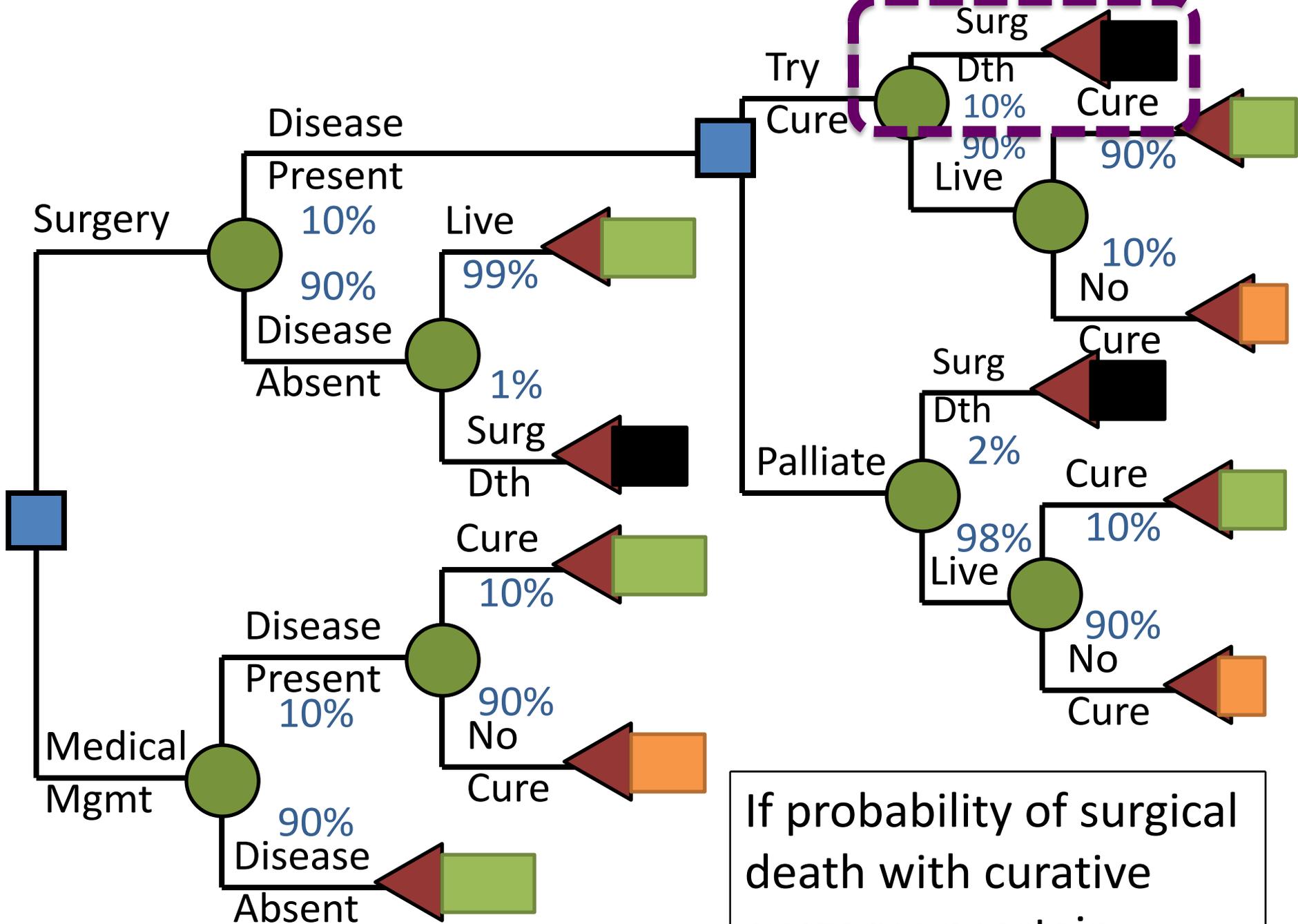
Surgery if willing to pay at least \$9,167 per life year gained, otherwise medical management

SENSITIVITY ANALYSIS



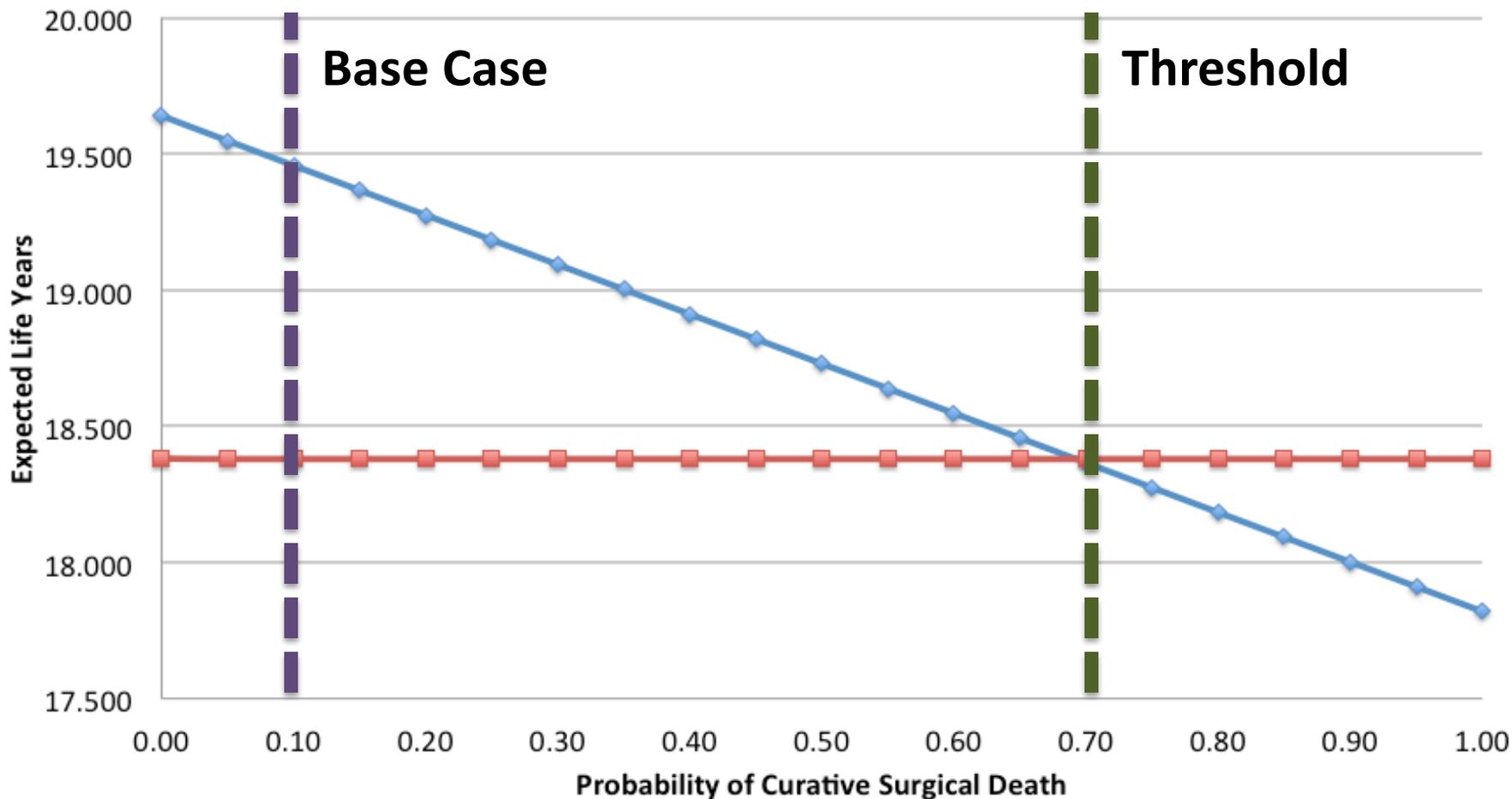
Sensitivity Analysis

- Systematically asking “what if” questions to see how the decision result changes
- Determines how “robust” the decision is
 - **Threshold analysis:** one parameter varied
 - **Multi-way analysis:** multiple parameters systematically varied

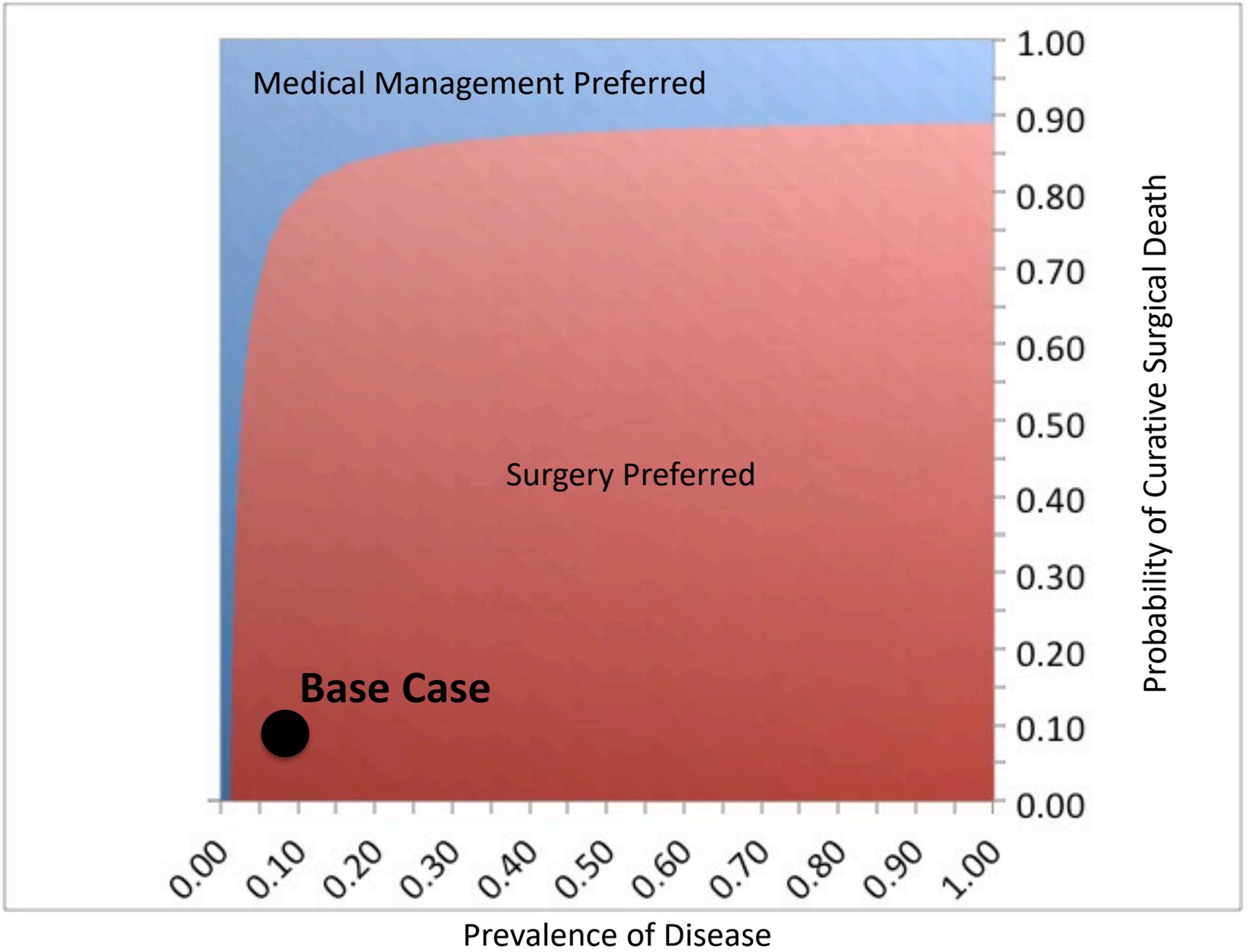


If probability of surgical death with curative surgery uncertain

1-way sensitivity analysis: Curative Surgical Death



—◆— Surgery - Curative —■— Med Mgmt



POLL SLIDE

- **Sensitivity analyses tell us (*choose all answers that you believe to be correct*):**
 1. How much model outputs change based on changes to the inputs
 2. Whether our decision would change with different inputs
 3. How uncertain we feel about the decision
 4. Whether the decision-problem is politically sensitive

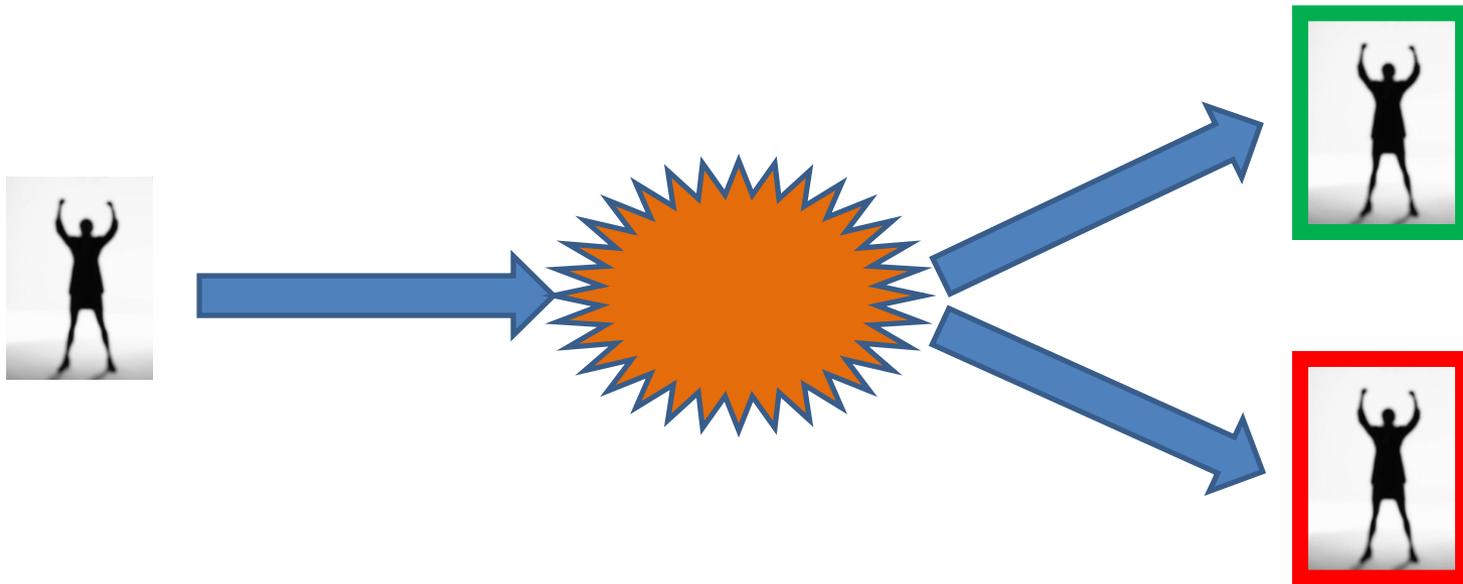
Advanced: Probabilistic Sensitivity Analysis (2nd order Monte Carlo)

- Estimates of probabilities and utilities in the decision tree are replaced with probability distributions (e.g. log-normal)
- The tree is evaluated *many* times with random values selected from each distribution
- Results include means and standard deviations of the expected values (standard errors) of each strategy

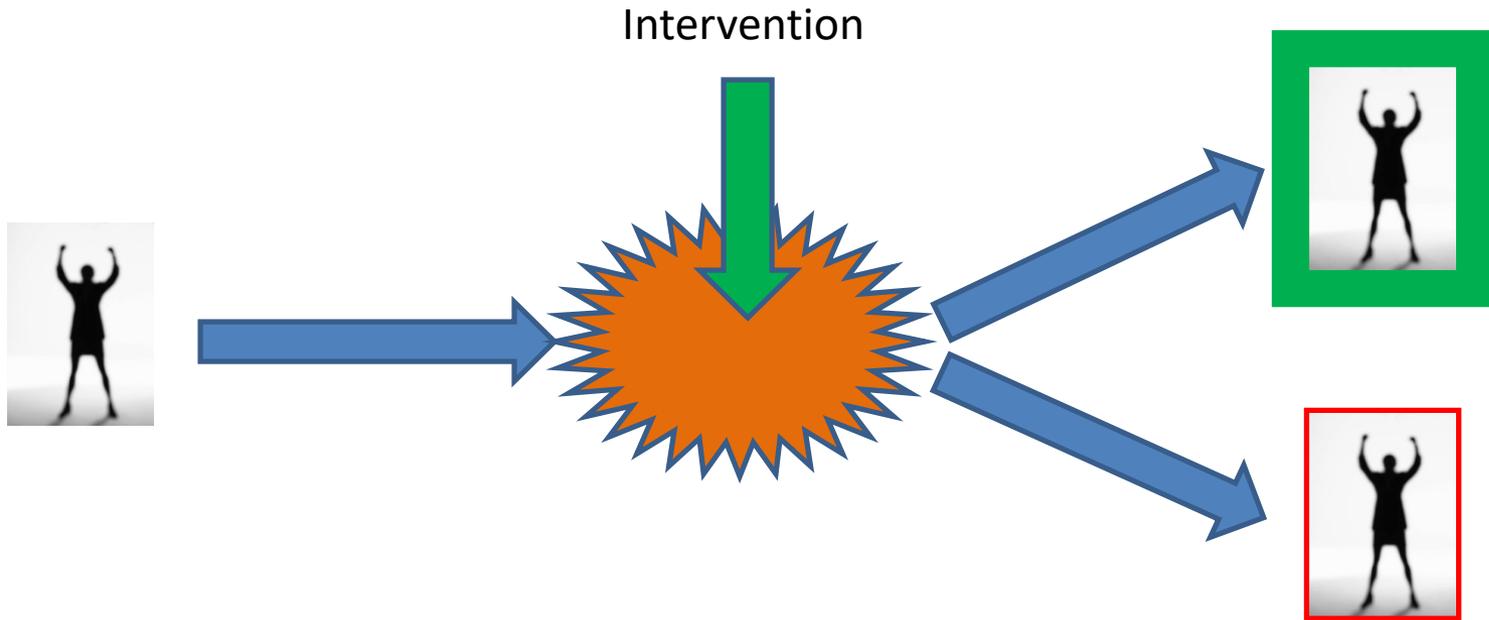
MARKOV MODELS VS. DECISION TREES

**WHAT TO DO WHEN THERE IS A
POSSIBILITY OF REPEATED EVENTS
AND/OR DECISIONS?**

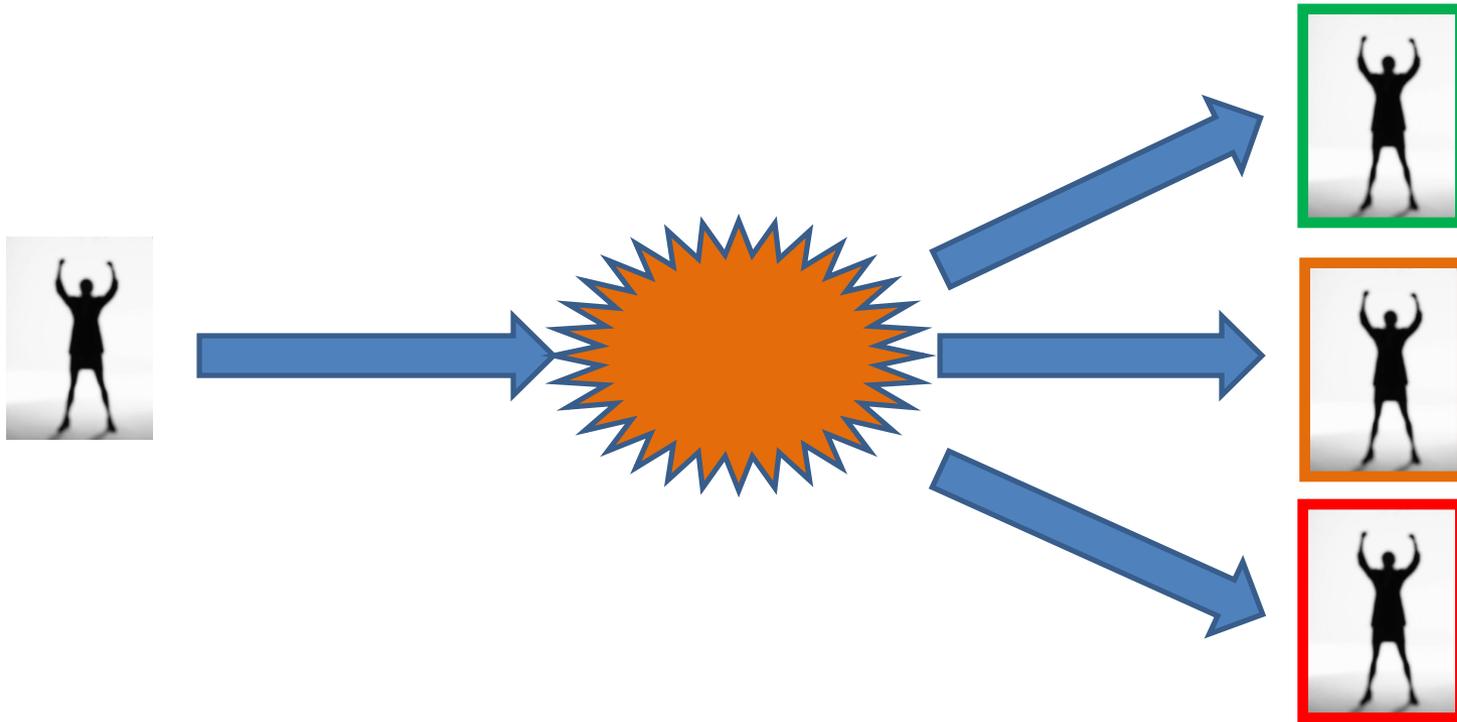
Decision about one-time, immediate action



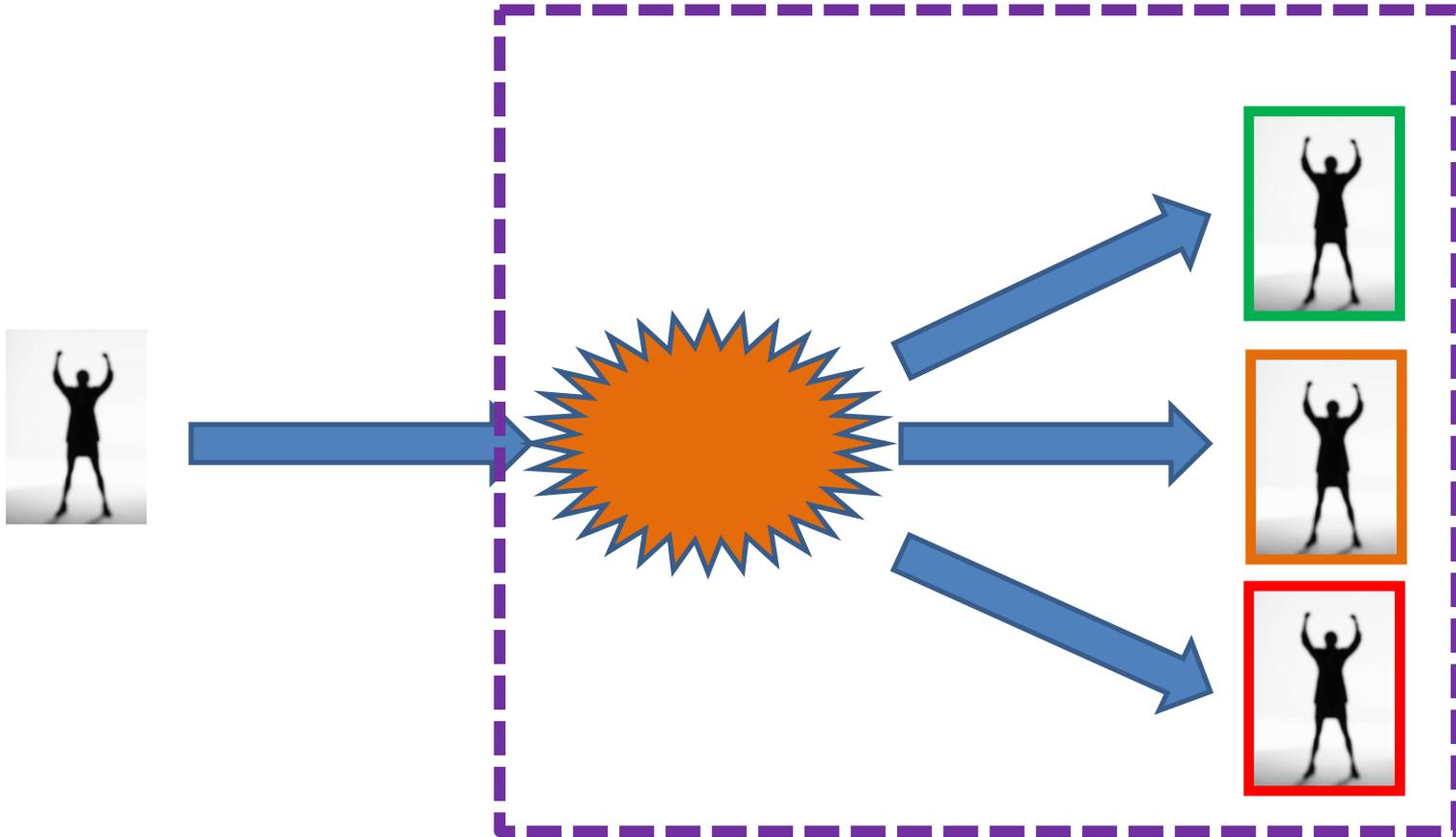
Decision about one-time, immediate action



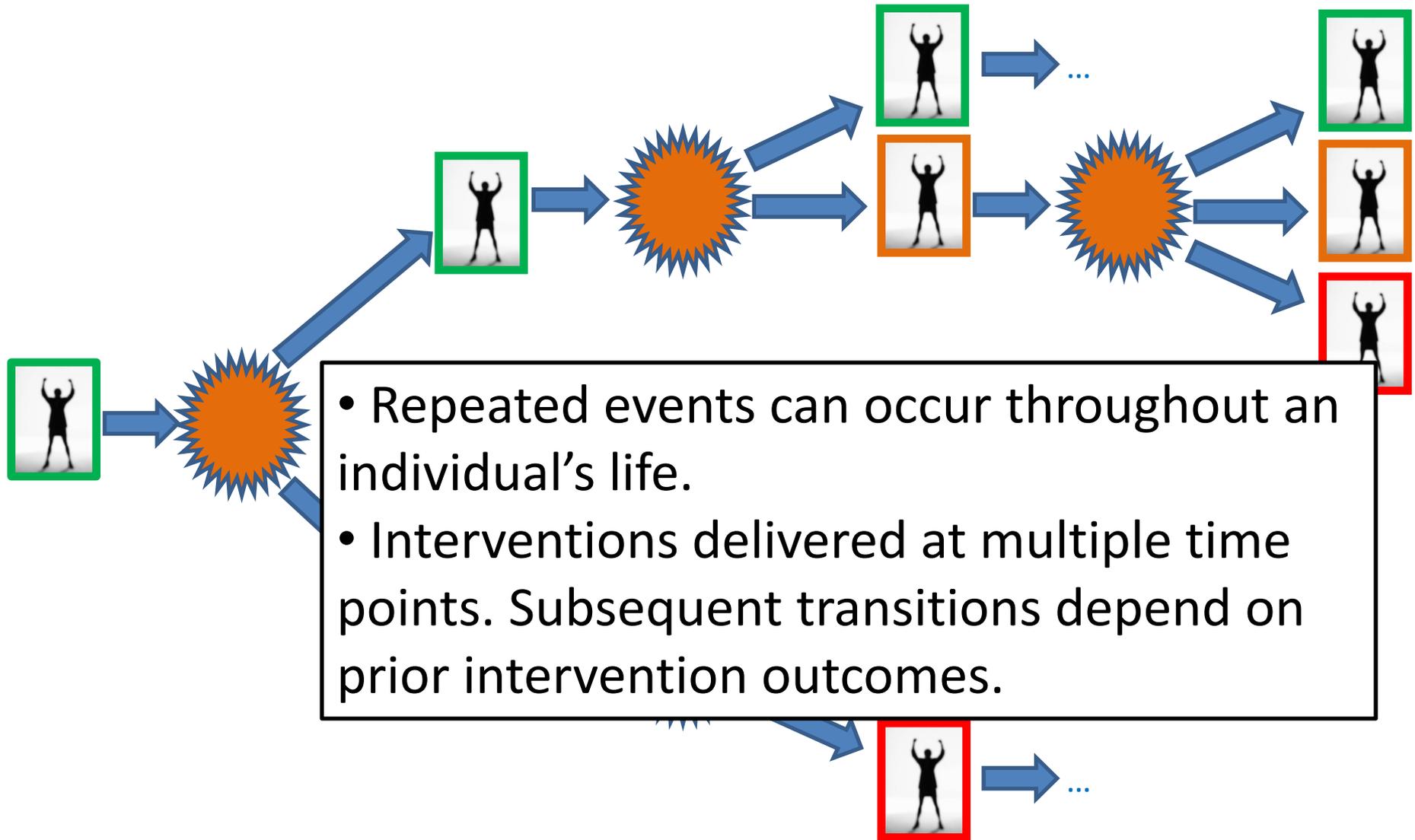
Decisions: repeated actions and/or with time-dependent events



Repeated in what sense?



Intervention (can) be delivered repeatedly too



What is a Markov Model?

- **Markov Model:** Mathematical modeling technique, derived from matrix algebra, that describes the transitions that a cohort of patients make among a set of mutually exclusive and collectively exhaustive health states during a series of short intervals or cycles

Properties of a Markov Model

- Individuals are always in one of a finite number of health states
- Events are modeled as transitions from one state to another
- Time spent in each health state determines overall expected outcome
 - Living longer without disease yields higher life expectancy and quality adjusted life expectancy
- During each cycle of the model, individuals may make a transition from one state to another

Constructing a Markov Model

- Define mutually exclusive health states
- Determine possible transitions between these health states
 - State transitions
 - Transition probabilities
- Determine clinically valid cycle length

Cycle Length

- Short enough that for a given disease being modeled the chance of two events/transitions occurring in one cycle is essentially 0
 - Many applications: weekly or monthly
 - Some (e.g., ICU) may hourly or daily

Natural history disease model: health states

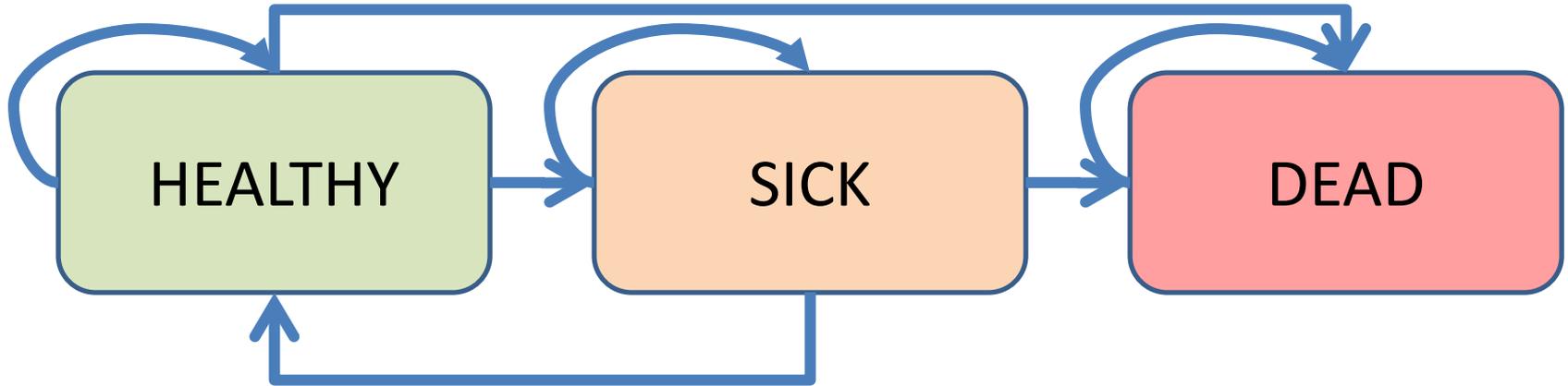
HEALTHY

SICK

DEAD

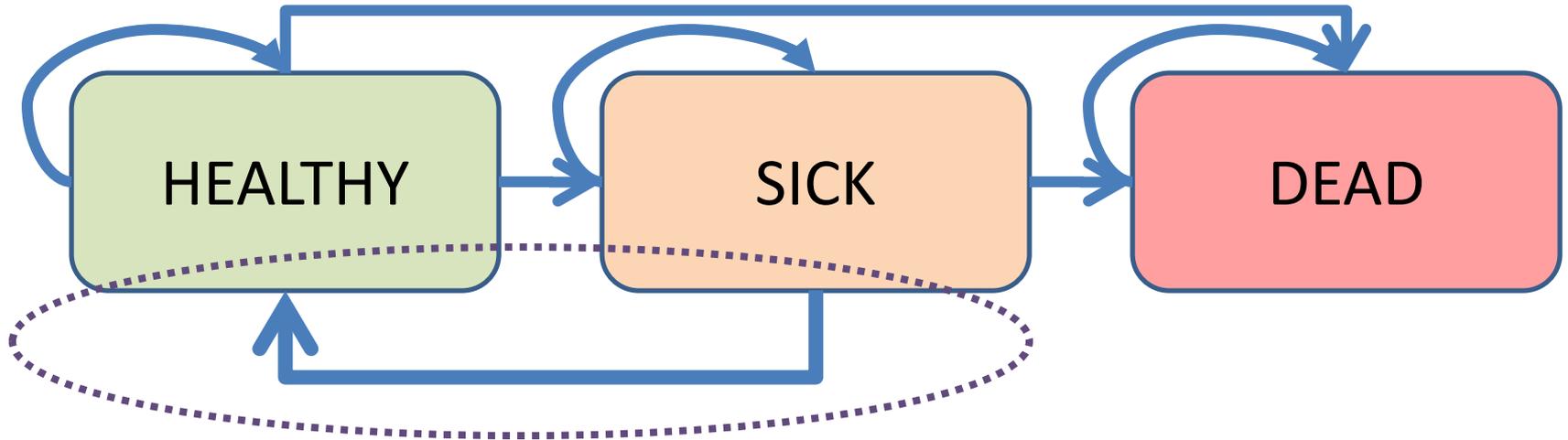
- Mutually exclusive and collectively exhaustive health states
- Best defined by actual biology/pathophysiology
- Markovian assumptions:
 - Homogeneity: All individuals in the same state have the same costs, quality of life, risks of transition
 - Memorilessness: The current state determines future risks
 - **Note: Stratification and tunnel states used to ensure Markov assumptions hold (advanced topic)**

Natural history disease model: transitions



- Transitions between health states (arrows)
- The proportion that do not transition stay in current state
- Risk of death at all times and from all states!
- If no transition out of a state = absorbing state (i.e., death)

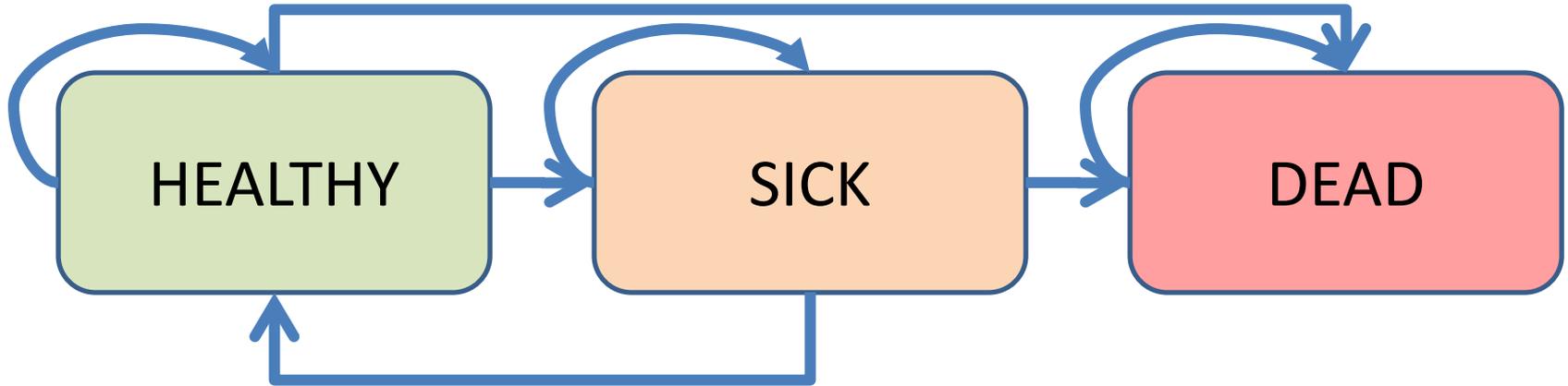
Natural history disease model: time and matrix representation



p_{HH}	p_{SH}	0
p_{HS}	p_{SS}	0
p_{HD}	p_{SD}	1

For example p_{SH} is the Probability of going from Sick to Healthy

Natural history disease model: time and matrix representation

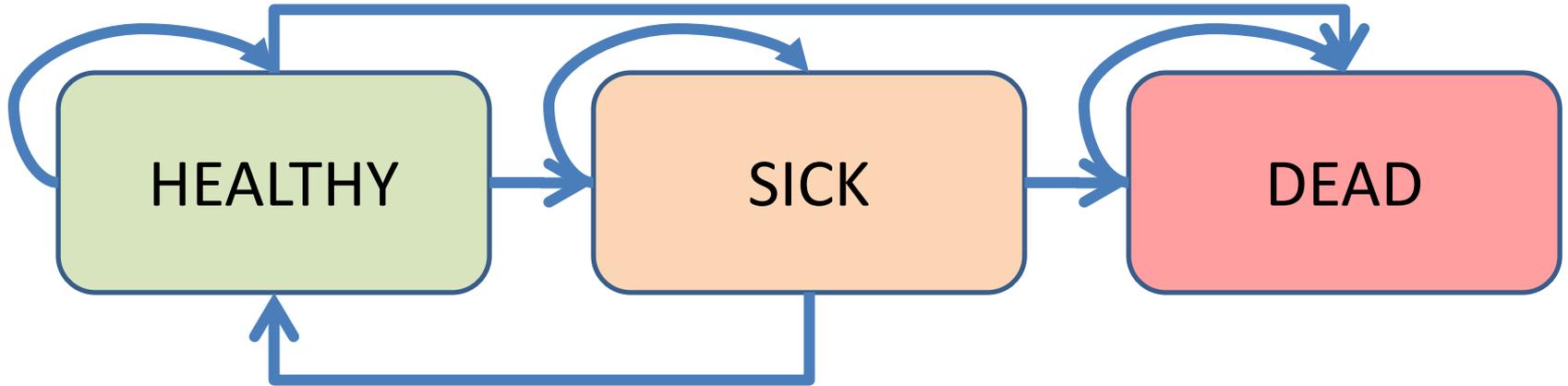


$$\begin{pmatrix} p_{HH} & p_{SH} & 0 \\ p_{HS} & p_{SS} & 0 \\ p_{HD} & p_{SD} & 1 \end{pmatrix} \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}$$

time=t

At time t, cohort has proportions in various states (Sum to 1!)

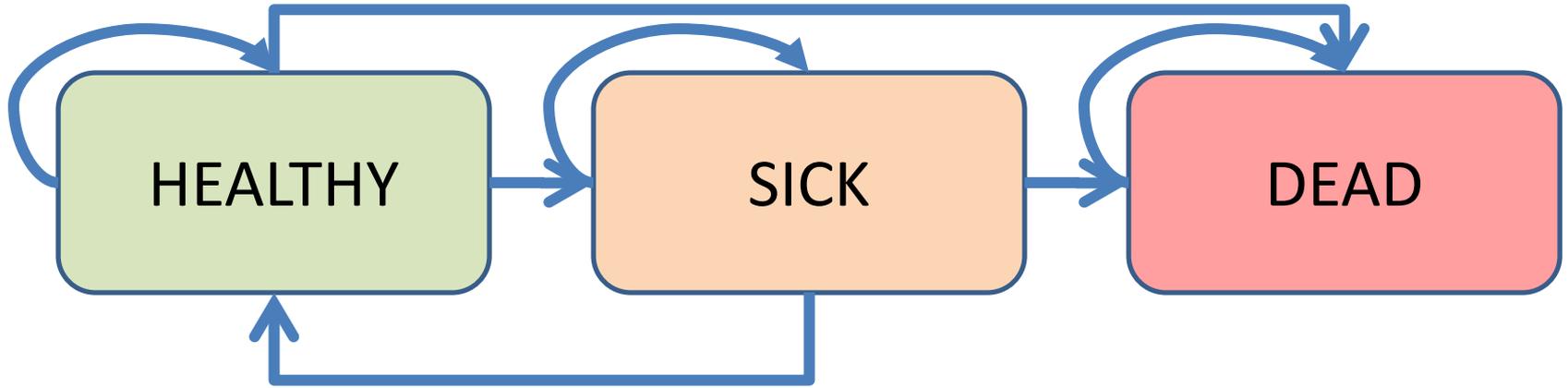
Natural history disease model: time and matrix representation



$$\begin{pmatrix} p_{HH} & p_{SH} & 0 \\ p_{HS} & p_{SS} & 0 \\ p_{HD} & p_{SD} & 1 \end{pmatrix} \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time}=t} = \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time}=t+1}$$

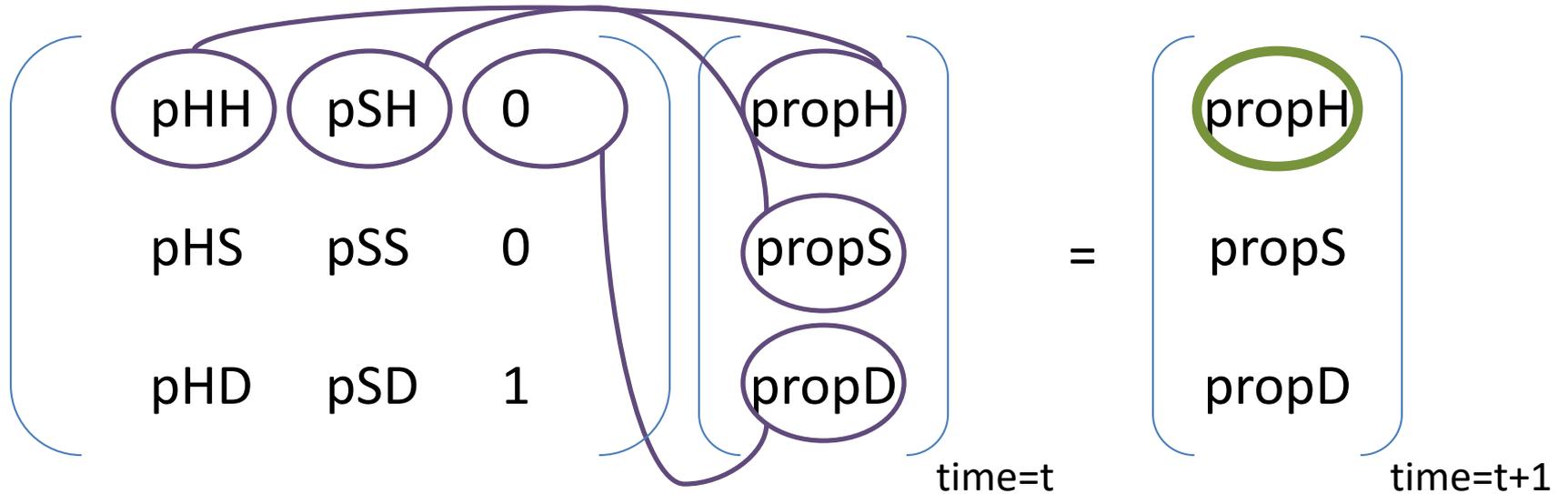
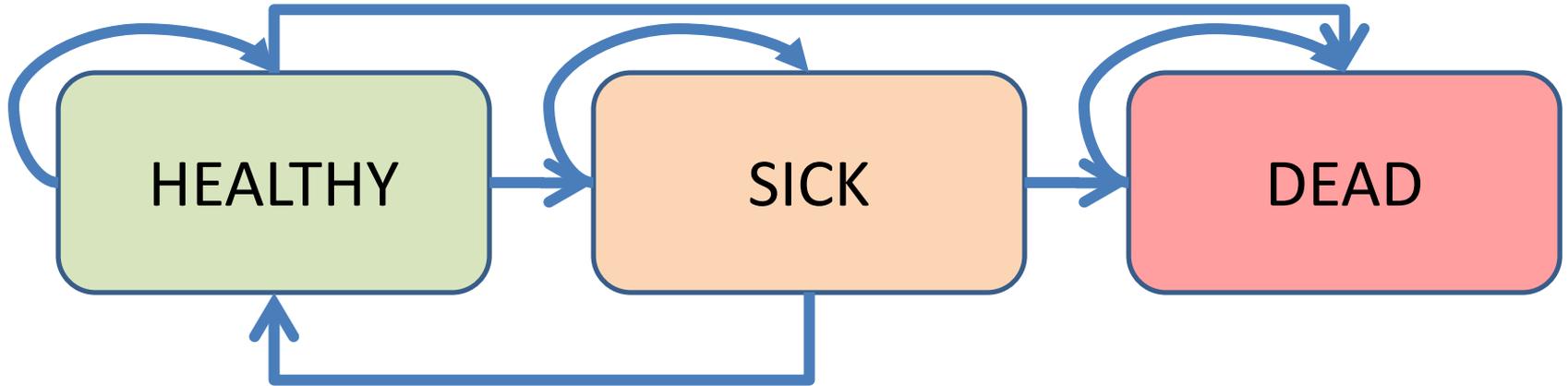
NOTE: transition probabilities can be time dependent as well

Natural history disease model: time and matrix representation

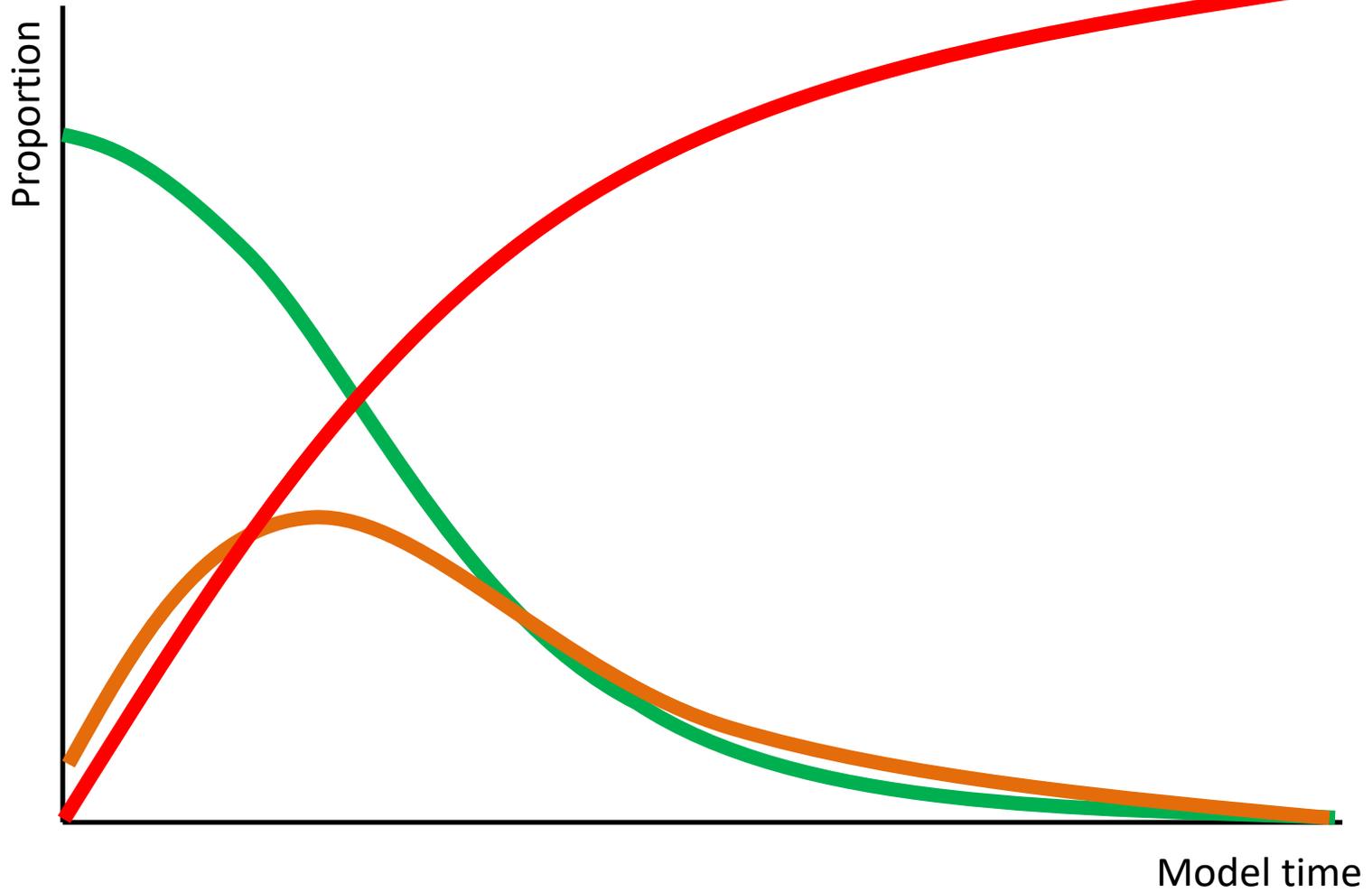


$$\begin{pmatrix} p_{HH} & p_{SH} & 0 \\ p_{HS} & p_{SS} & 0 \\ p_{HD} & p_{SD} & 1 \end{pmatrix} \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time}=t} = \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time}=t+1}$$

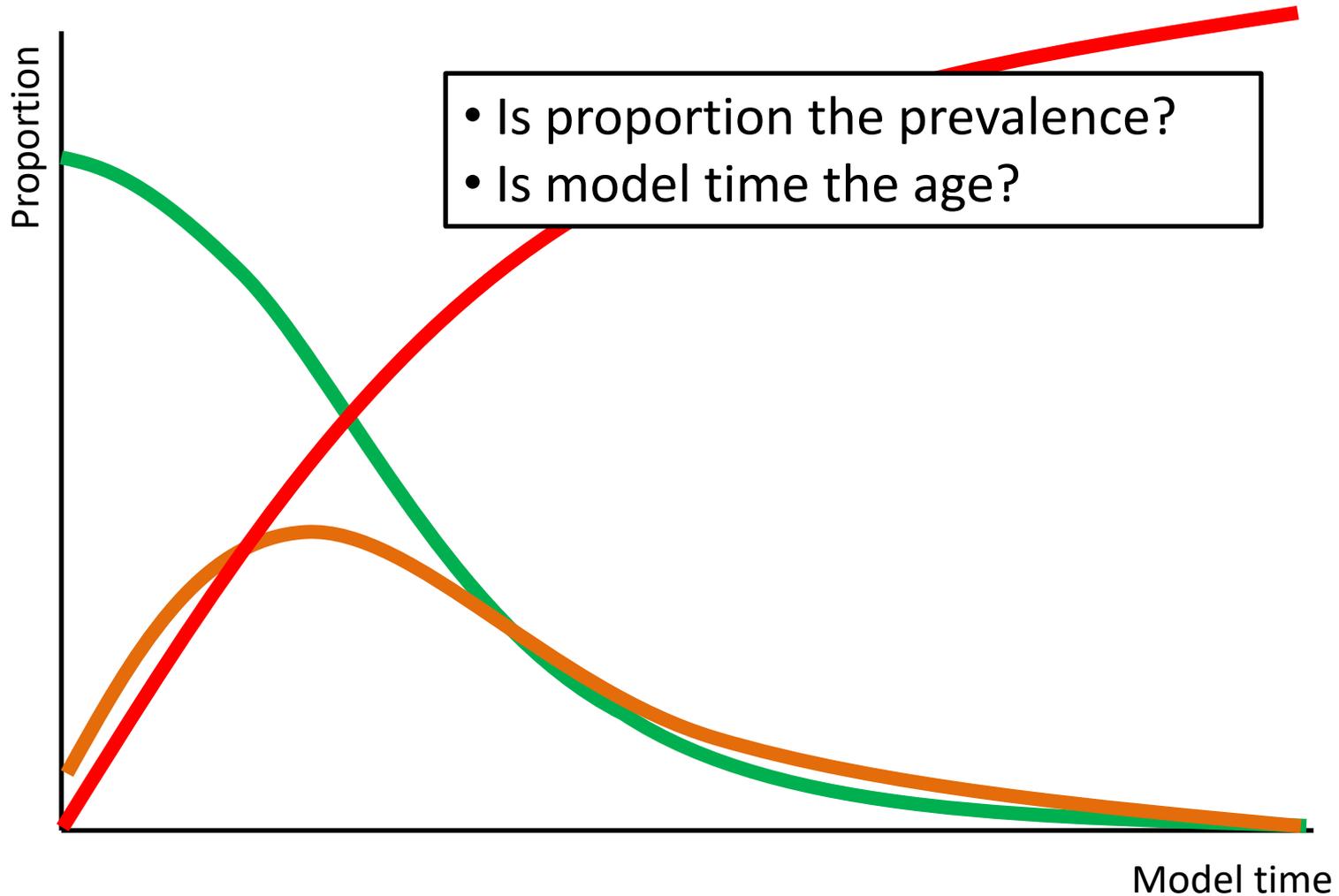
Natural history disease model: time and matrix representation



Model trace



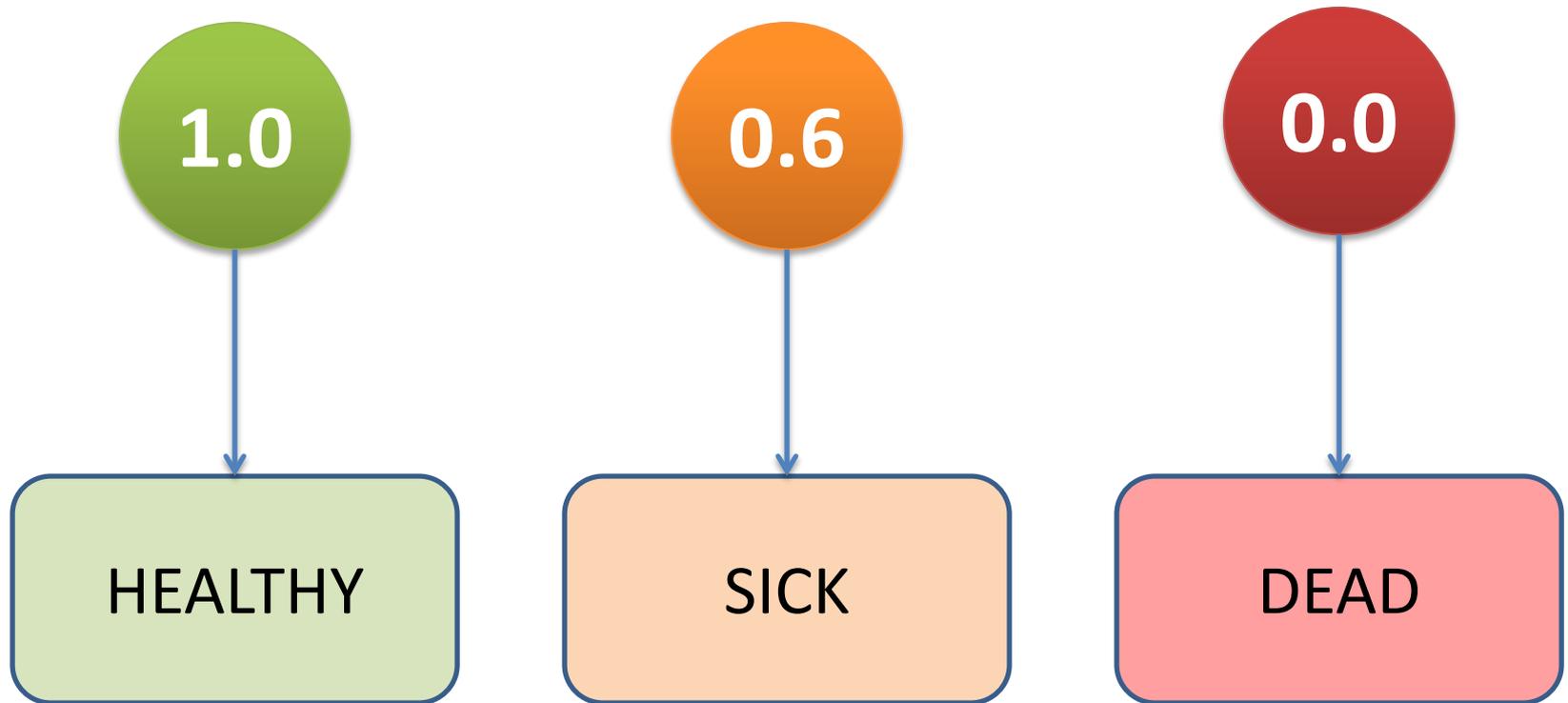
Model trace



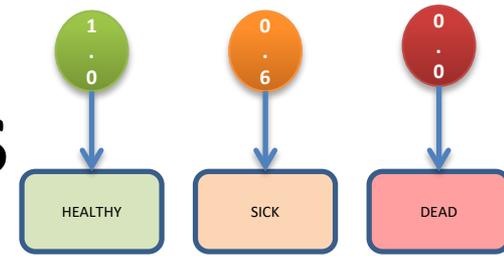
Underlying the trace

Stage	propH_t	propS_t	propD_t	NotD
0	1.00	0.00	0.00	1.00
1	0.90	0.09	0.01	0.99
2	0.75	0.10	0.15	0.85
3	0.50	0.25	0.25	0.75
4	0.20	0.40	0.40	0.60
5	0.10	0.30	0.60	0.40
6	0.05	0.15	0.80	0.20
7	0.00	0.00	1.00	0.00

Quality Adjusted Life Years (QALYS) & quality-of-life weights



Valuing outcomes

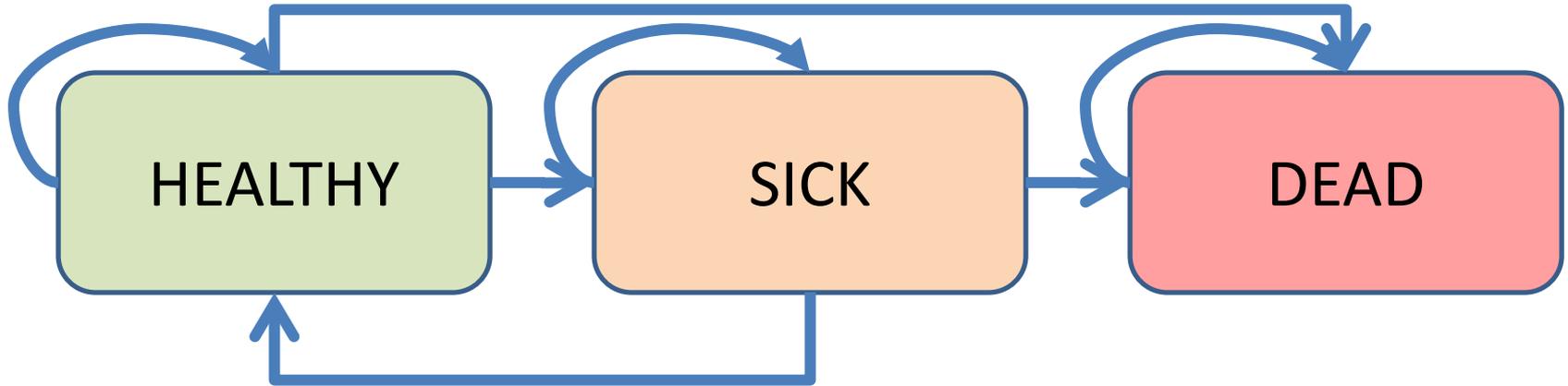


Stage	propH_t	propS_t	propD_t	NotD
0	1.00	0.00	0.00	1.00
1	0.90	0.09	0.01	0.99
2	0.75	0.10	0.15	0.85
3	0.50	0.25	0.25	0.75
4	0.20	0.40	0.40	0.60
5	0.10	0.30	0.60	0.40
6	0.05	0.15	0.80	0.20
7	0.00	0.00	1.00	0.00

$$QALYs = \sum_{t=0}^T [(propH_t * qH) + (propS_t * qS) + (propD_t * 0)]$$

$$COSTs = \sum_{t=0}^T [(propH_t * cH) + (propS_t * cS) + (propD_t * 0)]$$

Interventions?

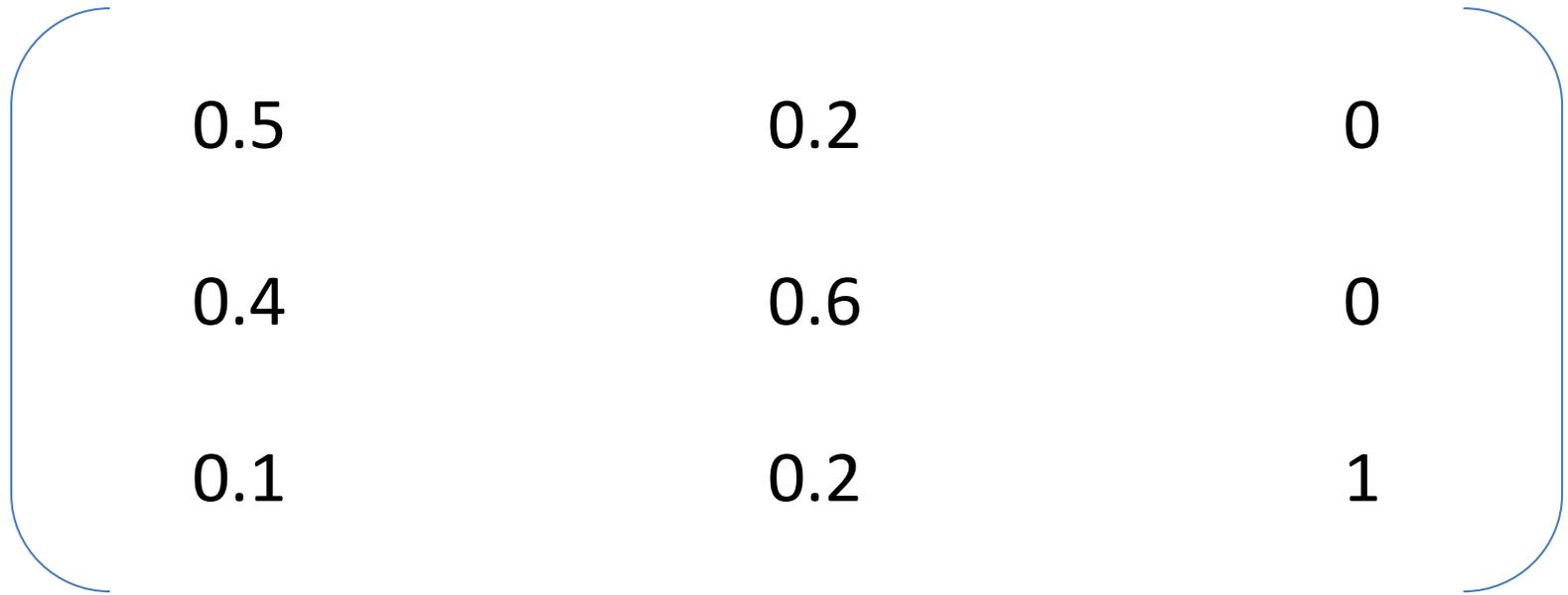


$$\begin{pmatrix} p_{HH} & p_{SH} & 0 \\ p_{HS} & p_{SS} & 0 \\ p_{HD} & p_{SD} & 1 \end{pmatrix} \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time=t}} = \begin{pmatrix} \text{propH} \\ \text{propS} \\ \text{propD} \end{pmatrix}_{\text{time=t+1}}$$

Screening before treatment

- Screening 70% sensitivity, 100% specific
- Treatment 90% effective
- Intervention occurs after natural hx transitions every cycle
- Calculations
 - $pHS_i = pHS*(0.3) + pHS*(0.7*0.1)$
 - $pSS_i = pSS*(0.3) + pSS*(0.7*0.1)$
 - $pSH_i = pSH + pSS*(0.7*0.9)$
 - $pHH_i = pHH + pHS*(0.7*0.9)$

Natural History



0.5	0.2	0
0.4	0.6	0
0.1	0.2	1

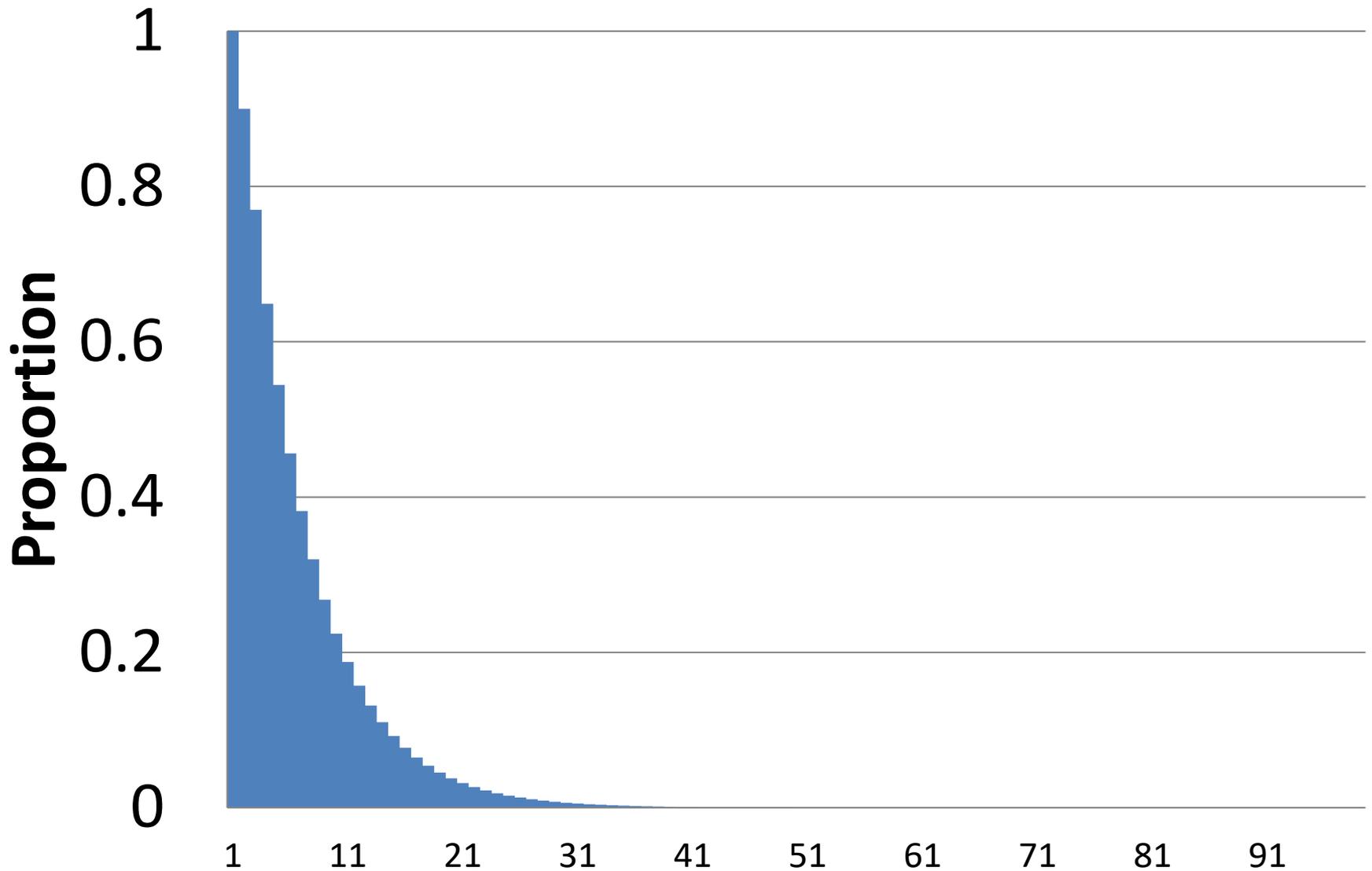
Screening before treatment

pHH_i	pSH_i	0
pHS_i	pSS_i	0
pHD	pSD	1

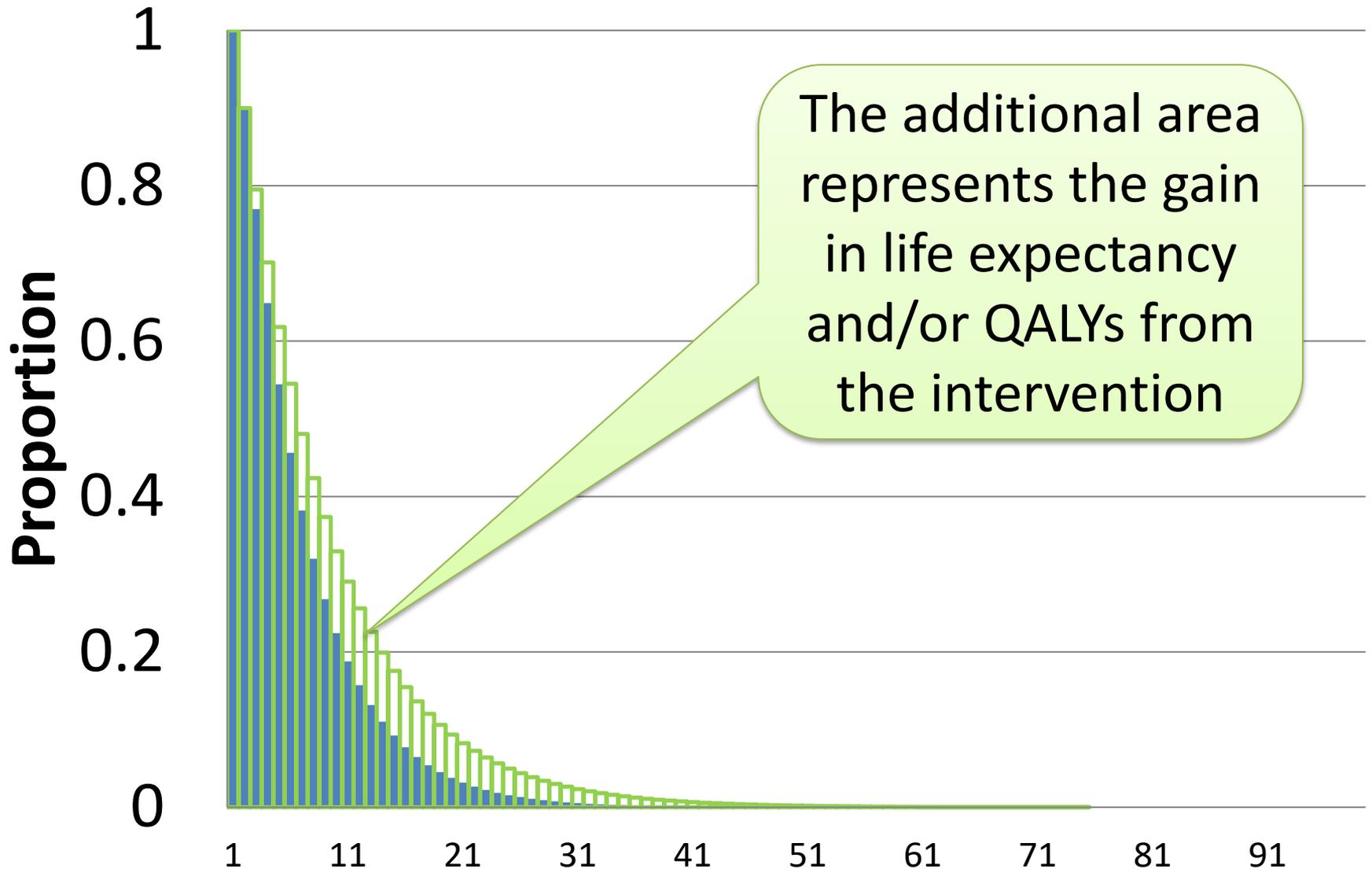
Screening before treatment

0.752	0.222	0
0.148	0.578	0
0.100	0.200	1

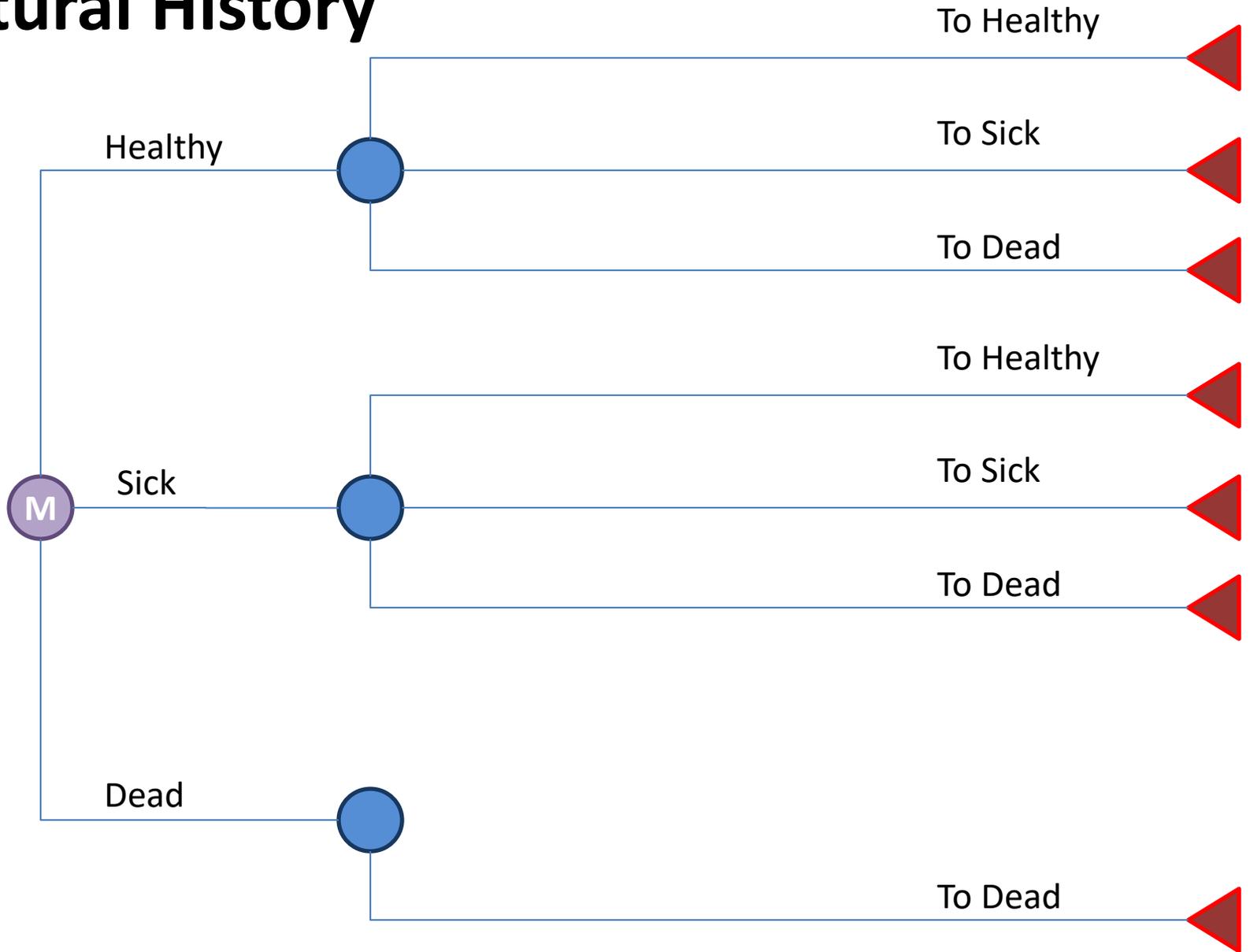
With and w/o intervention



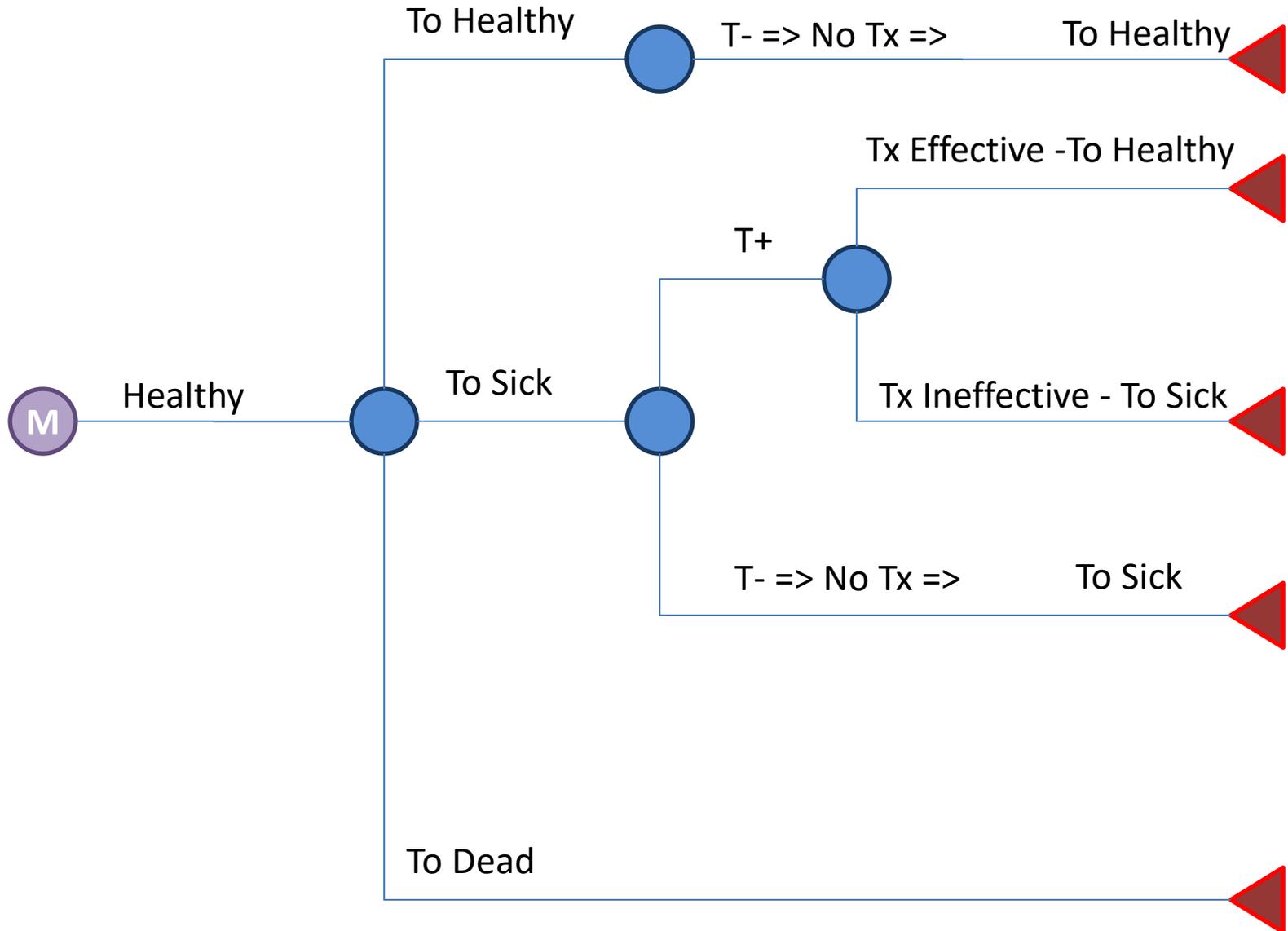
With and w/o intervention



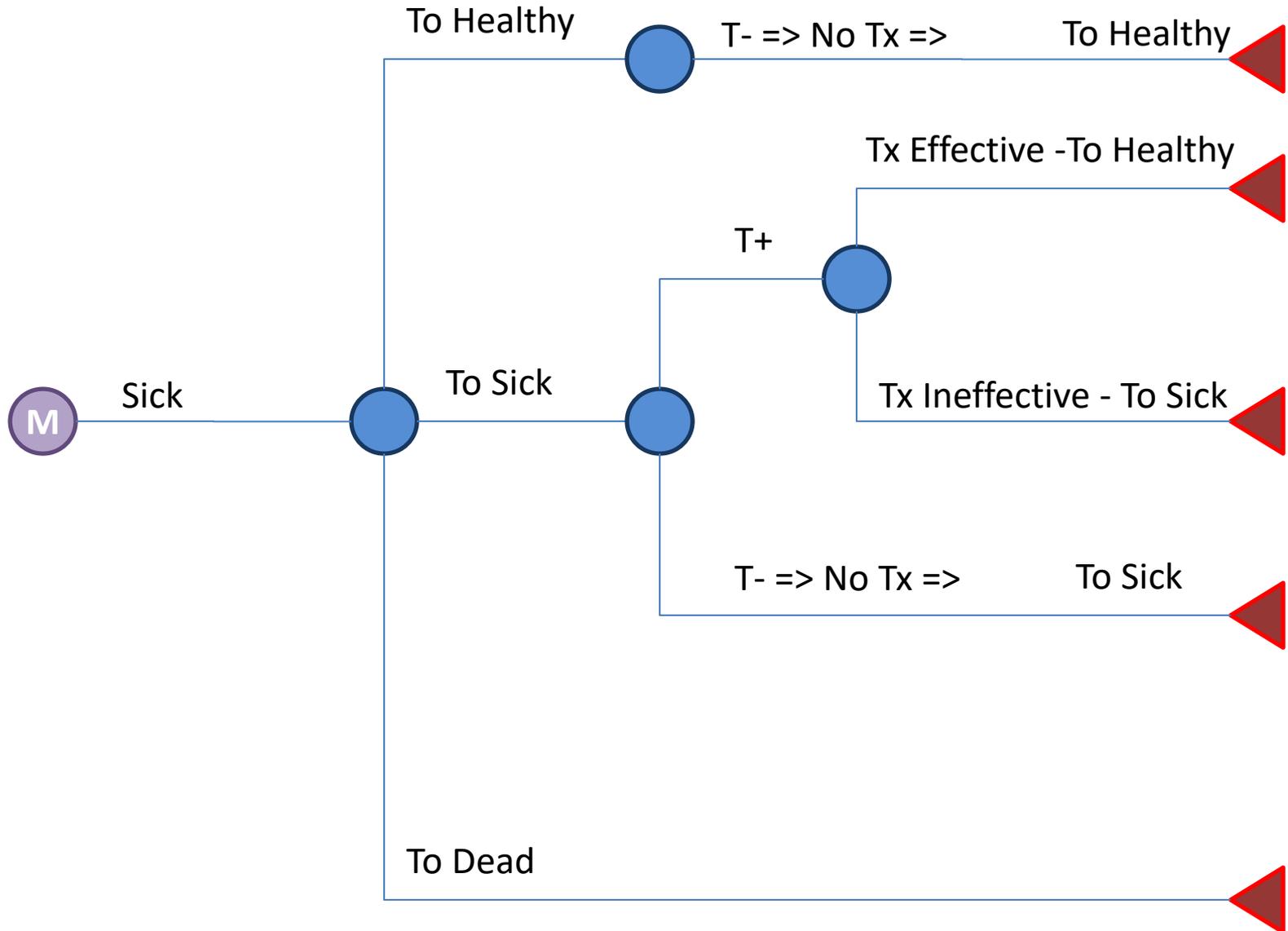
Natural History



Intervention



Intervention



Cohorts vs. individuals

Deterministic vs. stochastic

- Markov cohort model (i.e., the matrix version) is smooth model (infinite population size) of the proportion of a cohort in each state at each time
- Can use same structure to simulate many individuals (first-order Monte Carlo) (simple microsimulation)
- The matrix entries become the probabilities of an individual transition from one state to another instead of the % of those in a given state who deterministically flow into another state

Microsimulation

Healthy Sick Dead

0



1



2



3



4



5



Microsimulation

Healthy Sick Dead

0



pHS

1



pSS

2



pSH

3



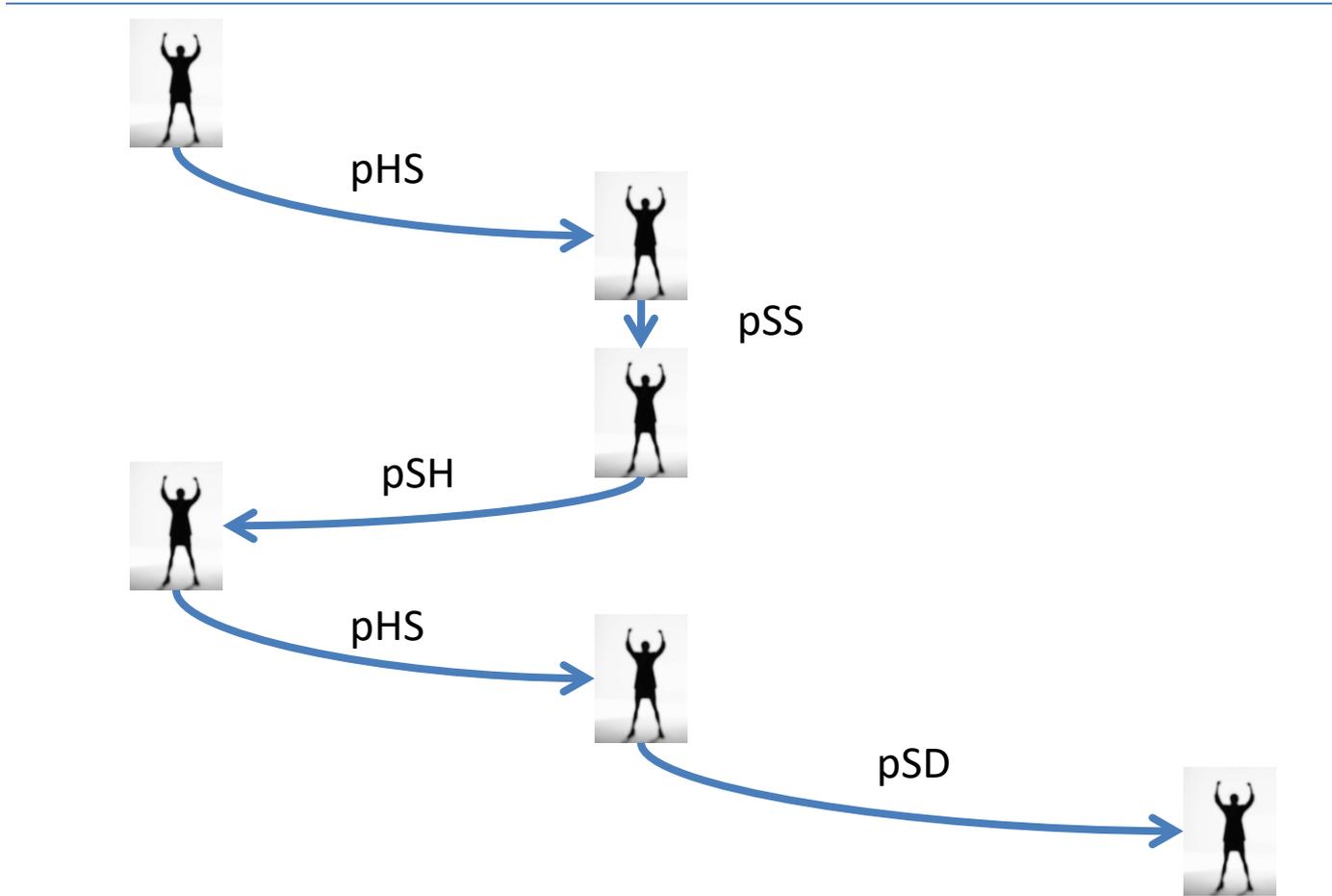
pHS

4



pSD

5



Microsimulation

Healthy

Sick

Dead

0



1



2



3



4



5



Microsimulation

Healthy

Sick

Dead

0



1



2



3



4



5



Recall the trace and calculation of outcomes from it

Stage	propH_t	propS_t	propD_t	NotD
0	1.00	0.00	0.00	1.00
1	0.90	0.09	0.01	0.99
2	0.75	0.10	0.15	0.85
3	0.50	0.25	0.25	0.75
4	0.20	0.40	0.40	0.60
5	0.10	0.30	0.60	0.40
6	0.05	0.15	0.80	0.20
7	0.00	0.00	1.00	0.00

$$QALYs = \sum_{t=0}^T [(propH_t * qH) + (propS_t * qS) + (propD_t * 0)]$$

$$COSTs = \sum_{t=0}^T [(propH_t * cH) + (propS_t * cS) + (propD_t * 0)]$$

Microsimulation

- Run with many individuals
- Calculate proportions in each state at each time (just like in our Markov cohort table)
 - Stage 2: 5100 sick / 100,000 people = 5.1%
- Approximates the “smooth” cohort version
 - 5.1% [CI] is \approx 5.0% in “smooth” cohort
 - **Advanced**
 - Larger the number of individuals the closer to the smooth cohort (tighter the CI)
 - See Kuntz/Weinstein chapter of Michael Drummond’s book on Economic Evaluation for more on this for more on this

Why consider microsimulation?

- It requires longer simulation times
- It is more complex
- Fewer people are familiar with it
- There is “Monte Carlo” noise (random error) even with simulating fairly large groups of individuals (at least for rare events)

State explosion!

- Suppose you want to use a Markov model of a disease with 2 states and death (H,S,D)
- Suppose you need it stratified by sex and smoking status (3 levels), BMI (4 levels), hypertension (4 levels)
- Now you need $2 \times 3 \times 4 \times 4 \times 2$ states (death is not stratified) = 192 states
- What if you need to stratify states by past history? (previous high hypertension, used to be obese) or Tx history (has a stent)?

Microsimulation as alternative

- Simulate 1 individual at a time
- Assign a set of attributes to the individual
 - Sex=M, Smoking=Y, BMI=Overweight, HT=Y
- Define a function for the probability of transitioning from H to S
 - $P(H \text{ to } S \mid \text{Sex, Smoking, BMI, HT})$
- Have functions for changing attributes
 - $P(\text{BMI=Obese} \mid \text{Sex, BMI})$
- Track previous health states
 - $P(H \text{ to } S \mid \text{Sex, Smoking, BMI, HT, } S \text{ in the past})$
- **Note: Could estimate these functions from logistic regressions**

Sage advice I have heard

- Know what information your consumers need
- Pick a model that is as simple as possible ... but no simpler
- Know the limits of what your model does and make statements within those limits – All research studies have limitations

Summary:

Medical Decision Analysis

- Clearly defines alternatives, events, and outcomes
- Formal method to combine evidence
- Can prioritize information acquisition
- Can help healthcare providers to make medical decisions under uncertainty

Classic sources on about decision analysis and modeling

- Sox HC, Blatt MA, Higgins MC, Marton KI (1988) Medical Decision Making. Boston MA: Butterworth-Heinemann Publisher.
- Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Parts 1-5. Med Decis Making. 1997;17(2):123-159.
- Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13(4):322-38.
- Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making. 1983;3(4):419-458.
- Society for Medical Decision Making (<http://www.smdm.org>)

A photograph of the Stanford University Main Quad at dusk. The central building, the Sather Gate, is illuminated with warm lights, and its facade is visible. The quad is a large, green lawn with a central path leading to the building. The sky is a mix of blue and orange, suggesting sunset. Palm trees are visible in the background.

THANK YOU

Jeremy Goldhaber-Fiebert
(jeremygf@stanford.edu)

HEALTH
POLICY
STANFORD

CENTER FOR HEALTH POLICY/
CENTER FOR PRIMARY CARE AND OUTCOMES RESEARCH