Clinical Decision Science: Informing Decision-Making Under Uncertainty

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3915 Course

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Overview

- Review of cost-effectiveness analysis
- Decision analysis introduction
- Framework for decision analysis
  - Decision Trees
  - Markov (cohort-based) models
    - Key concepts including health states, transition probabilities, half-cycle correction, discounting
    - Sensitivity analysis
  - Micro-simulation (individual-based) models
- 11/7: Clinical decision science as applied to cancer prevention/treatment examples:
  - Optimal (cost-effective) treatment of early-stage breast cancer for maximum survival and quality of life effect/benefits
  - Long-term impact of HPV vaccination on oral HPV infection and oropharyngeal cancer

CEA Overview (Review)

How much value for money invested will be received?

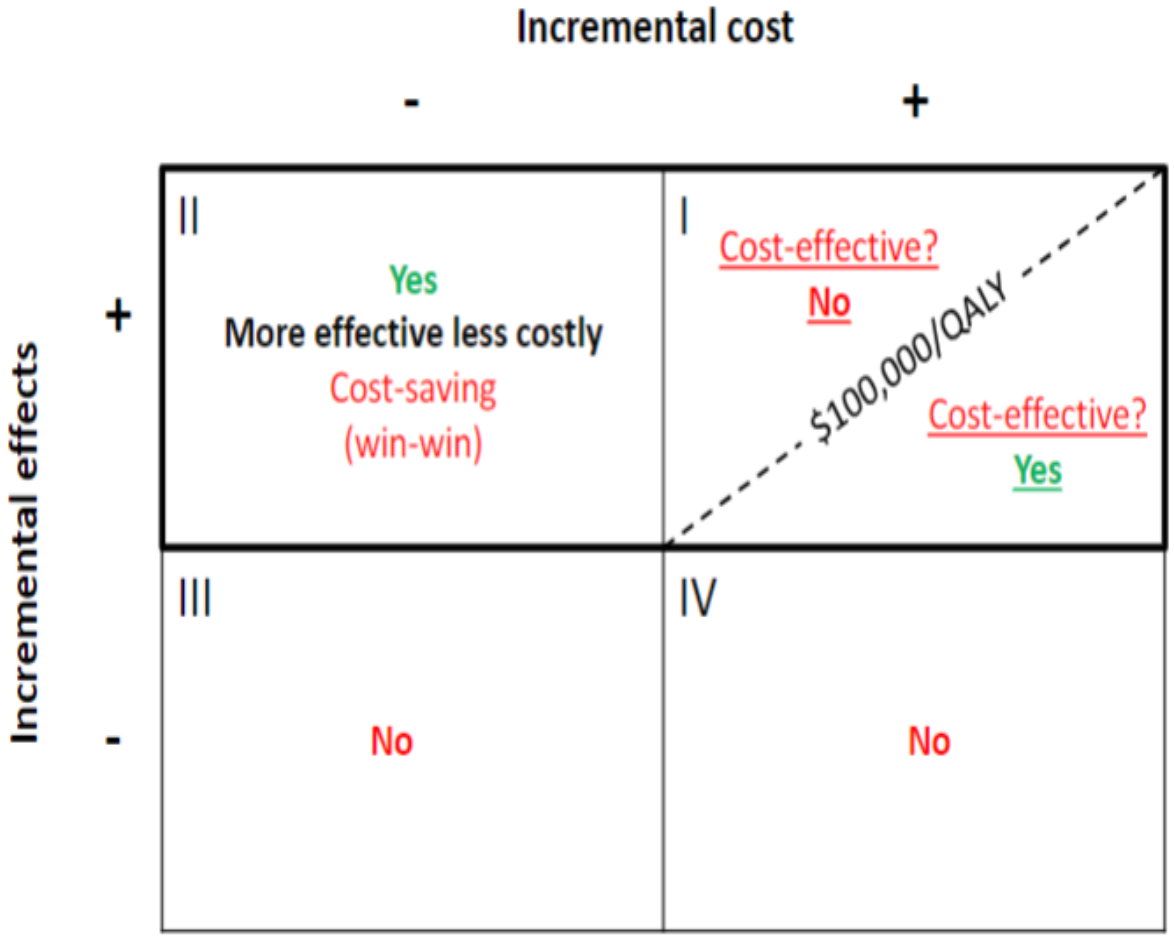
2 components (money & value)

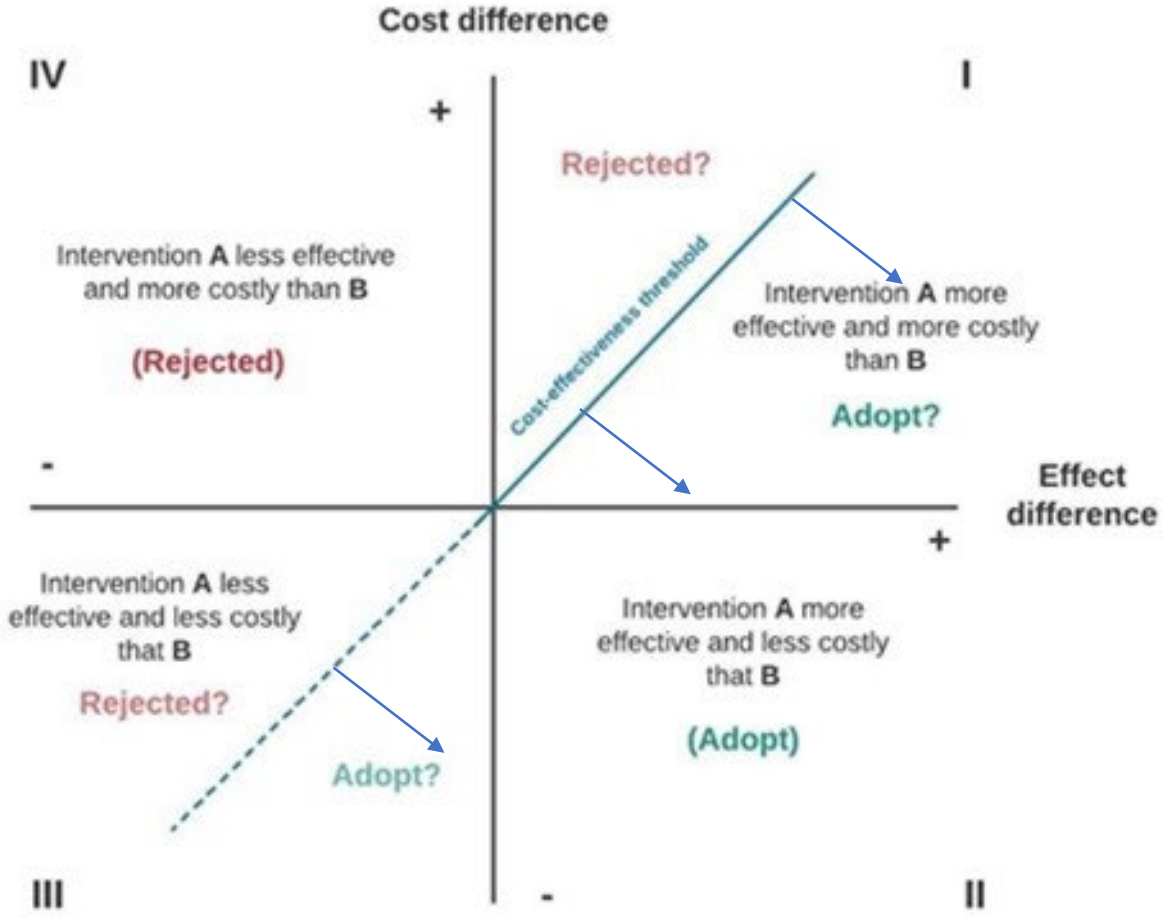
How do we measure?

Money = net resources consumed in providing alternative ($)

Value = improvement in health outcomes (life-years, QALYs)

Cost-Effectiveness Analysis Schematic



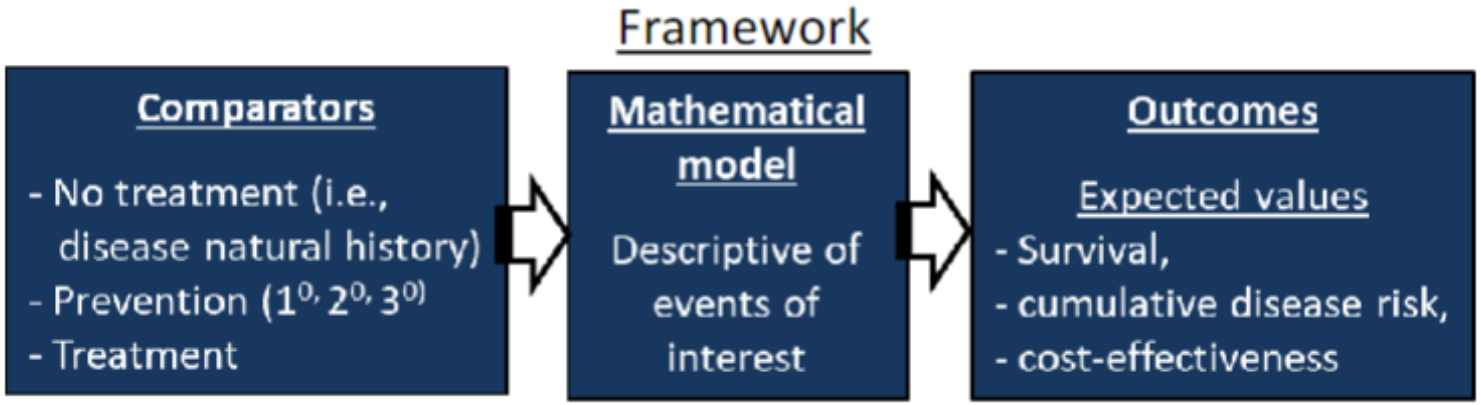


CEA Review Continued

- ICER = $\frac{Cost_{alternative} - Cost_{status\ quo}}{Effect_{alternative} - Effect_{status\ quo}}$
- Use literature-defined standard of willingness-to-pay (WTP) threshold
  - Dependent upon country, disease, and time
  - In U.S., we use $100,000/QALY (older papers may use $50,000 and newer papers use up to $150,000)
- Cost-effective if ICER < WTP threshold
- Cost-saving (best scenario: alternative absolutely dominates) if:
  - $Cost_{alternative} < Cost_{status\ quo}$
  - $QALY_{alternative} > QALY_{status\ quo}$

Clinical Decision Science

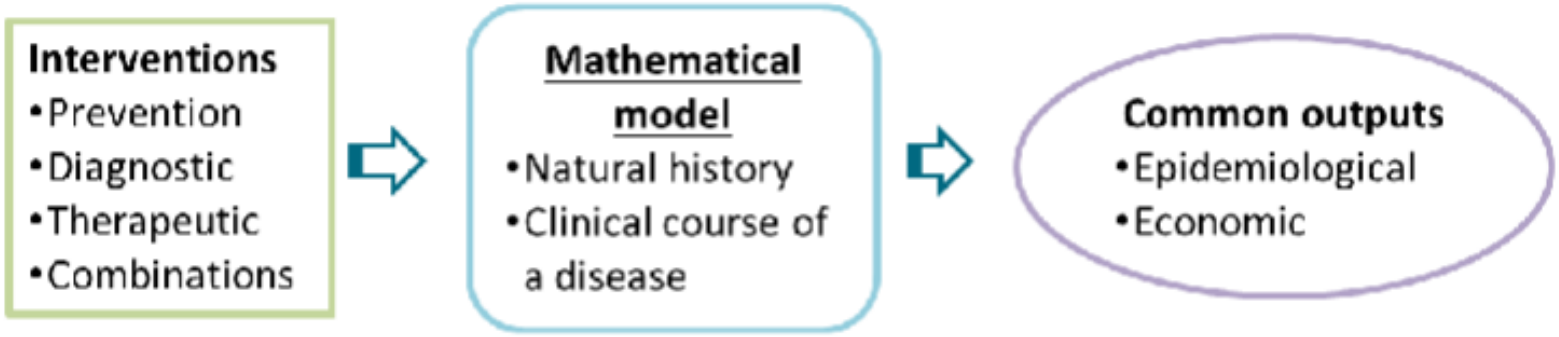
- A quantitative method for evaluating decisions between multiple alternatives under conditions of uncertainty
  - Is this like real life?



- Why use decision science analytics?
  - To **project** the future effects (and costs) of an intervention vs. status-quo
  - When it is **unethical or impractical** to run a clinical trial

Decision Science Modeling

- Mathematical model framework



- Disease natural history: disease progression without intervention
- Clinical course of disease: Disease prognosis and treatment outcomes after disease is initially diagnosed
- Epidemiological outcomes: Disease prevalence, incidence, burden
- Economic outcomes: Resource utilization for disease treatment, lifetime costs of treatment, cost-effectiveness, QALYs gained

Decision Analysis Framework

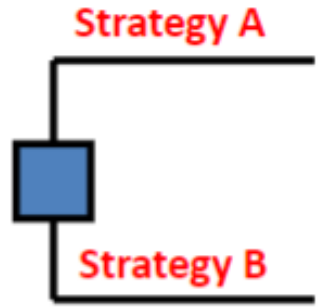
- For decision analysis, you combine evidence for different parameters from different sources into one analytical model
  - Parameters:
    - Disease progression/risk (health state transition probabilities)
    - Treatment efficacy/effectiveness
    - Adverse side-effects of treatment, including death probability
    - Quality of life (health utilities) for different health states or outcomes
    - Costs (direct and indirect)
  - Sources for data:
    - Epidemiological studies on the natural history of disease
    - RCTs
    - Systematic reviews, pooled analyses, meta-analyses
    - Clinical trials
    - Observational studies
    - Pharmacological studies
    - Quality-of-life studies
    - Resource utilization studies

Decision Tree

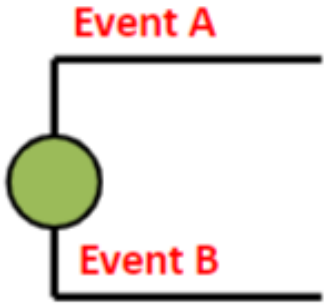
- **Simplest form** of decision model
- Represents individuals' **possible prognoses** (with or without intervention) by a series of pathways
- Useful for **short-term outcome** estimates

Decision Tree Features

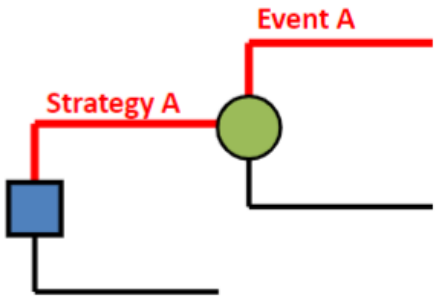
- **Square decision node**
  - Usually at start of tree
  - **Indicates decision point** between alternatives



- **Circular chance node**
  - Point where after a decision is made, there are two or more alternative outcomes (events) possible
  - Represents **uncertainty**

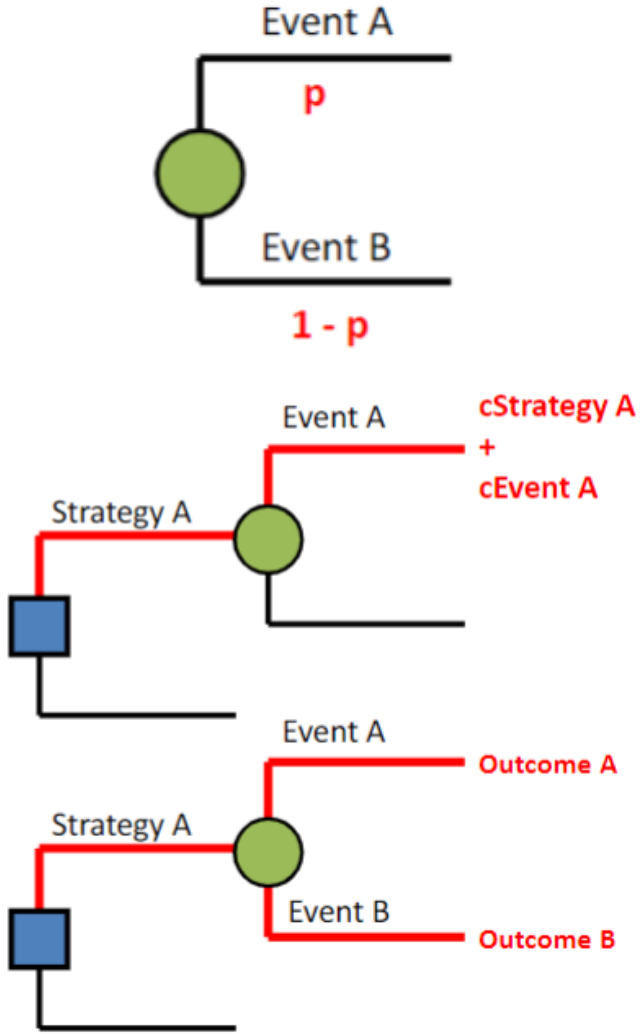


- **Pathways**
  - Mutually exclusive events that follow tree path linearly until its terminal node (outcome)



Decision Tree Features II

- Branch probabilities
  - Likelihood of event occurring at a chance node
- Pathway costs
  - Sum of costs of each event one patient experiences in a tree pathway
- Outcomes
  - Each tree pathway ends with outcome at its terminal node



Building a Decision-Analytic Model

- Define model structure
- **Assign probabilities** associated for all events at each chance node
- **Assign utility values to all outcomes in the terminal nodes** for each pathway
- **Evaluate expected values** of each decision alternative
- Conduct sensitivity analyses to account for uncertainty in analyses

Decision Tree: Application for a Clinical Question

- Question: You have been asked to assess the **cost-effectiveness of two proposed alternatives to routine practice in the follow-up of colorectal cancer survivors**
- What is our framework?
  - Specify the alternative strategies and outcomes
    - Status-quo comparator: routine care
    - Alternative 1: primary care-based follow-up approach
    - Alternative 2: hospital-based follow-up approach
    - Outcome for each strategy
      - Early detection of cancer recurrence
      - Late detection of cancer recurrence

Forming a Model for Our Research Question

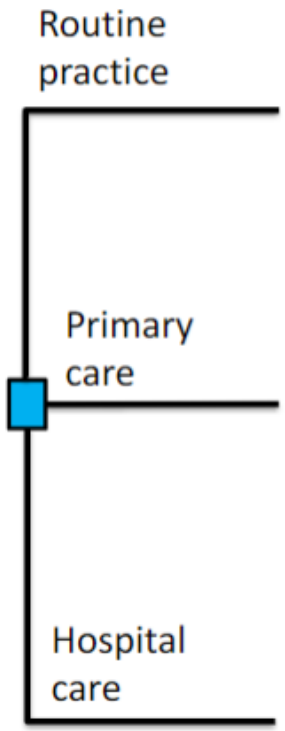
- Probabilities
  - In routine practice, the **rate** of patients with early detection of CRC recurrence is 43 out of 100 patients (0.43) in one year
    - Convert this to **probability so we can use it in the decision tree**:
    - Probability = $1 - e^{-rate*time}$ = 1 – $\exp^{(-0.43*1)}$ = **0.35**
    - Probability of late detection of cancer recurrence = 1-p, or **0.65**
  - Primary care approach: probability of early detection of cancer recurrence is 0.40 (95% CI: 0.36-0.44) based on the literature
    - Probability = **0.4**; therefore, late detection of cancer recurrence = 1- p, or **0.6**
  - Hospital-based approach: early detection cancer recurrence is 0.45
    - Probability= **0.45;** Late detection of cancer recurrence is therefore 1-0.45, or **0.55**

Model Parameters From Literature: Cost and Effectiveness of Each Tree Pathway

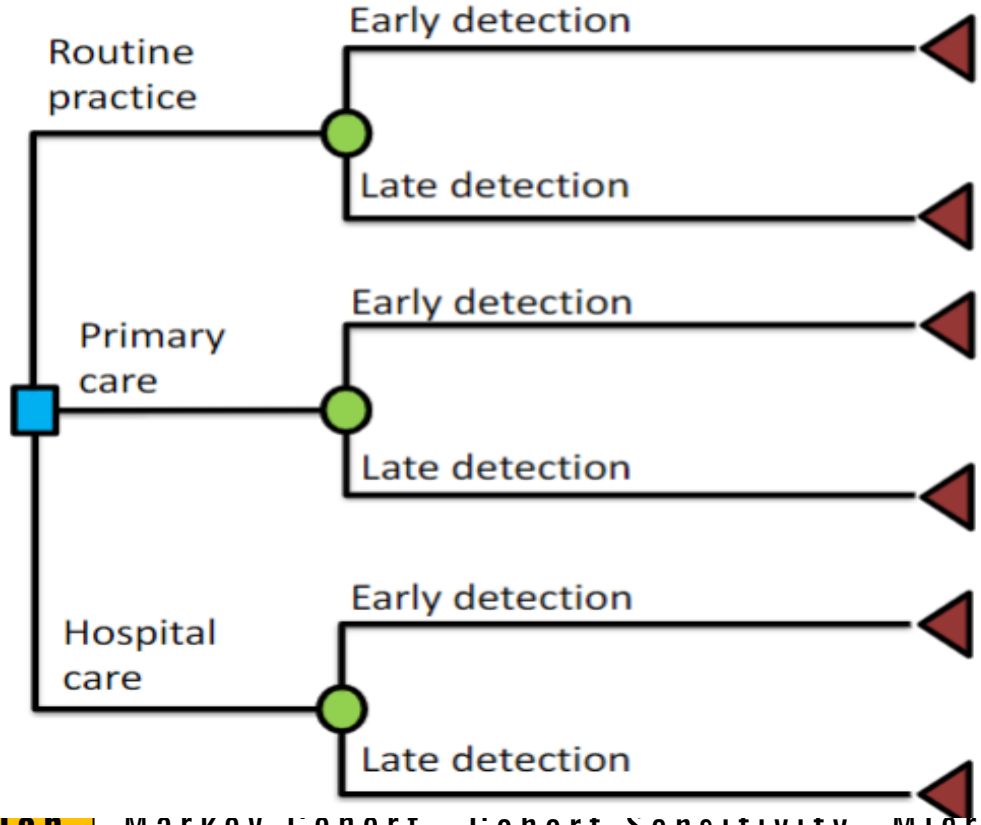
Tree pathway cost per year	
Routine practice	
Early detection	$3,030
Late detection	$12,020
Primary care based approach	
Early detection	$3,900
Late detection	$12,800
Hospital based approach	
Early detection	$6,200
Late detection	$14,400
Effectiveness (life expectancy)	
Early detection of cancer recurrence	7 years
Late detection of cancer recurrence	1.5 years

Designing the Decision Tree

- Initial decision node is what?
  - The three strategies



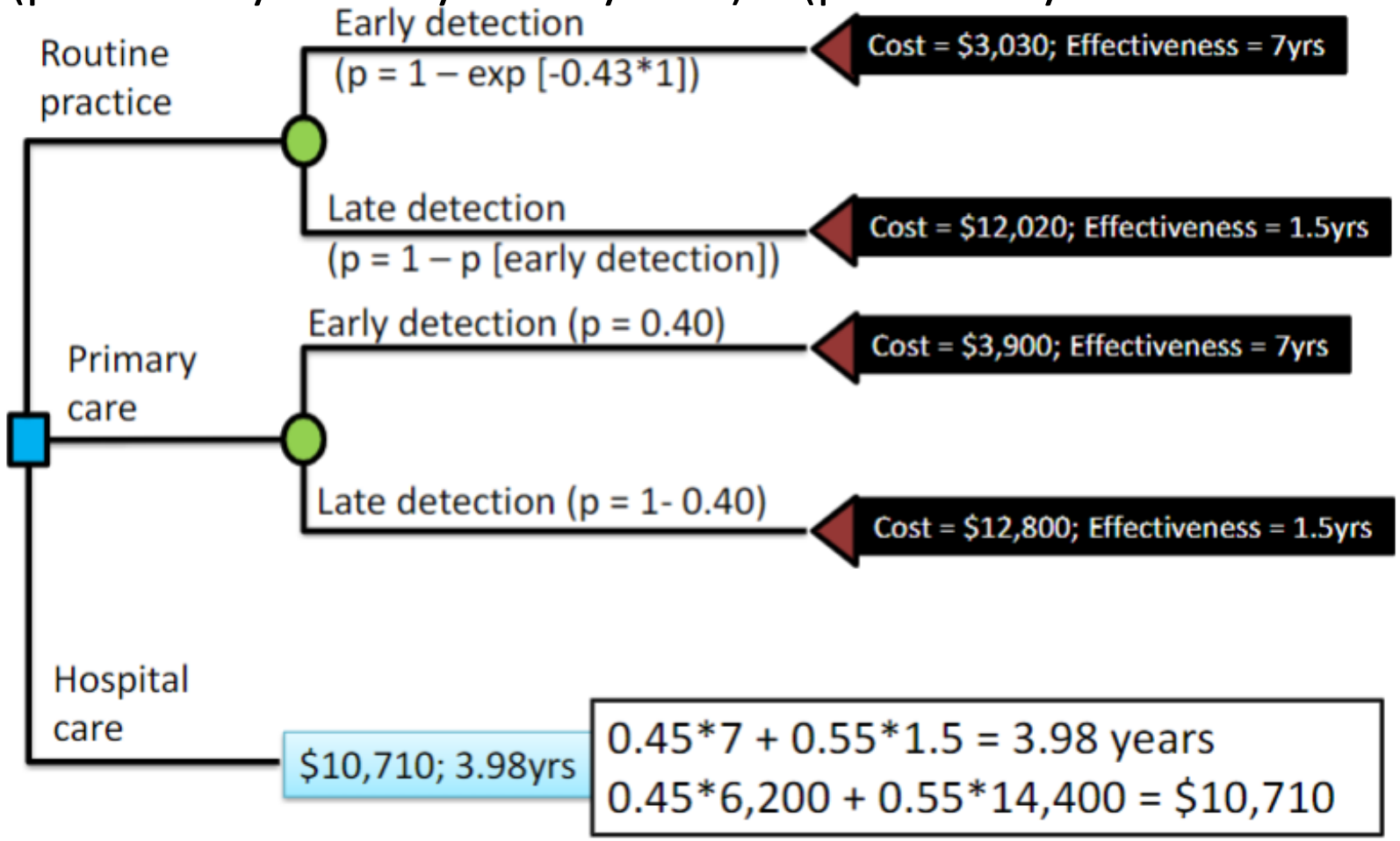
- What about the chance node?
  - The two outcomes



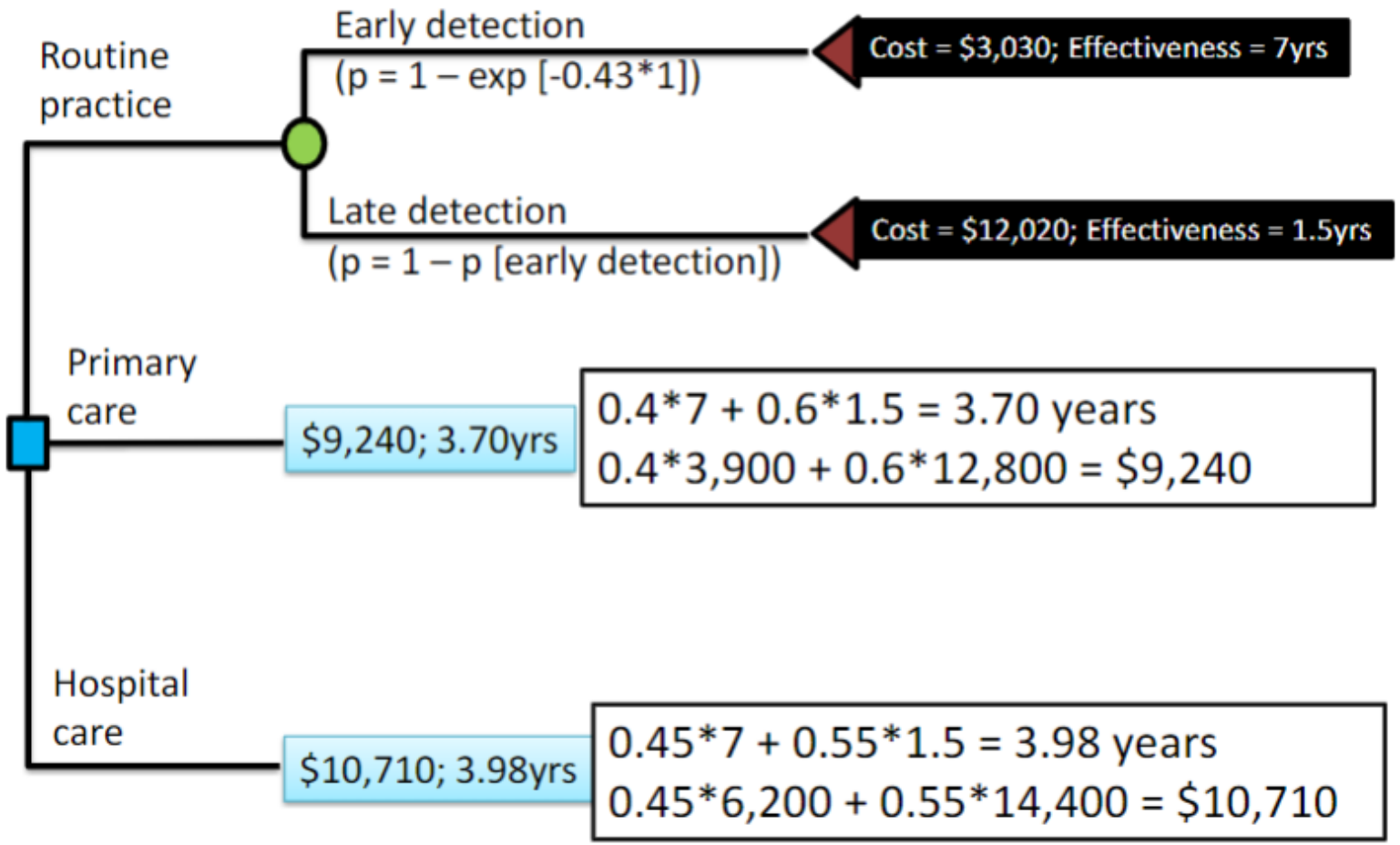
Decision Tree Model: Add Probability, Cost, and Effectiveness Parameters

Decision Tree: Average Roll-Back Analysis

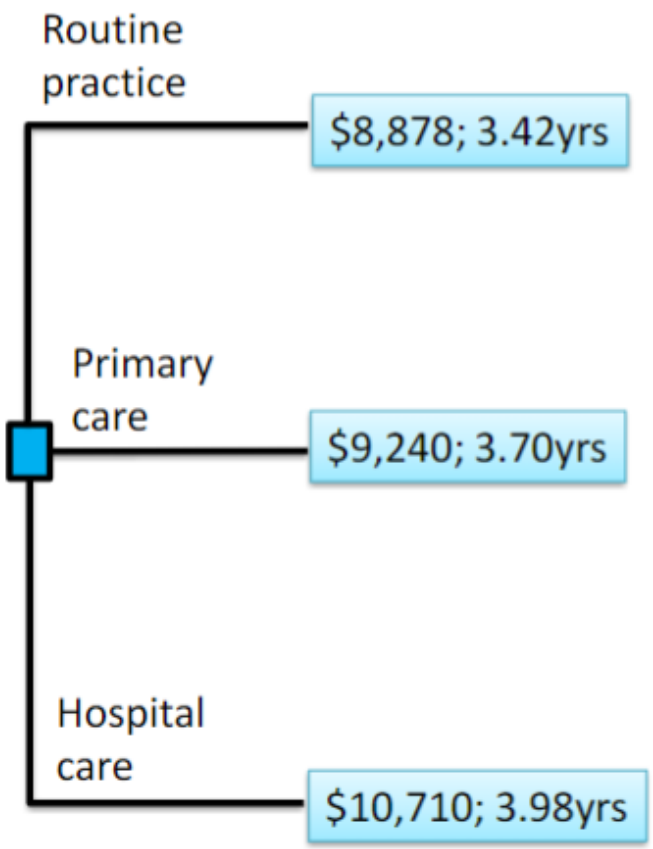
- Overall effect = (probability of early * early effect) + (probability of late * late effect)
- Overall cost = (probability of early * early cost) + (probability of late * late cost)



Decision Tree: Average Roll-Back Analysis



Decision Tree: Calculate ICER for Cost-Effectiveness Analysis



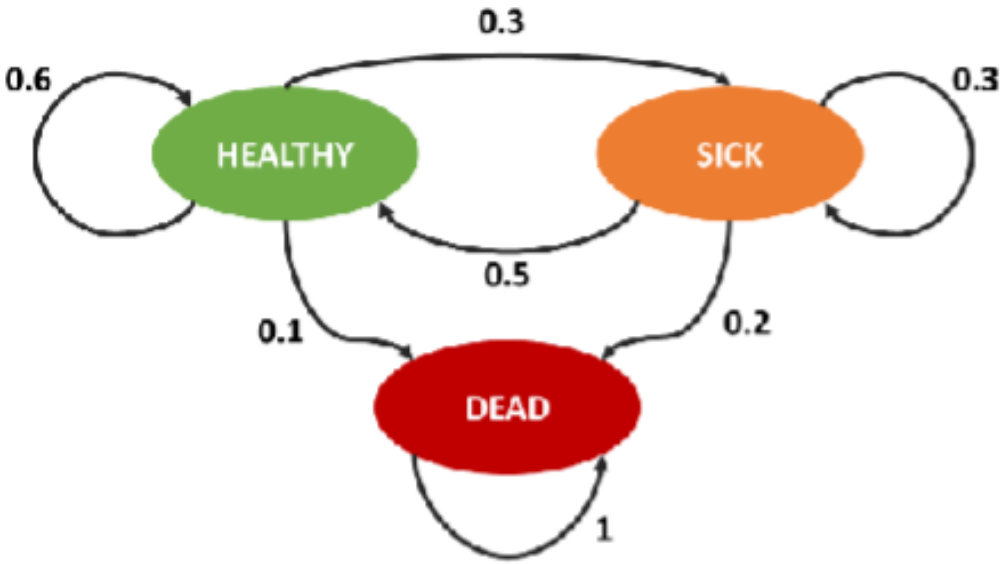
Strategy	Incr Cost	Incr Effect (life-year gained)	ICER ($/life-year gained)
Routine practice	---	---	---
Primary care	$362	0.28	$1,293
Hospital care	$1,470	0.28	$5,250

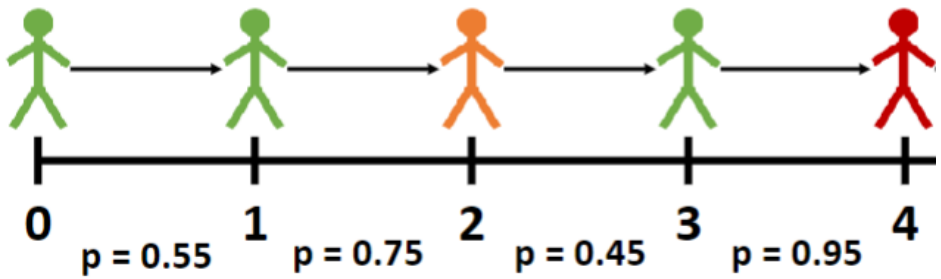
Decision Tree Analysis Limitations

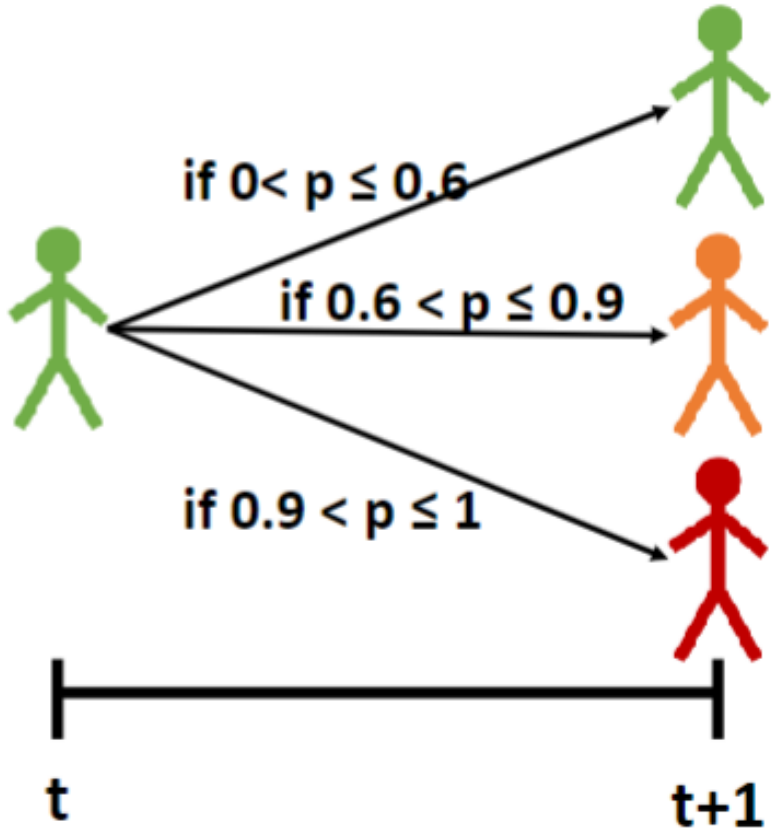
- Time is not explicitly defined
- Complexity increases exponentially for longer-term prognoses or outcomes
  - What if we modeled long-term outcomes related to diabetes comorbidities?
  - We have potential for retinopathy, nephropathy, cardiometabolic, neurological disease, in addition to death

Markov State-Transition Cohort Models

- Markov models are repetitive decision trees
- Based on series of "**health states**" a patient can occupy at any time point
  - **Health states**: **mutually exclusive and collectively exhaustive clinical events/states** that can occur to a patient
  - A person can only be in one health state
  - All health states for a particular chance node represent all possibilities of prognosis for a person
- **Time elapses**
- "Probability" of patient occupying health states is assessed over series of time periods (**cycles**)
  - **Transition probability:** probability of transitioning from one health state to another


0.3
0.6
0.3
HEALTHY
SICK
0.5
0.1
0.2
DEAD
1

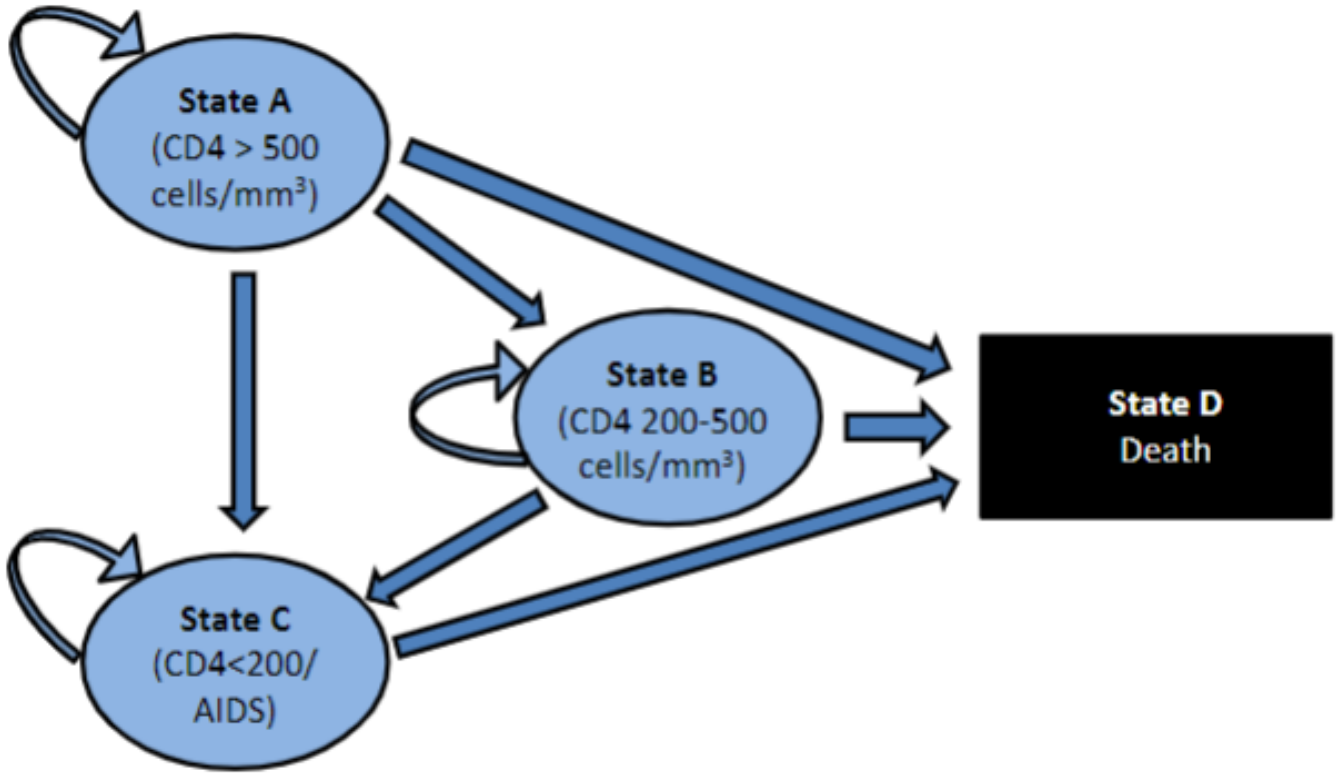

0
p = 0.55
1
p = 0.75
2
p = 0.45
3
p = 0.95
4


if 0< p ≤ 0.6
if 0.6 < p ≤ 0.9
if 0.9 < p ≤ 1
t
t+1

Markov Cohort Model Analysis Example: Framework

- A cost-effectiveness analysis of zidovudine monotherapy compared with zidovudine plus lamivudine combination therapy (Chancellor et al., 1997)
- Population of interest: Patients with HIV infection
- Baseline cohort: HIV patients with CD4 count>500
- Outcome of interest: ICER of incremental cost/life-year gained

Example Markov Cohort Analysis II: Model



Example Markov Cohort Analysis III: Probabilities

- Combination therapy has a RR of 0.509 (derived from meta-analysis)
- Therefore, health state transition in monotherapy from state A to B, C, and D can be multiplied by 0.509 for combination therapy
- Staying in one health state (e.g., State A to State A) is always 1-sum of the probabilities of transitioning to all other states

Transition probabilities—monotherapy

Transition from	Transition to			
	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.01
State B	0	0.581	0.407	0.012
State C	0	0	0.75	0.25
State D	0	0	0	1

Transition probabilities—combination therapy

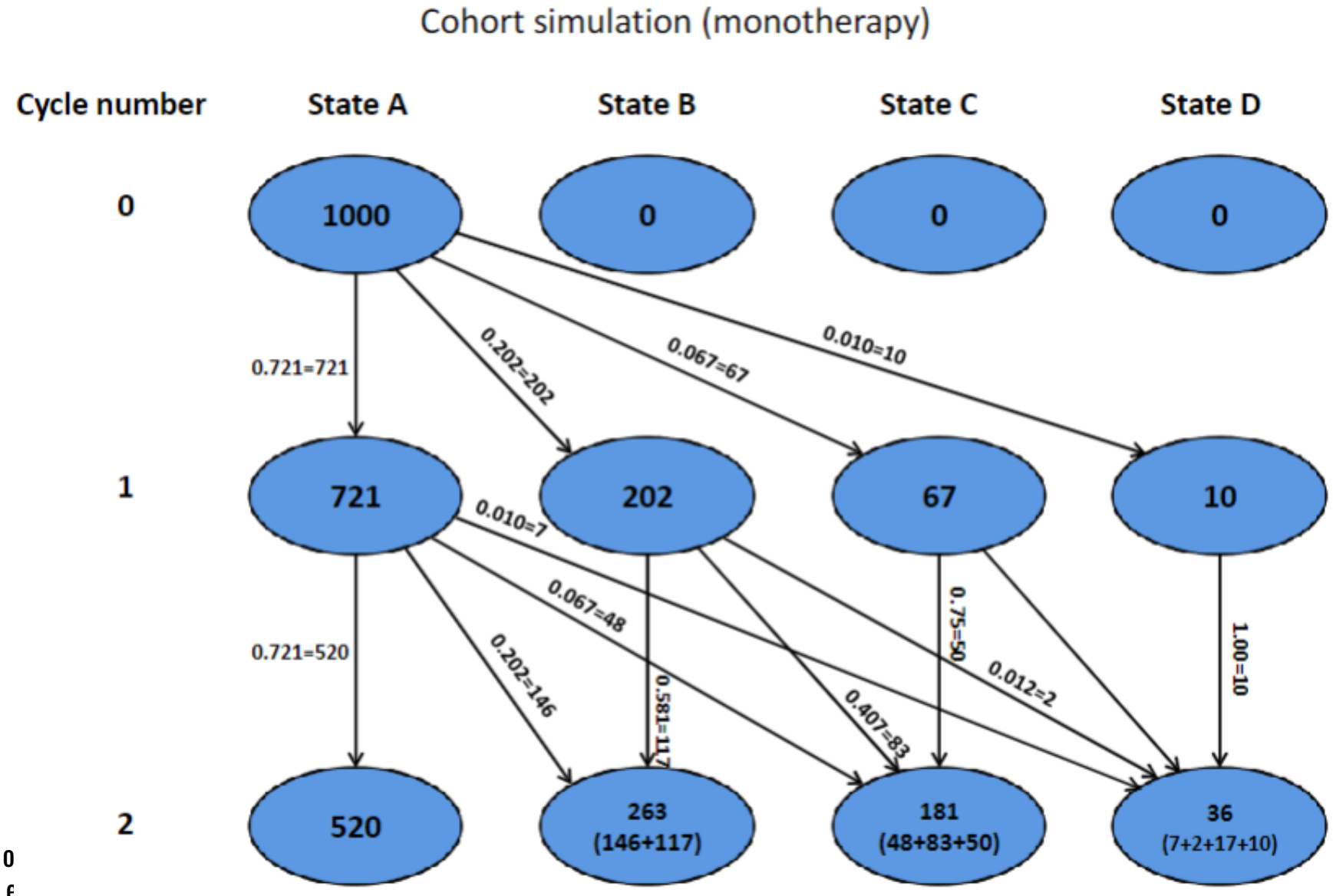
Transition from	Transition to*			
	State A	State B	State C	State D
State A	0.858 (1-sum)	0.103	0.034	0.005
State B	0	0.787 (1-sum)	0.207	0.006
State C	0	0	0.873 (1-sum)	0.127
State D	0	0	0	1

Estimated using the relative risk of 0.509 (original study obtained this from a meta-analysis)

Example Markov Cohort Analysis IV: Costs

	Annual Healthcare Cost			
Zidovudine	$2,278			
Lamivudine	$2,086			
Health states	State A (CD4>500)	State B (CD4 200-500)	State C (AIDS, CD4 <200)	State D (death)
Direct medical	$1,701	$1,774	$6,948	
Community	$1,055	$1,278	$2,059	
Total costs	**$2,756**	**$3,052**	**$9,007**	$0

Example Markov Cohort Analysis V: Cohort simulation (monotherapy)



Example Markov Cohort Analysis VI: Cohort simulation (monotherapy)

- We can manually calculate expected costs PER cycle (year) of simulation with monotherapy:
- Note: we may apply 3-6% discounting per year to convert future dollar and health outcomes to their NET PRESENT VALUE TODAY
- Expected cost = (721(**2756**+2278) + 202(3052+2278) + 67(9007+2278))/1000
- Discounted cost = $5463/[(1+0.06)^{1}]$

Cycle (year)	Proportion of cohort in each state				Costs ($)	
	A	B	C	D	Undiscounted	Discounted
0	1000	0	0	0		
1	721	202	67	10	**5463**	5153

Example Markov Cohort Analysis VII: Cohort simulation (monotherapy)

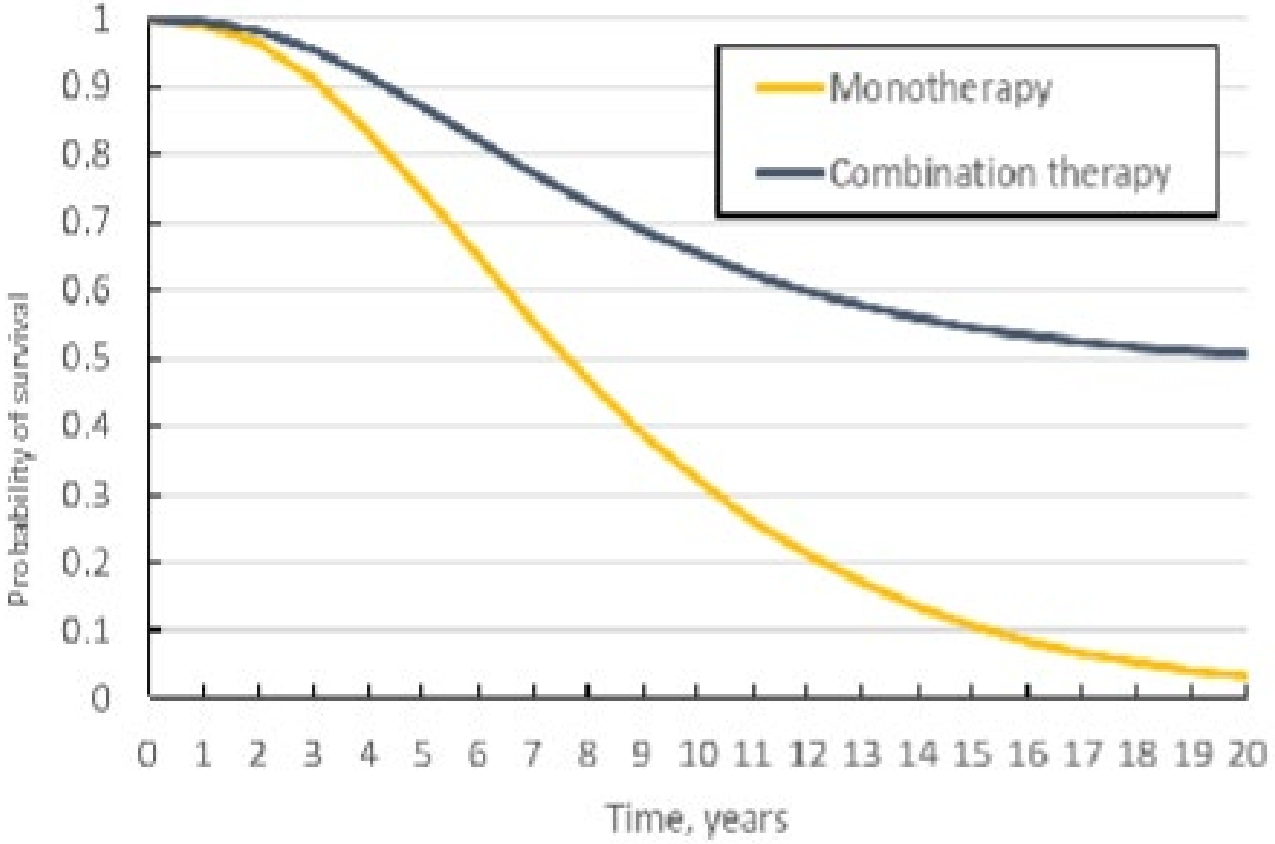
Cycle (year)	Proportion of cohort in each state				Costs ($)	
	A	B	C	D	Undiscounted	Discounted*
0	1000	0	0	0		
1	721	202	67	10	5463*	5153*
2	520	263	181	36	6060	5393
3	376	258	277	89	6394	5368
4	271	226	338	165	6381	5055
5	195	186	364	255	6077	4541
6	141	147	361	350	5574	3929
7	102	114	341	444	4963	3301
8	73	87	309	531	4316	2708
9	53	65	272	610	3682	2179
10	38	49	234	679	3092	1727
11	28	36	198	739	2564	1350
12	20	26	165	789	2102	1045
13	14	19	136	830	1708	801
14	10	14	111	865	1377	609
15	7	10	90	893	1103	460
16	5	8	72	915	878	346
17	4	5	57	933	695	258
18	3	4	45	948	548	192
19	2	3	36	959	431	142
20	1	2	28	968	337	105
					63 745	44 663

Example Markov Cohort Analysis VIII: Cohort simulation (monotherapy) half-cycle correction

- We apply half-cycle correction to assume mean average state transition occurs in the exact middle of a cycle

Cycle (year)	Proportion of cohort in each state				Effect (survival probability)	
	A	B	C	D	All transitions occur at beginning of cycle	Mean transition occur at middle of cycle
0	1000	0	0	0		
1	721	202	67	10	(721+202+67)/ 1000 = 0.990	(721+202+67+(**0.5*10**))/1000 = **0.995**

Example Markov Cohort Analysis IX: Cohort simulation (monotherapy vs. combination)



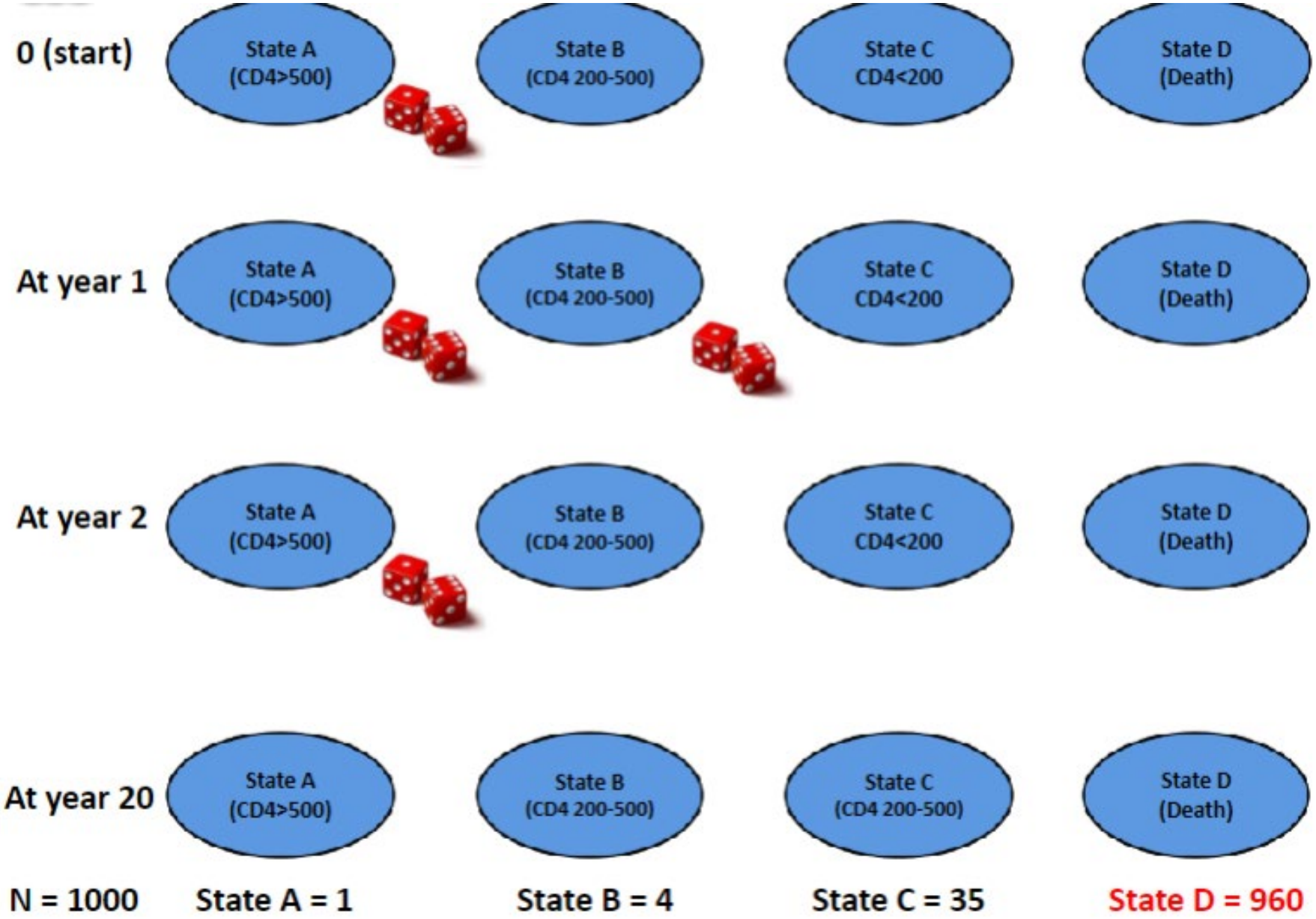
Strategy	Incr Cost	Incr Effect (life-year gained)	ICER ($/life-year saved)
Monotherapy	---	---	---
Primary care	$35,170	5.90	$5,976

Markov Model Sensitivity Analysis & Limitations

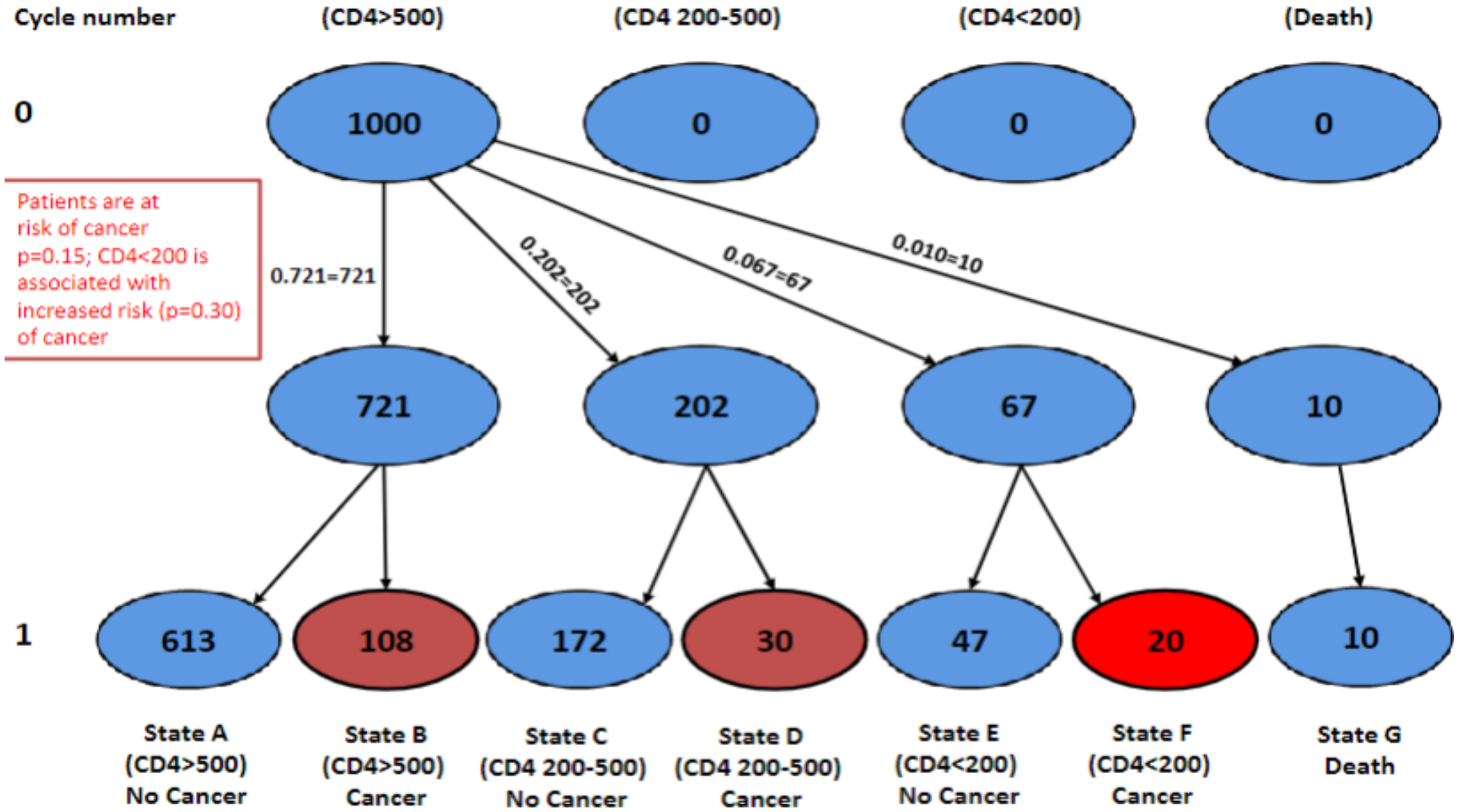
- Account for parametric uncertainty
- For example, in Chancellor et al., 1997 paper, the relative risk of progression due to combination therapy was 0.509 (95% CI: 0.365-0.710)
- We can run the analysis seeing how varying each parameter value impacts ICER (one-way sensitivity analysis → form Tornado diagram)
  - Can visualize which parameters have the largest impact on ICER
- We can also run analysis seeing how MULTIPLE parameter value changing at the same time can impact ICER (two-way or three-way sensitivity analysis)
- Markov model is "memoryless"- once a patient transitions, the Markov model has no memory regarding the patient's prior disease history or their preceding health states
  - Is this realistic?

Microsimulation (Individual-level) simulation modeling

- More realistic
- Markov models may make assumptions that are not realistic
- Individual patient moves from one health state to another based on their baseline demographics/risk factors
- Allows for individual-level complexity to be captured using “tracker” variables in the model


0 (start)
State A (CD4>500)
State B (CD4 200-500)
State C CD4<200
State D (Death)
At year 1
State A (CD4>500)
State B (CD4 200-500)
State C CD4<200
State D (Death)
At year 2
State A (CD4>500)
State B (CD4 200-500)
State C CD4<200
State D (Death)
At year 20
State A (CD4>500)
State B (CD4 200-500)
State C (CD4 200-500)
State D (Death)
N = 1000
State A = 1
State B = 4
State C = 35
State D = 960

Cohort simulation (monotherapy) complexity: HIV and cancer



The Markov model will explode if we are to keep track of possibility of receiving treatment by cancer stage, disease recurrence by stage, etc.

Decision Analytic Modeling

- Determine what is your ultimate goal for the model?
  - The model is a PLATFORM for you to achieve your goal
  - Goals can change with increasing insight
- Conceptual model: determine your alternatives, health states, outcomes
- Collect data (e.g. literature) from populate model
- Develop simulation model using Excel, Treeage, etc.
- Ensure that model results make sense. Computation = specification model
- Compare results to another model or population data, other models