Decision Analysis: Clinical Examples

PAUL GERARDO YEH, MD, DRPH

3915 COURSE

NOVEMBER 7, 2023

Readings

Drummond et. al.., 2015, Chap. 9 "Econ Eval. Using Decision Analytic Modeling

Portnoy et al. Impact and cost-effectiveness of strategies to accelerate cervical cancer elimination: A model-based analysis.

Further Reading:

- Briggs et al. (2015) Chap. 3 Further developments in decision analytic models for economic evaluation. In Decision Modeling for Health Economic Evaluation. Oxford, pp. 45-76.
- Cantor, Scott B. (1995). Decision Analysis: Theory and Application to Medicine Primary Care (Review for Nov. 3, no presentation)
- Rafia, Rachid, Brennan, Alan et al. Modeling the Cost-Effectiveness of Alternative Upper Age Limits for Breast Cancer Screening in England and Wales (Review for Nov. 3, no presentation)
- Deshmukh et al. Cost-effectiveness Analysis Comparing Conventional, Hypofractionated, and Intraoperative Radiotherapy for Early-Stage Breast Cancer.

Objectives of Economic Evaluation using Decision Analytic Modeling (Review)

Evaluation

- Provides a means of translating the relevant evidence into estimates of the costs and effects of the alternative options being compared.

Uncertainty & Variability

- Facilitate an assessment of the various types of uncertainty relating to the evaluation.

Future Research

- Through assessment of uncertainty, identify likely priorities for future research.

Example I

Systematic Approach to Decision-Making Under Uncertainty Applied to Mammography Screening in Older Women

Example I: Optimal Radiation Therapy for early-stage (I/II) breast cancer

- Breast cancer account for highest number of incident cases of cancer in the U.S.
- Economic burden is over $158 billion as of 2020
- Almost 60% of 250,000 incident cases of breast cancer is early stage (stage I/II) disease

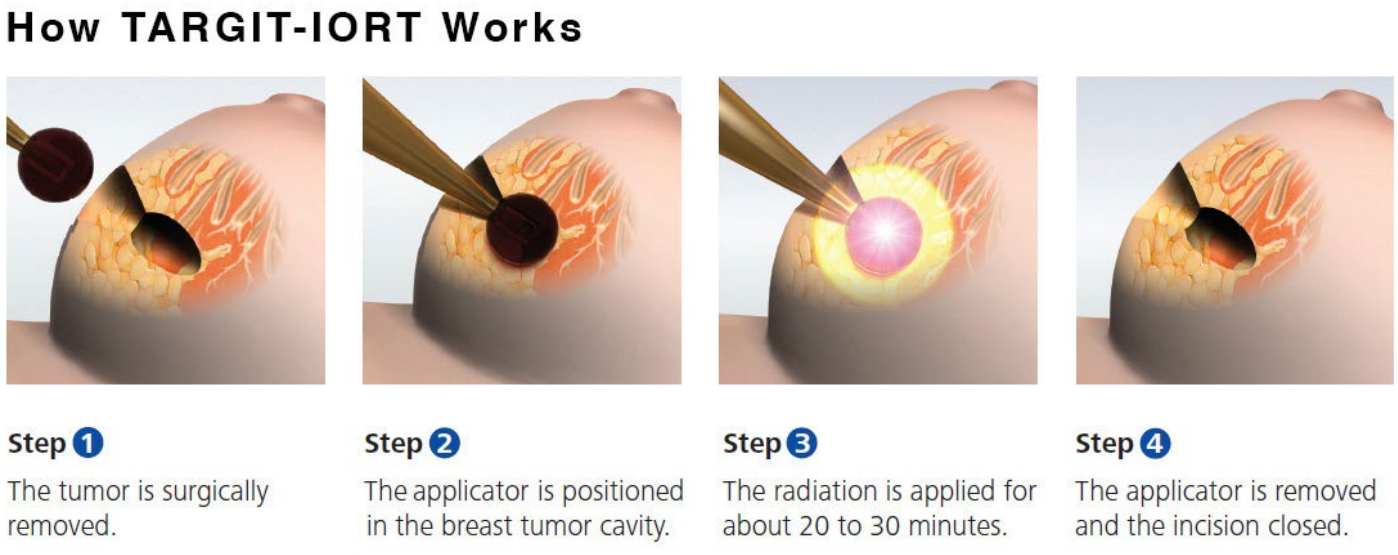
Source: Deshmukh et al., 2017

Treatment choices after lumpectomy

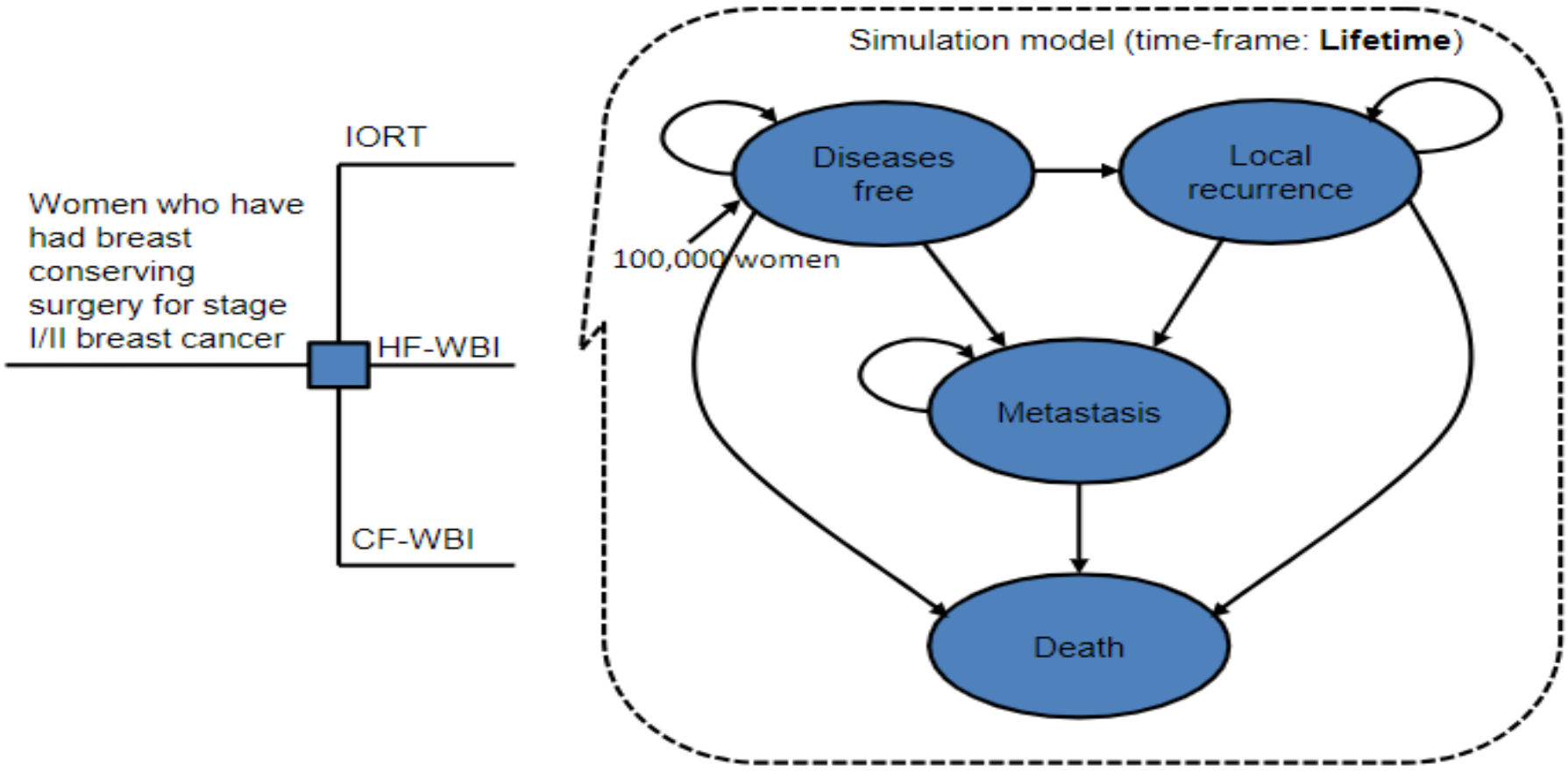
- Conventional fractionated whole breast irradiation (CF-WBI)
  - Main adjuvant radiation modality
  - Externally delivered whole breast radiation treatment (50 Gy in 25 fractions)
  - Daily treatment for 5-7 weeks
    - Associated with side-effects, hardships for certain patients (e.g. rural)
- Hypofrationated whole breast irradiation (HF-WBI)
  - Larger dose over shorter time (42.5Gy in 16 fractions)
  - Equally efficacious with less toxic side-effects vs. CF-WBI
  - Needs 15-20 sessions of daily treatment

Treatment choices after lumpectomy continued

- Intraoperative radiotherapy (IORT)
  - Single-dose radiation given during breast cancer surgery
  - More convenient
  - Cost-saving?



Optimal radiation therapy cost-effectiveness simulation model



Sources:

Costs

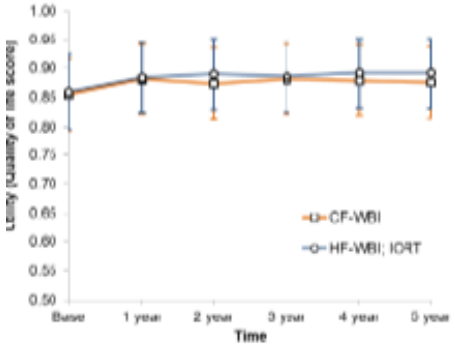
Deshmukh et al. Ann of Surg Oncol . 2014
Riley et al. Med Care. 1995
Medicare Fee Schedule
US Bureau of Labor Statistics

Transitions

Veronesi et al. Lancet Oncol. 2013 (ELIOT)
Haviland et al. Lancet Oncol. 2013 (START)
Whelan et al. NEJM. 2010 (Canadian)
Vaidya et al. Lancet. 2014 (TARGIT-A)

QOL (self-reported)

Smith et al. Cancer. 2016
Other literature



Cost

IORT, CF-WBI, HF-WBI, BCS, salvage mastectomy & reconstruction, travel, lost income, Follow-up

Transitions

LRR, Metastasis, Mortality risk (breast cancer and non breast cancer)

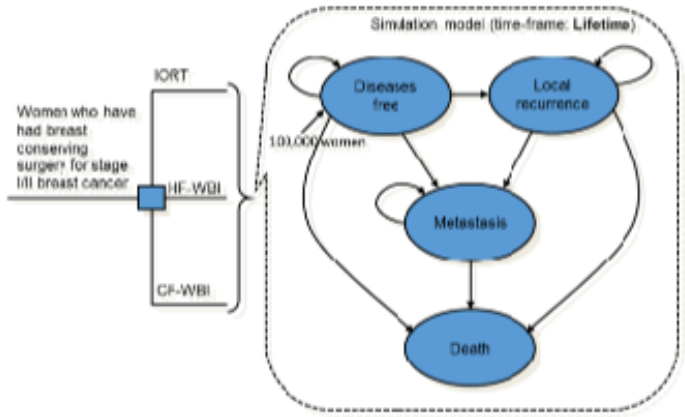
QOL

IORT, CF-WBI, HF-WBI, Salvage mastectomy, reconstruction, salvage lumpectomy

Other factors

Age-related decrement in QOL, Inconvenience

Framework



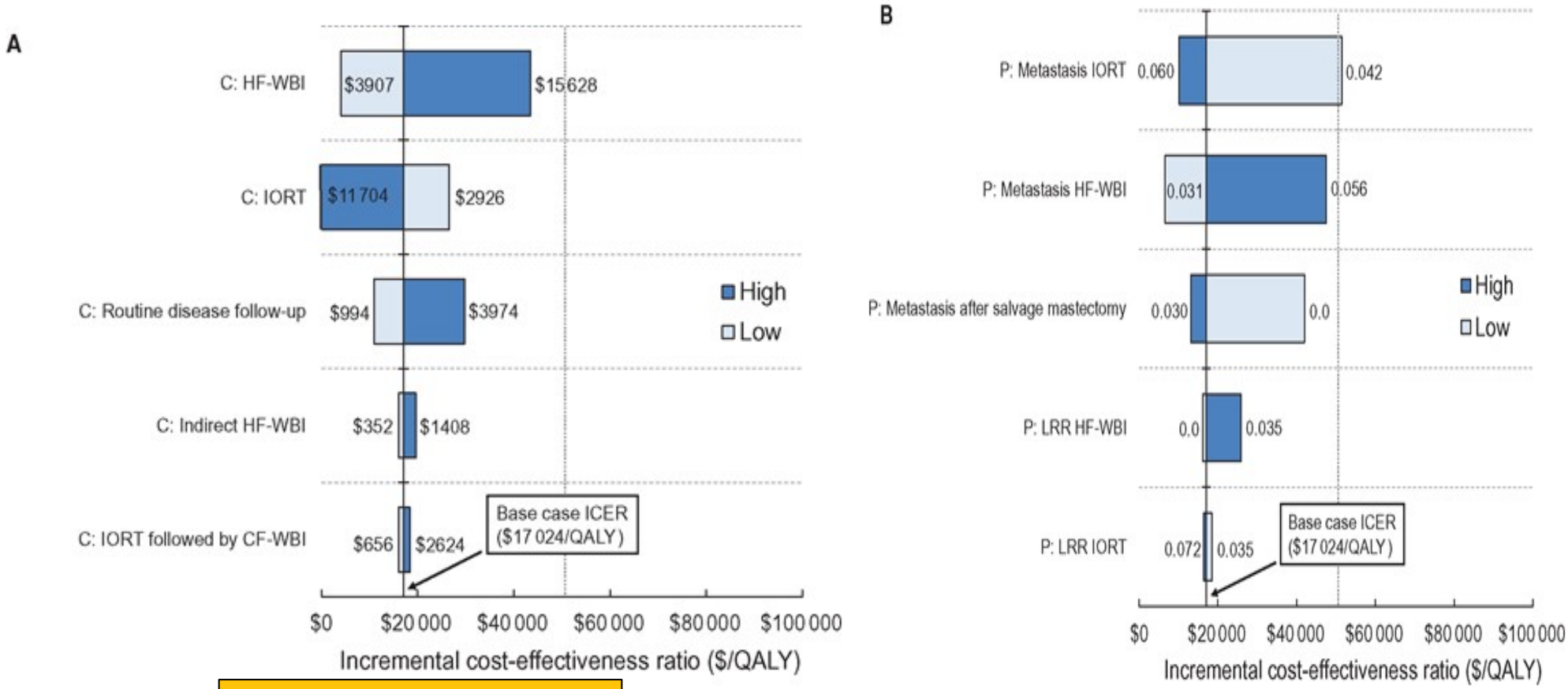
Cost-effectiveness?

Cost-effectiveness results

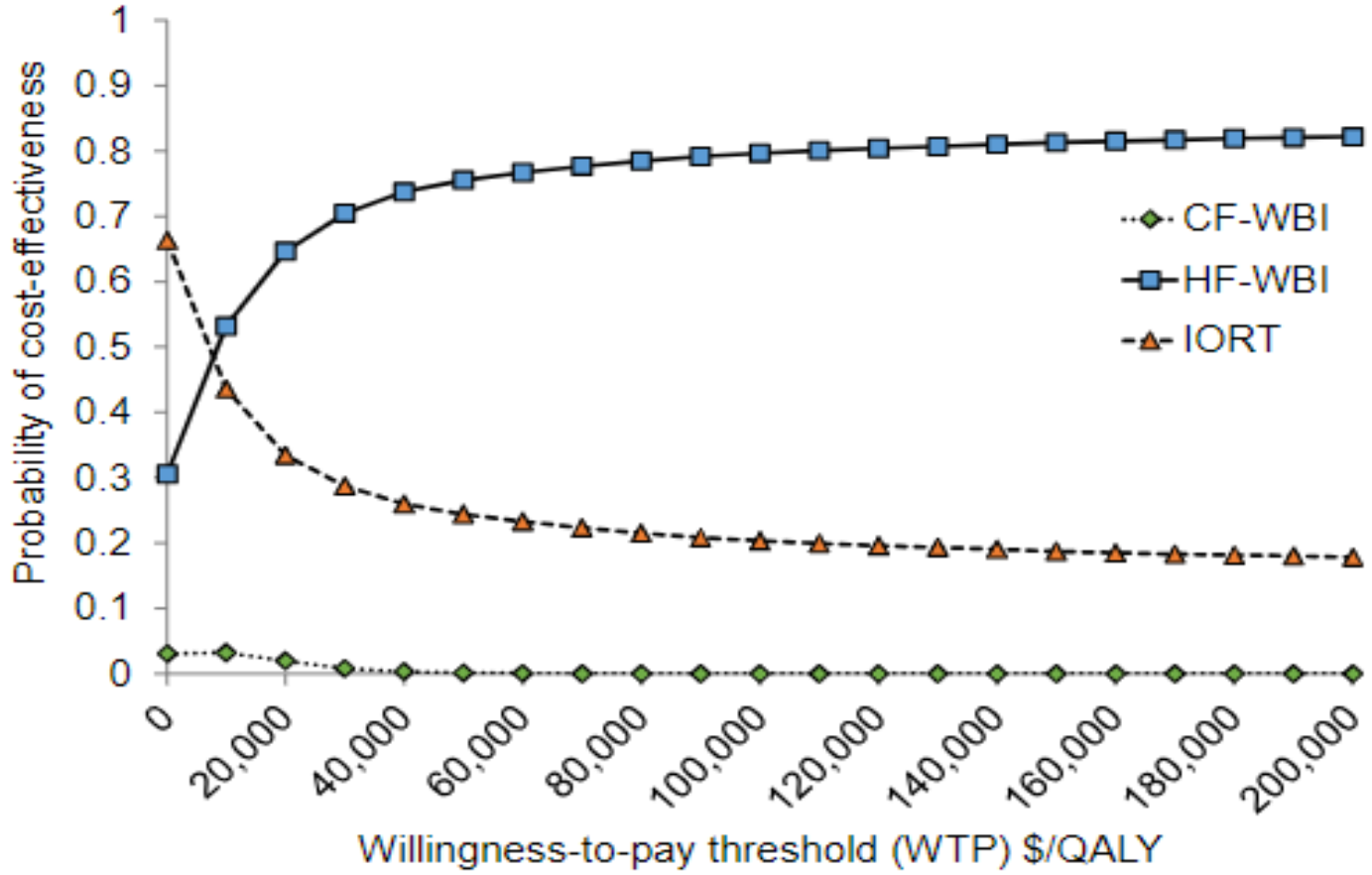
Strategy	Cost	QALYs	ICER ($/QALY)	Probability of cost-effectiveness at $50,000/QALY	Probability of cost-effectiveness at $100,000/QALY
Societal perspective					
IORT	42,410	12.176	---	25%	20%
CF-WBI	50,981	12.293	Dominated	0%	0%
HF-WBI	47,486	12.4745	17,024	75%	80%

Sensitivity Analyses: Tornado diagrams

Figure 2.



Sensitivity Analyses: Probabilistic sensitivity analysis



Conclusions of Breast Cancer Radiation Study

- Hypofrationated whole breast irradiation (HF-WBI) is the most optimal cost-effective strategy for early stage breast cancer
  - But what if the cost of IORT decreases? If HF-WBI cost increases?
- Older women and women in rural areas with difficulty traveling long distances daily for treatment may benefit from IORT

Table 3. Additional one-way sensitivity analysis

Variable	IORT		HF-WBI		CF-WBI*		ICER†
	Cost, $	QALY	Cost, $	QALY	Cost, $	QALY	
Age, y							
45	44307	13.0659	49810	13.4207	53305	13.2236	15511
50 (base case)	42410	12.1764	47486	12.4745	50981	12.2929	17024
55	40184	11.1927	44817	11.4358	48312	11.2711	19055
60	37534	10.0886	41716	10.2794	45211	10.1338	21919
65	34462	8.8701	38204	9.0132	41699	8.8883	26162
70	31017	7.5736	34348	7.6751	37843	7.5720	32816
75	27240	6.2348	30208	6.3021	33703	6.2212	44088
80	23284	4.9162	25953	4.9574	29448	4.8977	64803

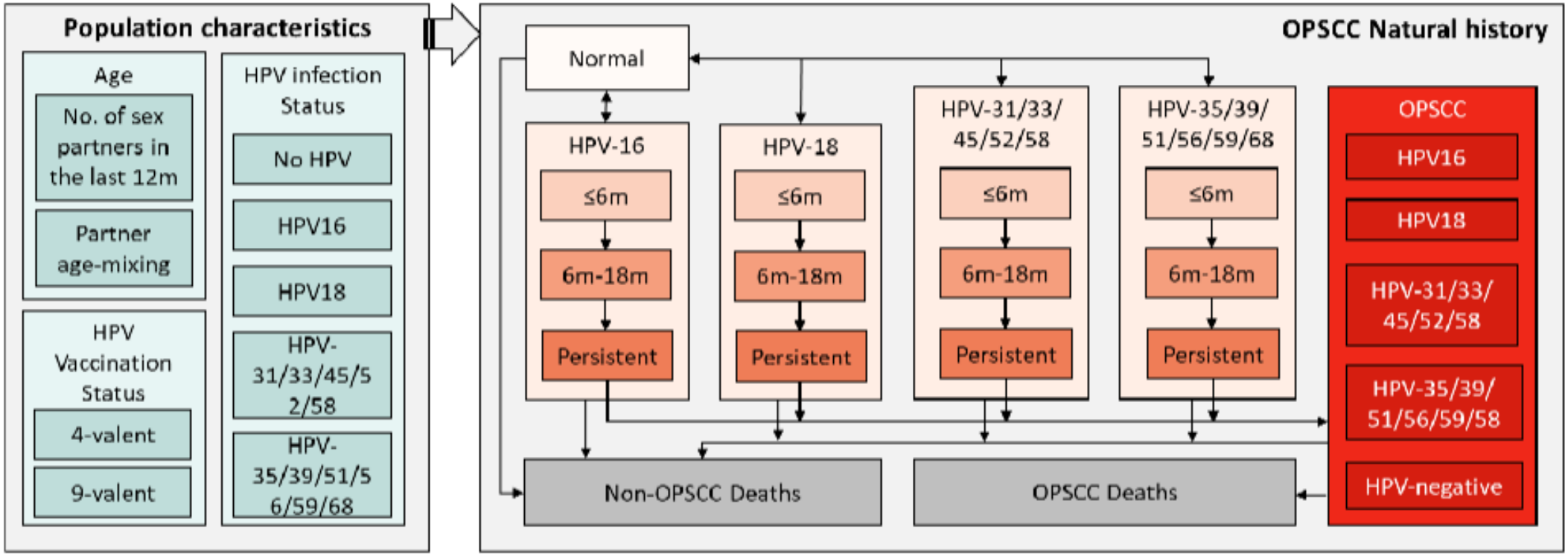
Example II

Long-term impact of HPV vaccination on oral HPV infection and oropharyngeal cancer

Long-term impact of HPV vaccination on oral HPV infection and oropharyngeal cancer

- Every year, 33,000 are diagnosed with HPV-related cancer
- Oropharyngeal cancer has recently surpassed cervical caner as most common cancer by HPV infection (>13,000 incident cases)
  - Includes cancer of tonsil, base of tongue, pharyngeal wall, uvala, soft palate
  - Incidence in men> women
  - Squamous cell carcinoma is 95% of all oropharyngeal cancers
  - One of fasting growing causes of cancer death among men
  - Entirely preventable with HPV vaccination

Oropharyngeal cancer simulation model: framework

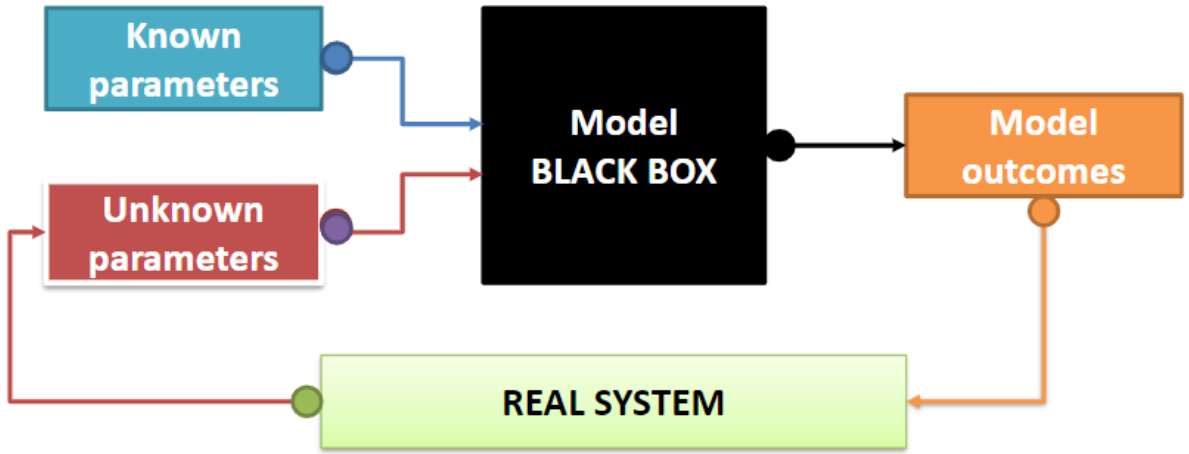


Oropharyngeal cancer simulation model: parameters

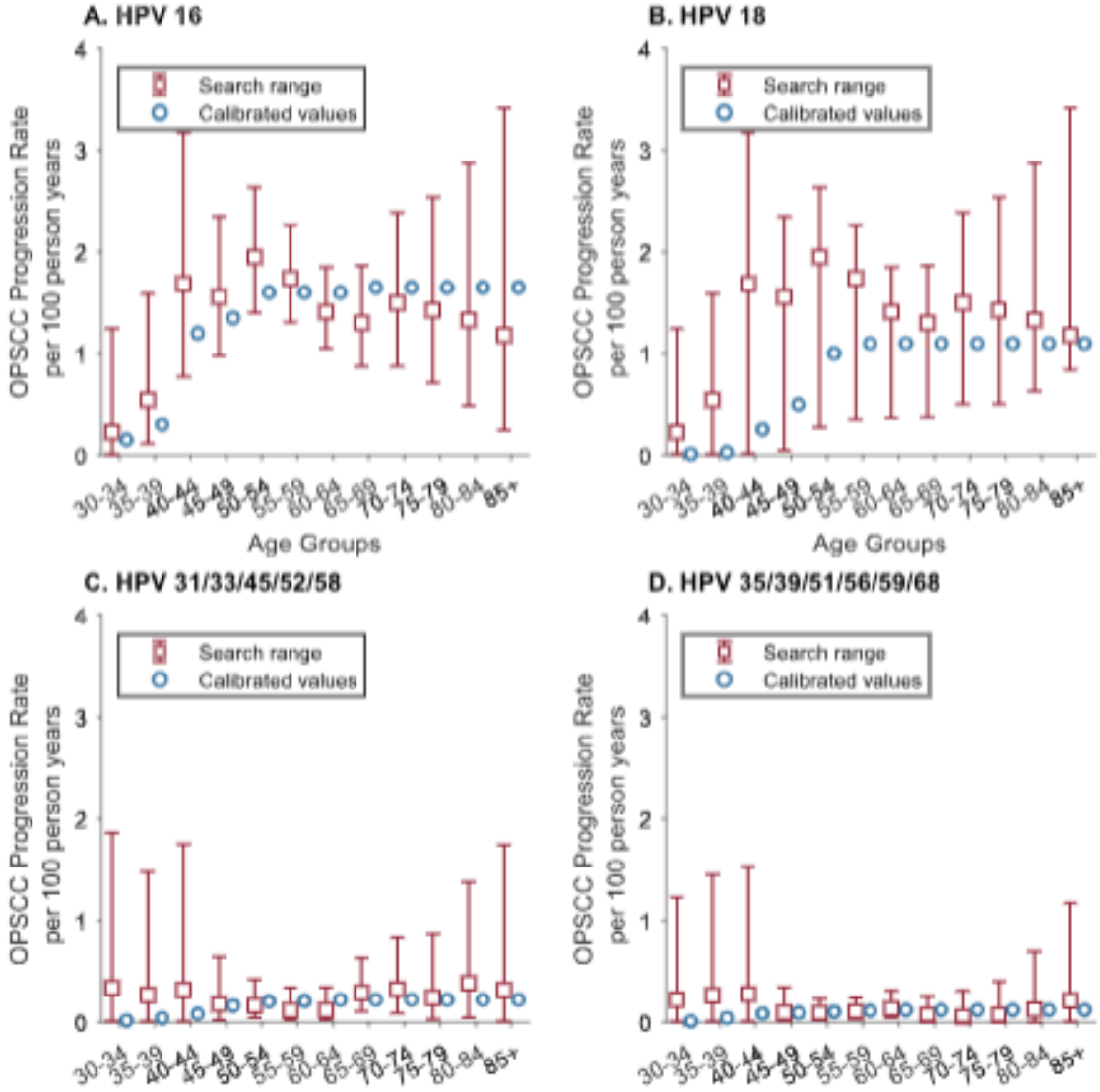
- Parameters for microsimulation model can be estimated through biological, clinical, or epidemiological studies
  - Survival time following cancer diagnosis can be derived from CDC SEER data
  - Other-cause mortality probabilities can be based on Census Bureau Life Tables for each age group
  - NHANES for epidemiological population-level data
  - Other sources: HIM Study

Oropharyngeal cancer simulation model: parameters

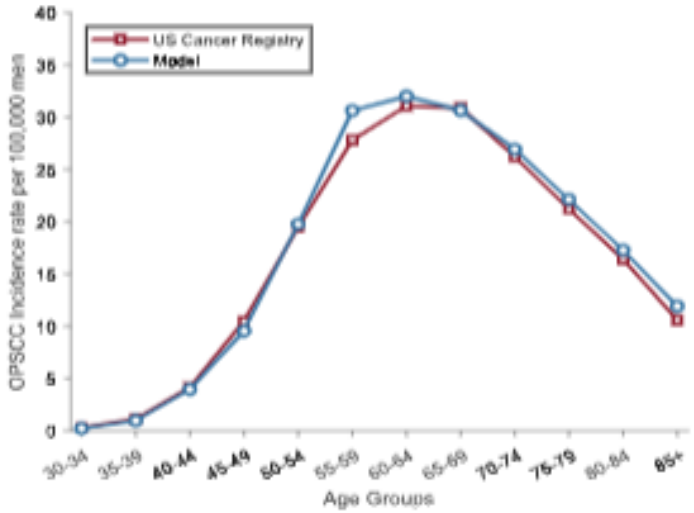
- Calibration to estimate model parameters to ensure that model reproduces observed results (transition from oral HPV to oropharyngeal squamous cell carcinoma)
- Calibration is iterative process of comparing model results to real observed data and making adjustments to model to ensure that results parallel reality



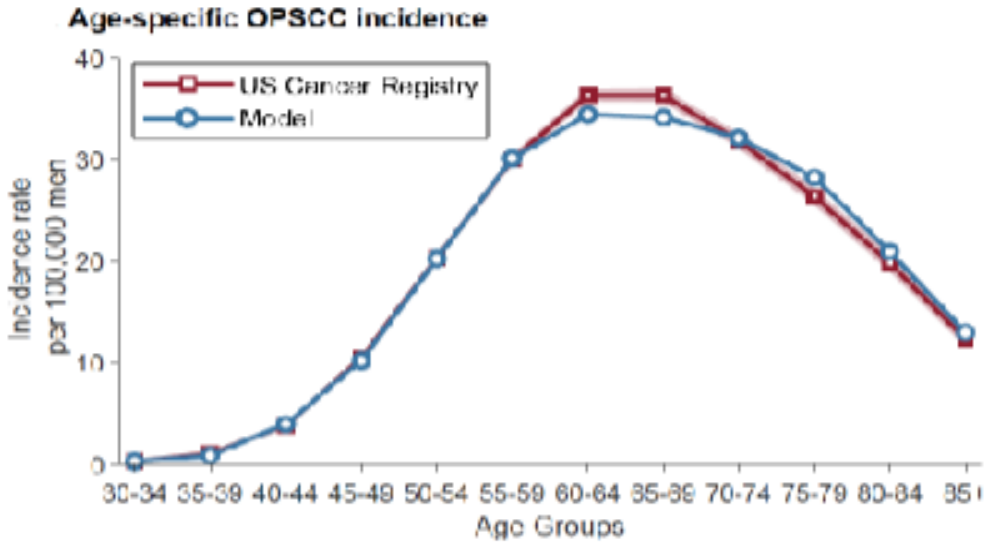
OPSCC Progression Parameters

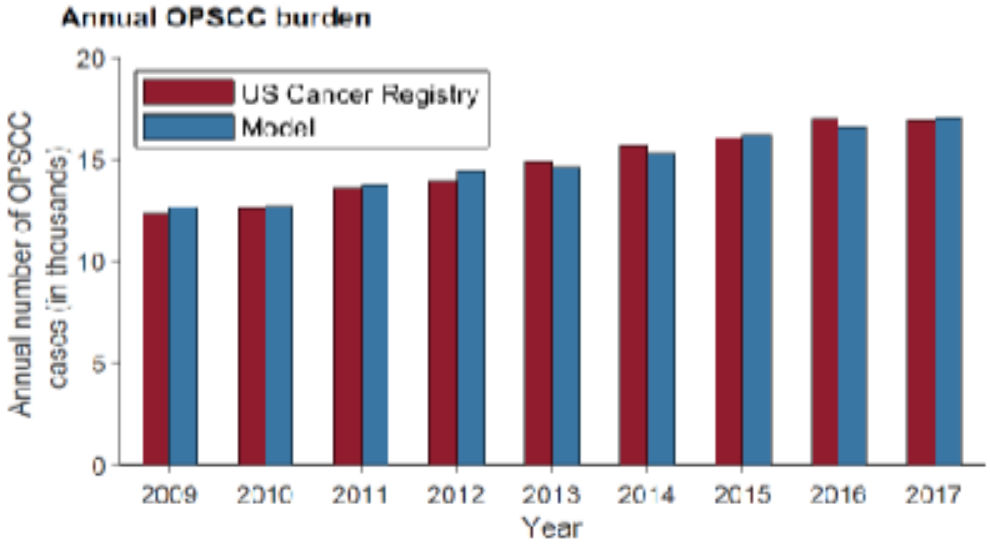


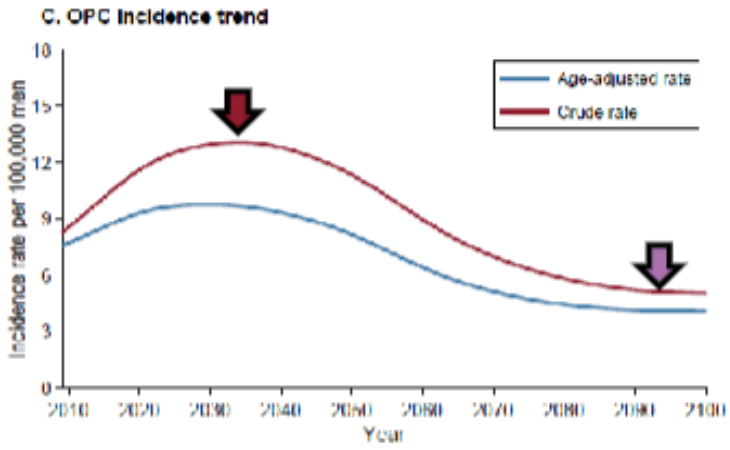
OPSCC Incidence

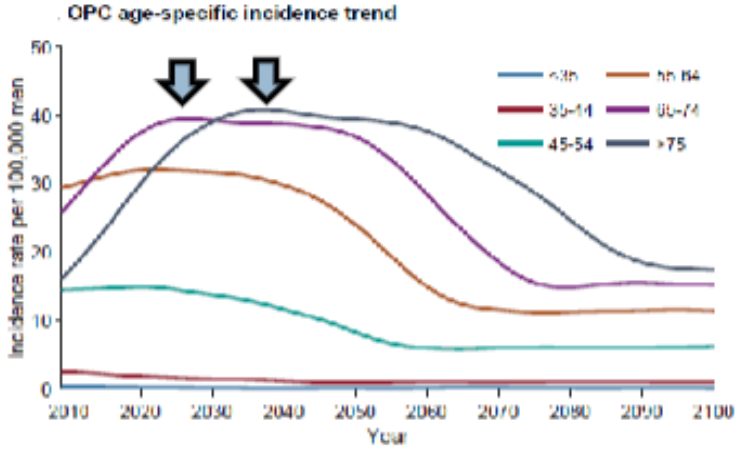


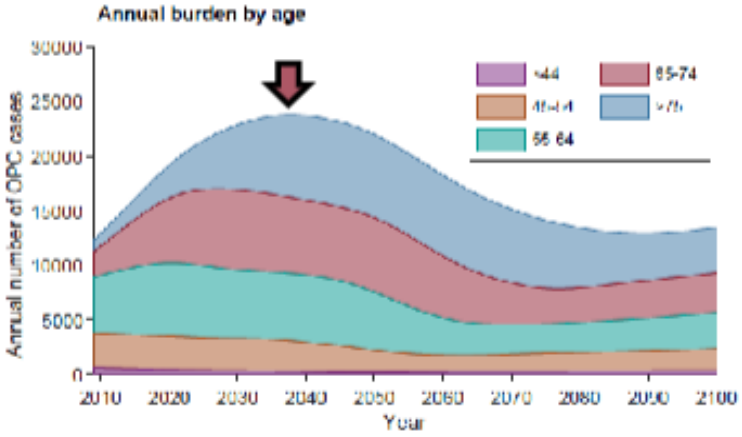
Validating the model

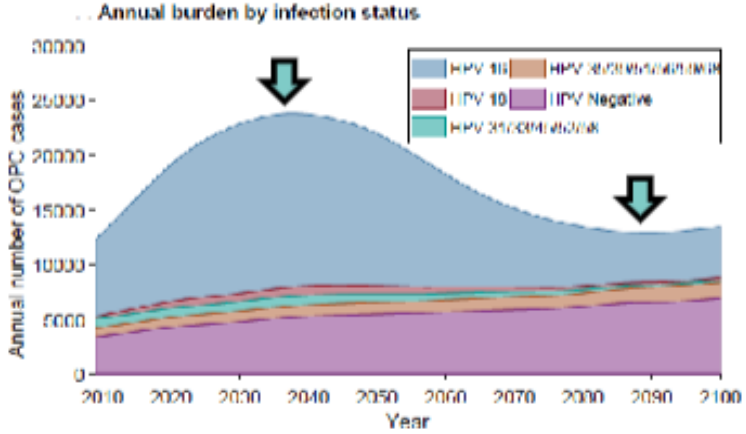












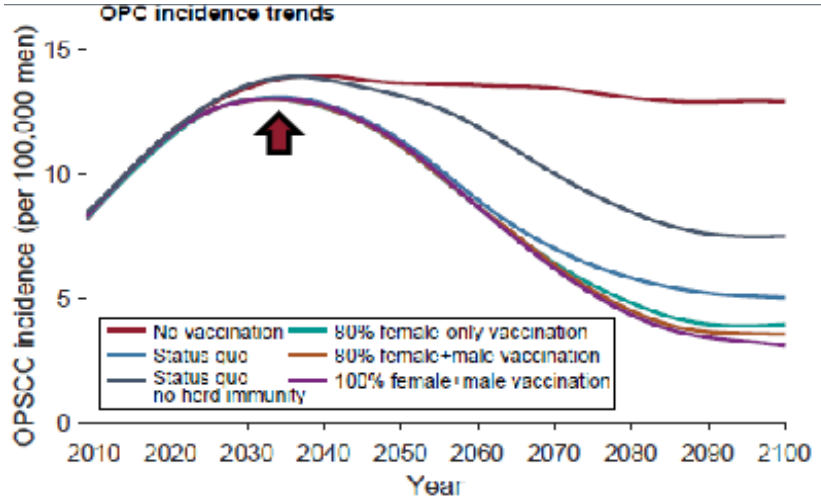
OPSCC will peak at 13/100,000 in 2038

The incidence will drop to 6.1/100,000 in 2086

Rising trend will portend among older age groups

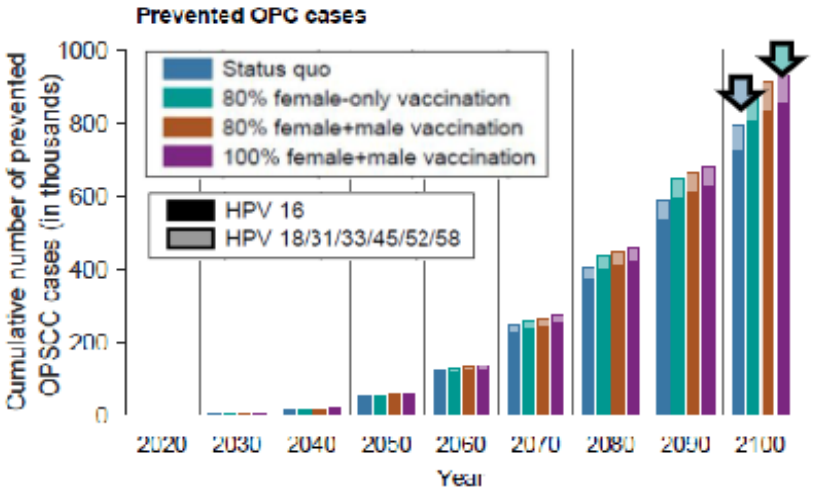
The burden will peak (24,000 cases/year) in 2038

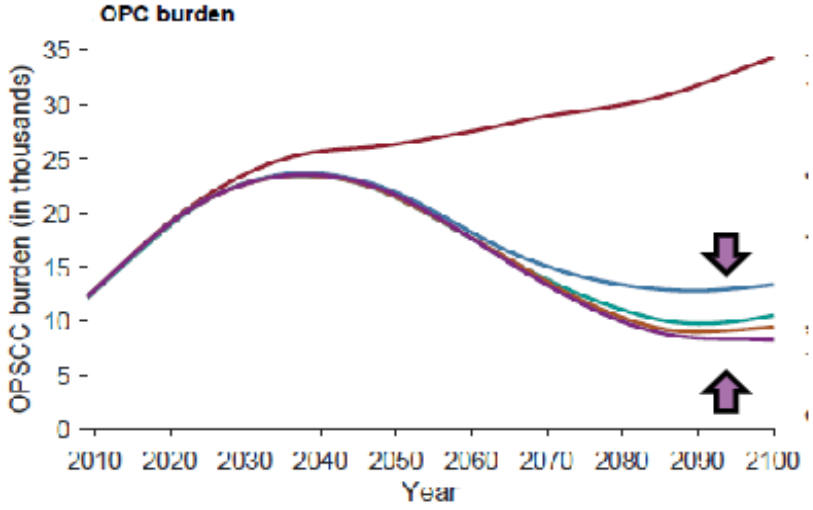
HPV attributable fraction will increase to 80% in 2038 and will drop to 57% in 2086



Under all scenarios incidence trends will reverse starting from 2038

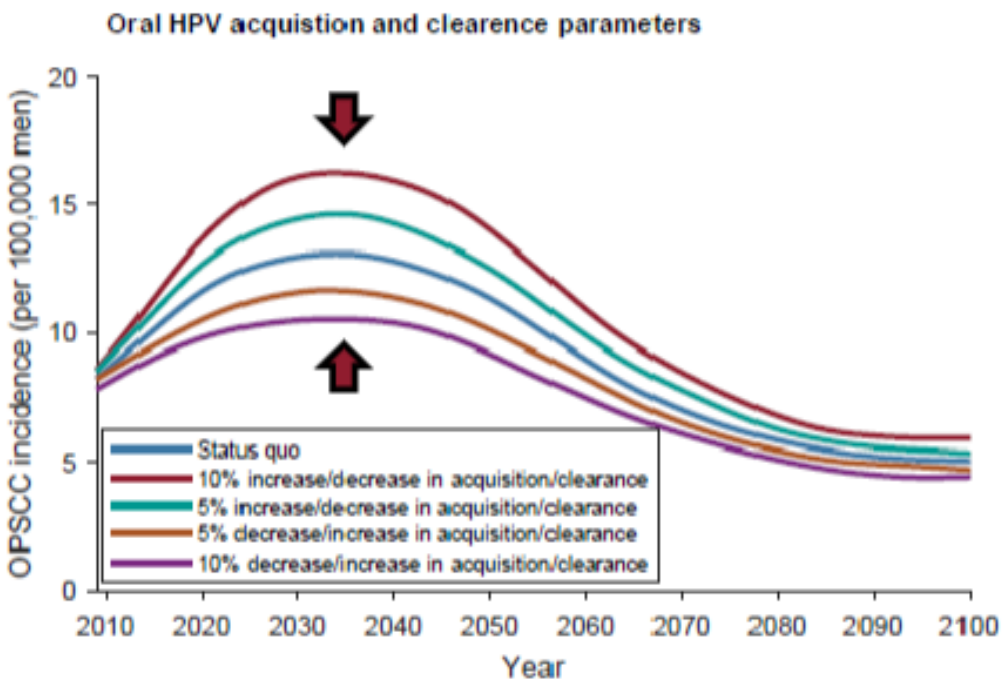
Current vaccination coverage can prevent cumulative number of about 700,000 OPSCC cases up to 2100

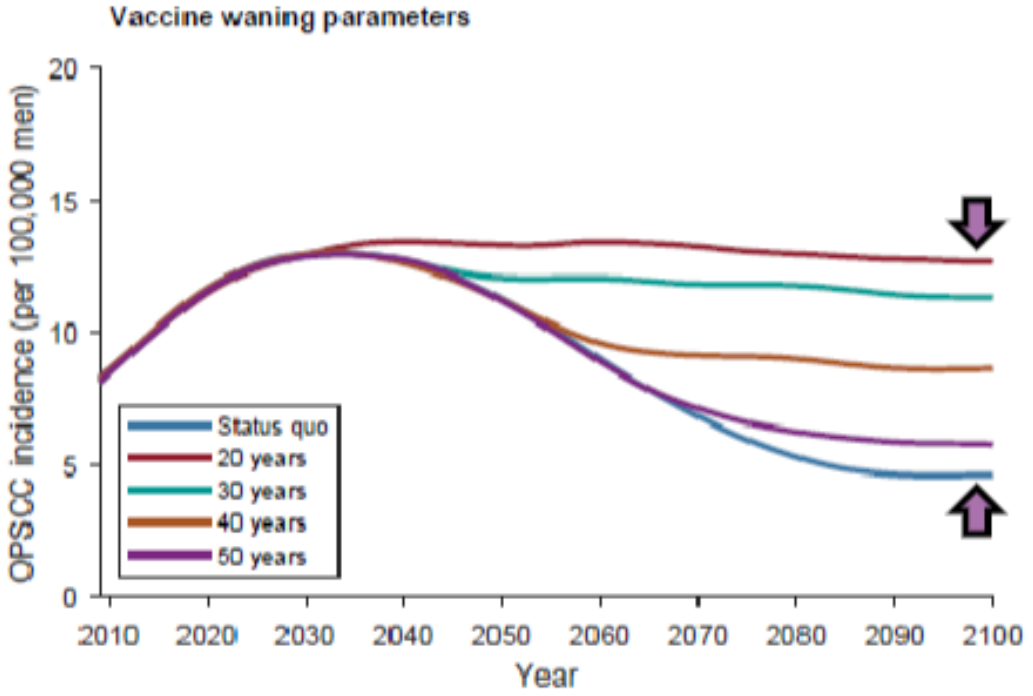




Achieving 100% coverage can prevent cumulative number of 930,000 OPSCC by 2100

improving HPV vaccination coverage could substantially decrease the annual number of cases.





Model is sensitive to natural history parameters

OPSCC trends are very sensitive to waning (the duration of vaccine protection)

Conclusion of Study Example II

- Microsimulation is powerful took for modeling prevention and intervention policies in public health
- Requires long time and programming skills
- Living model that can be updated with updated data or elaborated with new functionalities (e.g., investigating new intervention or population)
- More dynamic microsimulations exist (transmission-based microsimulations of infection/cancer)

Example III

A Simplified Didactic Example of Cost-Effectiveness Analysis of Mammography Screening

Utilizing a Decision Tree Model

Based on: JS Mandelblatt, ME Wheat, M Monane, R Moshief, JP Hollenberg, J Tang. Breast cancer screening for elderly women with and without comorbid conditions: a decision analysis model. *Annals of Internal Medicine. 1992;116:722-730.*

Breast Cancer Scrn. Background

- Breast cancer most common type of cancer among women **and second leading cause of death**
  - **2022: 287,850 new cases and 43,250 deaths***
- Incidence and death rates highest in older women**
  - **Of all incident BC cases (2010-14) about 20% occurred in women ≥ 75 yrs.**
  - **In (2010-14, among all BC related mortality 36.8% of women were ≥ 75 yrs.**

Background (cont.)

- **Guidelines for older women are inconsistent**
  - **CDC (2020)**
    - **Age 40-49, individual choice.**
    - **Age 50-74 average risk; once every two years.**
    - **Age ≥ 75 years insufficient evidence to judge balance of risks and benefits.**
  - **ACS (2021)**
    - **Age 45 to 54 annual,**
    - **Age 55 & older** can switch to a mammogram every other year, or they can choose to continue yearly mammograms. Screening should continue as long as a woman is in good health and is expected to live **≥ 10 years**

Background (cont.)

- **Clinical trials evidence: Screening reduces mortality 15-30% after 4 years for women 40-69 years.**
- **Screening rate is lower in older women**
  - **60-70% age 50-69**
  - **50-60% age 70 and older**

Mack, D. and Lapane, K. Screening Mammography Among Older Women: A Review of United States Guidelines and Potential Harms. Journal of Women's Health, Vol. 28, No. 6, 2019.

Policy Issue

Medicare Part B covers annual screens and waves the co-pay

Should the government be doing more?

Yes:

- If mammography screening is cost-effective in older women
- If there are cost-effective interventions to increase screening

Mandelblatt et al. Study Objectives

Determine the incremental cost-effectiveness of mammography screening compared to no screening to prevent late stage breast cancer.

Study Population

Women in five different age groups, three health groups (average health, HTN, CHF), and average-health African American women.

Research Design

Decision tree model using probabilities and expected survival from related literature to **predict outcomes of the average person who chooses to screen or not**.

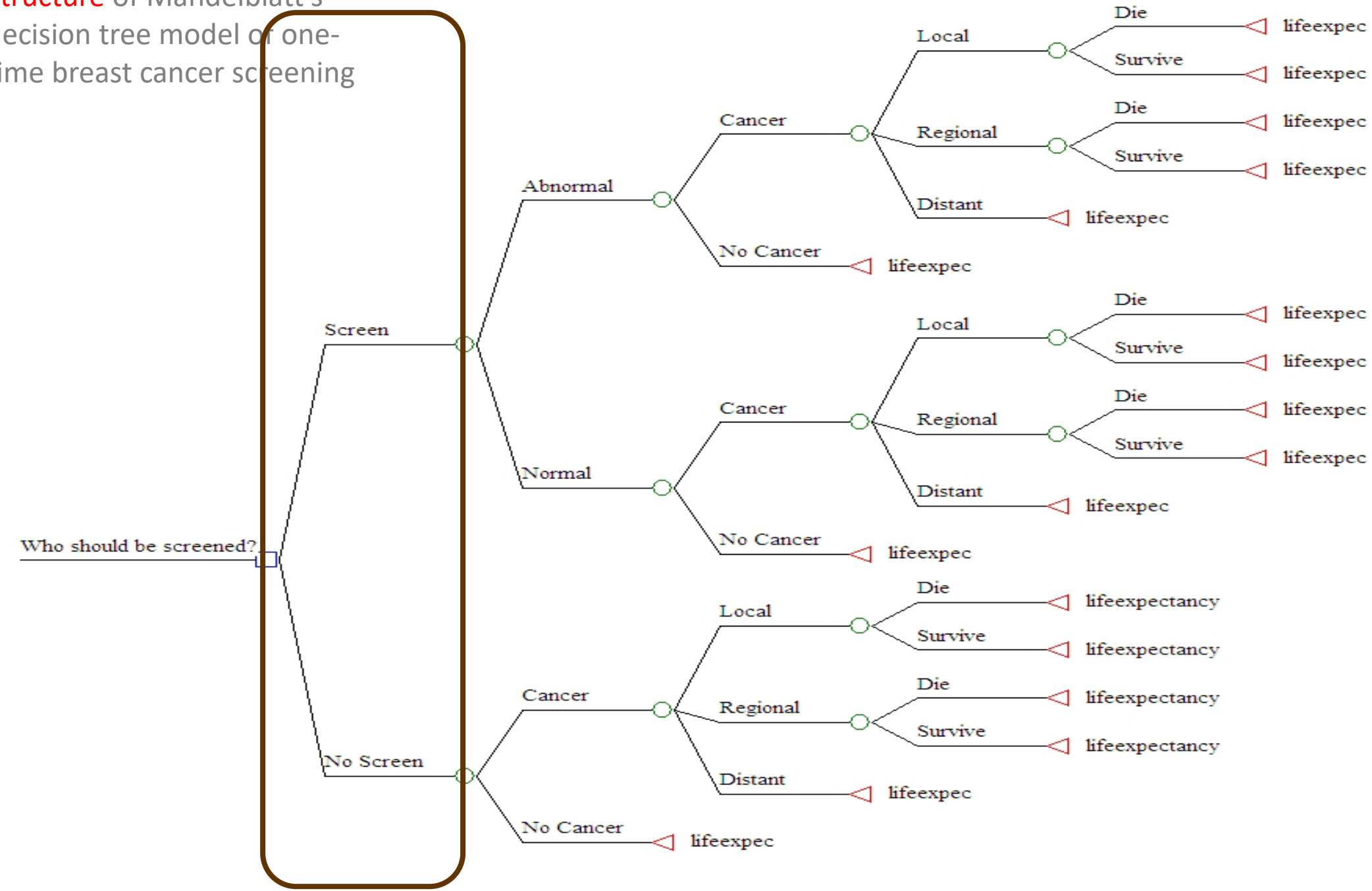
Basic Decision Tree Model

Alternative Actions: Expected value of screening vs. no screening

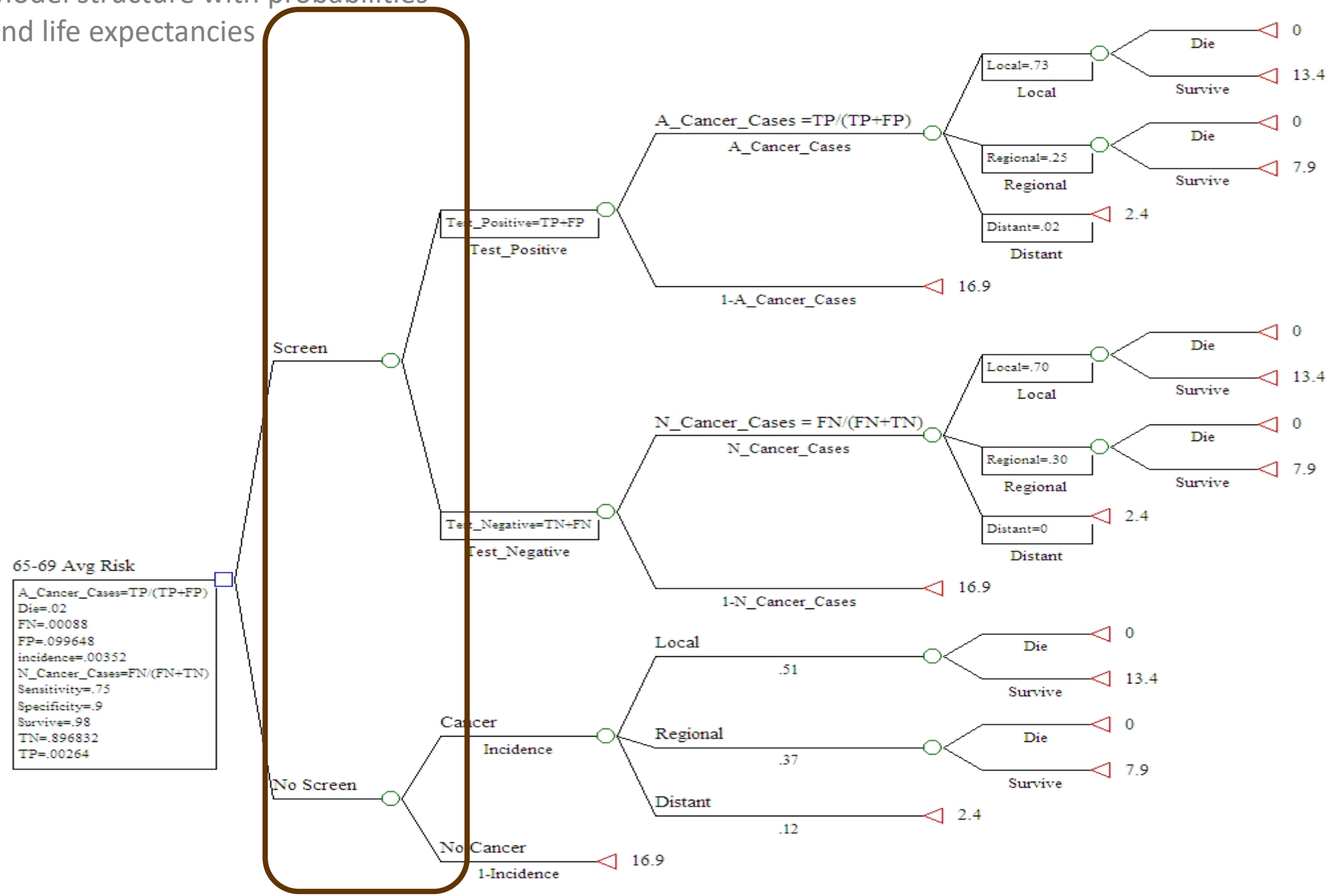
Uncertainties: Cancer, no cancer, Screen results, follow-up results, stage at diagnosis, survival

Outcomes: Expected life years and cost

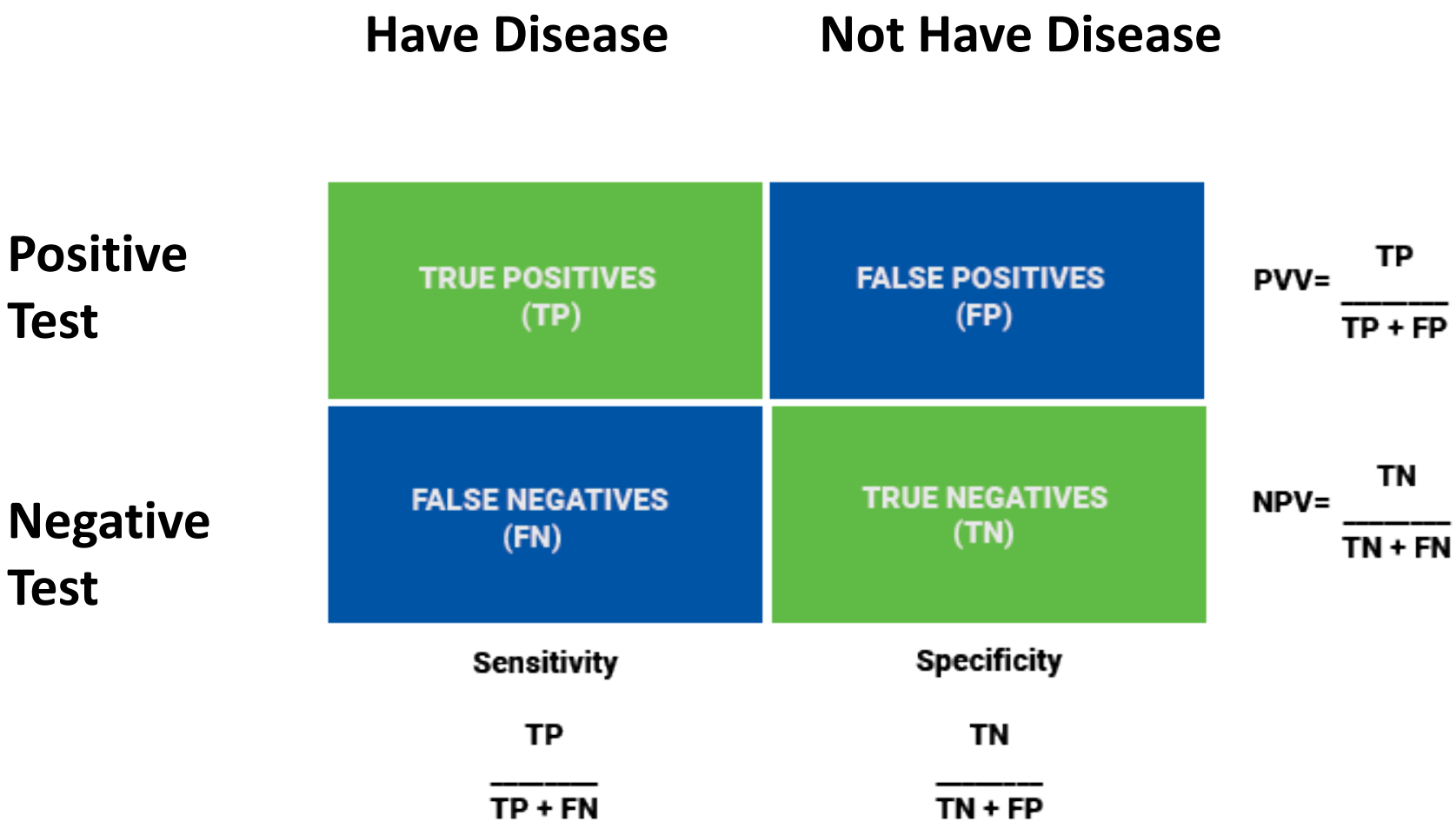
Structure of Mandelblatt's decision tree model of one-time breast cancer screening



Model structure with probabilities and life expectancies



Screening Test Parameters



Probabilities for Decision Tree

Prob. Test Positive = True Positive + False Positive

TP=(incidence*sensitivity) FP=((non-disease in pop*(1-specificity))

Prob. Test Negative = True Negative + False Negative

TN=(non-disease in pop*specificity) FN= ((incidence*(1-sensitivity))

Prob. Cancer If Test Positive: TP/(TP+FP)

Prob. No Cancer if Test Positive: FP/(TP+FP)

Estimates from screening test studies and incidence of the disease in the target population.

Prob Local if Cancer: .73 for TP, .70 for FN, .51 for Nonscreeners

Prob Regional if Cancer: .25 for TP, .30 for FN, .37 for Nonscreeners

Prob Distant if Cancer: .02 for TP, .00 for FN, .12 for Nonscreeners

Prob Operative Death: .02 (*Estimates based on cancer Epi. Studies)*

Screening Test Probabilities

	Disease Present	Disease Absent	Total
Test +	.00264 TP	.099648 FP	.102288 TP+FP
Test -	.00088 FN	.896832 TN	.897712 TN+FN
Total	.00352	.99648	1.00

Source: Mandelblatte et al. 1992

Calculating test probabilities for mammography screening, incidence rate of .00352

Mammography Result	Breast Cancer	No Breast Cancer	Total
Step 1: Use incidence for column totals: **.00352** x 100,000 = 352			
Positive			
Negative			
Total by column	352	99,648	100,000

Calculating test probabilities for mammography screening, incidence rate of .00352

Mammography Result	Breast Cancer	No Breast Cancer	Total
Step 1: Use incidence for column totals: **.00352** x 100,000 = 352			
Positive			
Negative			
Total by column	352	99,648	100,000
Step 2: Use sensitivity for disease present cells: **.75** x 352 = 264			
Positive	264 **TP**		
Negative	88 **FN**		
Total by column	352	99,648	100,000

Calculating test probabilities for mammography screening, incidence rate of .00352

Mammography Result	Breast Cancer	No Breast Cancer	Total
Step 1: Use incidence for column totals: **.00352** x 100,000 = 352			
Positive			
Negative			
Total by column	352	99,648	100,000
Step 2: Use sensitivity for disease present cells: **.75** x 352 = 264			
Positive	264		
Negative	88		
Total by column	352	99,648	100,000
Step 3: Use specificity for disease absent cells: **.90** x 99648 = 89683.2			
Positive	264 **TP**	9,964.8 **FP**	
Negative	88 **FN**	89,683.2 **TN**	
Total by column	352	99,648	100,000

Calculating test probabilities for mammography screening, incidence rate of .00352

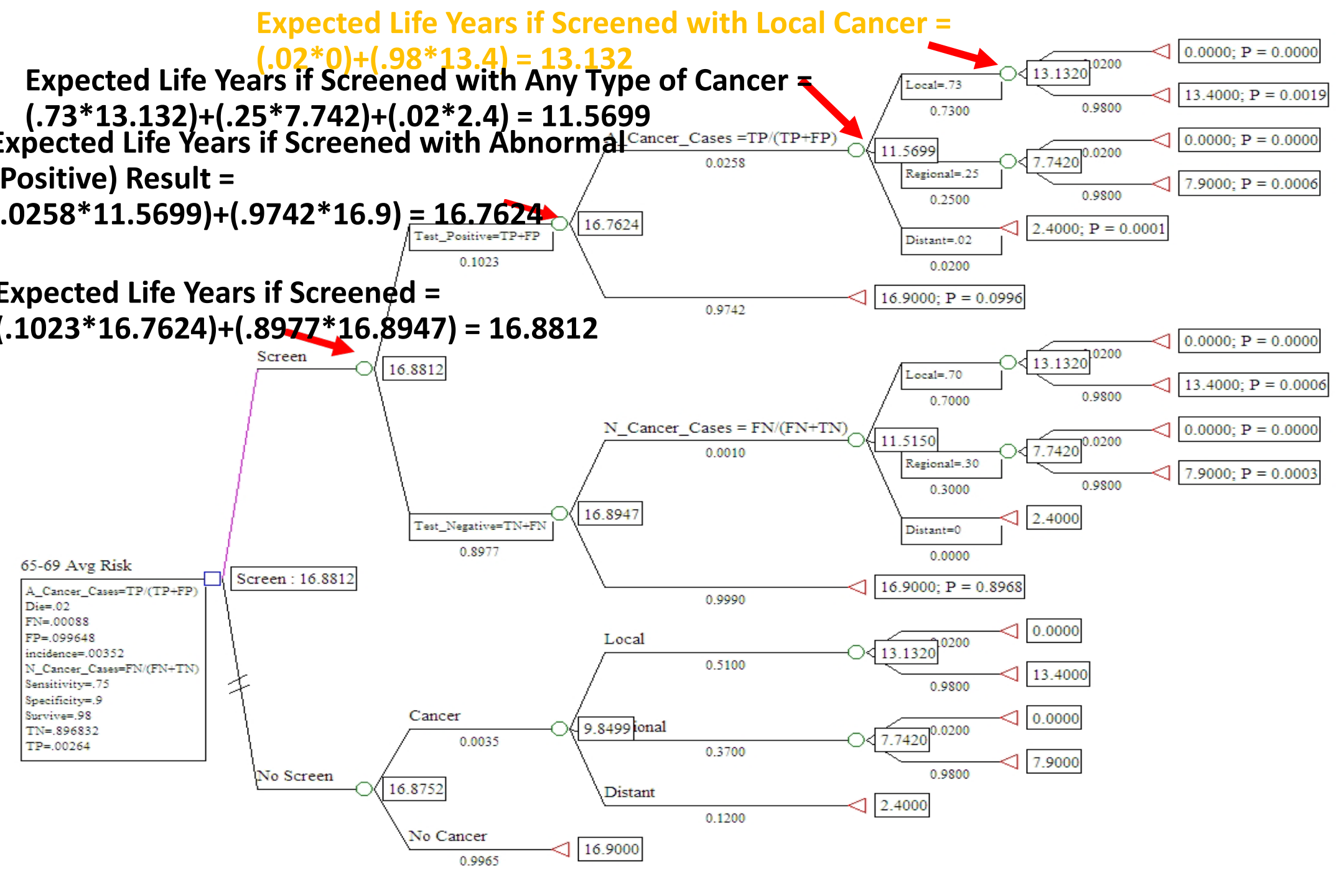
Mammography Result	Breast Cancer	No Breast Cancer	Total
Step 1: Use incidence for column totals: **.00352** x 100,000 = 352			
Positive			
Negative			
Total by column	352	99,648	100,000
Step 2: Use sensitivity for disease present cells: **.75** x 352 = 264			
Positive	264		
Negative	88		
Total by column	352	99,648	100,000
Step 3: Use specificity for disease absent cells: **.90** x 99648 = 89683.2			
Positive	264	9,964.8	
Negative	88	89,683.2	
Total by column	352	99,648	100,000
Step 4: Compute row totals: 264 + 9,964.8 = 10,229			
Positive	264 **TP**	9,964.8 **FP**	10,228.8
Negative	88 **FN**	89,683.2 **TN**	89,771.2
Total by column	352	99,648	100,000

Outcomes

Survival

- Age 65 to 69 years, average health
  - **Local BC** **13.4**
  - **Regional BC** **7.9**
  - **Distant BC** **2.4**
  - **No Cancer** **16.9**

- **Do the numbers make sense (face validity)?**


Expected Life Years if Screened with Local Cancer = (.02*0)+(.98*13.4) = 13.132
Expected Life Years if Screened with Any Type of Cancer = (.73*13.132)+(.25*7.742)+(.02*2.4) = 11.5699
Expected Life Years if Screened with Abnormal (Positive) Result = (.0258*11.5699)+(.9742*16.9) = 16.7624
Expected Life Years if Screened = (.1023*16.7624)+(.8977*16.8947) = 16.8812
65-69 Avg Risk
A_Cancer_Cases=TP/(TP+FP)
Die=.02
FN=.00088
FP=.099648
incidence=.00352
N_Cancer_Cases=FN/(FN+TN)
Sensitivity=.75
Specificity=.9
Survive=.98
TN=.896832
TP=.00264
Screen : 16.8812
No Screen
Screen
16.8812
Test_Positive=TP+FP
0.1023
Test_Negative=TN+FN
0.8977
16.7624
16.8947
A_Cancer_Cases =TP/(TP+FP)
0.0258
N_Cancer_Cases = FN/(FN+TN)
0.0010
0.9742
0.9990
11.5699
Local=.73
0.7300
Regional=.25
0.2500
Distant=.02
0.0200
13.1320
7.7420
2.4000; P = 0.0001
16.9000; P = 0.0996
0.0200
0.9800
0.0000; P = 0.0000
13.4000; P = 0.0019
7.9000; P = 0.0006
11.5150
Local=.70
0.7000
Regional=.30
0.3000
Distant=0
0.0000
2.4000
16.9000; P = 0.8968
0.0000; P = 0.0006
7.9000; P = 0.0003
16.8752
Cancer
0.0035
No Cancer
0.9965
16.9000
Local
0.5100
9.8499ional
0.3700
Distant
0.1200
13.4000
0.0000
7.9000
2.4000

Calculation of Expected Survival for Screening

Work decision tree backward from right to left:

- Value of a terminal node is its expected payoff
  - **Expected Life Years if Screened with Local Cancer = (.02*0)+(.98*13.4) = 13.132**
  - **Expected Life Years if Screened with Any Type of Cancer = (.73*13.132)+(.25*7.742)+(.02*2.4) = 11.5699**
  - **Expected Life Years if Screened with Abnormal (Positive) Result = (.0258*11.5699)+(.9742*16.9) = 16.7624**
  - **Expected Life Years if Screened = (.1023*16.7624)+(.8977*16.8947) = 16.8812**

Value of Screening: Practical

Expected Life Years Gain of Screening vs. Non-Screening

= 16.8812-16.8752

= .006 years

= .006*365

= 2.19 days

Costs of Screening, 1992 USD

Category	Cost $
Marginal cost of clinical breast exam during routine visit for other conditions	8
Screening mammography (two-view)	65
Total outpatient costs of diagnostic work-up for abnormal screening Mammogram	657
Incisional biopsy	170
Localization	46
Pathology reading	30
Two physician visits	62
Facility costs	275
Mammogram for diagnosis	74

Expected Incremental Cost of Screening per Individual

Cost of mammography $73.58

Expected cost of biopsy for true- and false- positives of screening
.1023*$657= $67.20

Total Cost of Screening **$73.58 + $67.20 = $140.78**

Diagnostic Cost of Non-Screen **0.00352 * $657 = 2.30**

Incremental Cost of Screening **$140.78 – $2.30 = $138.48**

Cost-Effectiveness Analysis
Average Risk Women 65-69 yrs.

Strategy	Cost $	Incr. Cost $	Avg. Eff yrs. of life	Incr. Eff yrs. of life	ICER $
No Screen*	2.30	0	16.8752	0	0
Screen	140.78	**138.48**	16.8812	**0.006**	**23,080**

*Non-screeners experience diagnostic cost when identified by symptoms.

Results

Compared with no screening, the incremental cost-effectiveness of screening a 65-69 year old asymptomatic woman with average health

Incremental C/E ratio = $ 138/.006

~ $ 23,000

Sensitivity Analysis: Changing the Incidence Rate of BC

Base Case Incidence = 0.00352

VARIABLE	VARIABLES	STRATEGY	COST	EFF	CE	INCRCOST	INCREFF	INCRCE
0.00176	incidence	No Screen	1.15	16.88	0.068	0	0	0
0.00176	incidence	Screen	139.74	16.89	8.273	138.58	0.00298	46,559
0.00308	incidence	No Screen	2.02	16.87	0.119	0	0	0
0.00308	incidence	Screen	140.52	16.88	8.322	138.49	0.00521	26,588
0.0044	incidence	No Screen	2.89	16.86	0.171	0	0	0
0.0044	incidence	Screen	141.30	16.87	8.372	138.41	0.00744	18,600
0.00572	incidence	No Screen	3.75	16.85977	0.222	0	0	0
0.00572	incidence	Screen	142.08	16.86945	8.422	138.32	0.00967	14,299,
0.00704	incidence	No Screen	4.62	16.85049	0.274	0	0	0
0.00704	incidence	Screen	142.86	16.8624	8.472	138.23	0.01191	11,610

Base Case ICER= $23,080

Replicate for 85+ Age Group with Major Comorbidity

- Calculate Probabilities
- Roll Back to Estimate Expected Life Years of Screeners and Nonscreeners
- Assume Incremental Cost of Screening = $140
- Calculate C/E ratio

Value of Screening 85+

Increase in Expected Life Years=

4.9958 - 4.9944 =

.0014 years =

.0014*365 = .51 days

Results 85+

Compared with no screening, the incremental cost-effectiveness of screening a 85+ year old woman with major co-morbidity

Incremental C/E ratio =

$140/.0014 = $100,000

Sensitivity Analysis

Results were most sensitive to:

- The incidence of cancer
- Quality of life adjustments.

Results were less sensitive to:

- Perioperative mortality
- Test characteristics (e.g., PPV, NPV, Specificity, Sensitivity)
- Stage distribution with false negative screening results.

Sensitivity Analysis (quality of life)

Impact of Long-Term Quality of Life Adjustments (Mandelblatt et al. Table 4)

- **Savings gained from screening persisted for all age, race, and health groups.**

Impact of Short- and Long-Term Quality of Life Adjustments (Mandelblatt et al. Table 5)

- All QALYS were about .5 days lower than in unadjusted model. This resulted in a net loss in QALYS due to screening for women ≥ 85 years old.

Study Limitations

Assumed 100% adherence to screening.

Quality of life assumed, not measured.

Screen test estimates from studies of younger women.

Cost of cancer treatment not included.

Summary

Screening is effective for older women with and without comorbidity.

Screening is more cost-effective in Black women and less cost-effective in oldest women and women with comorbidity.

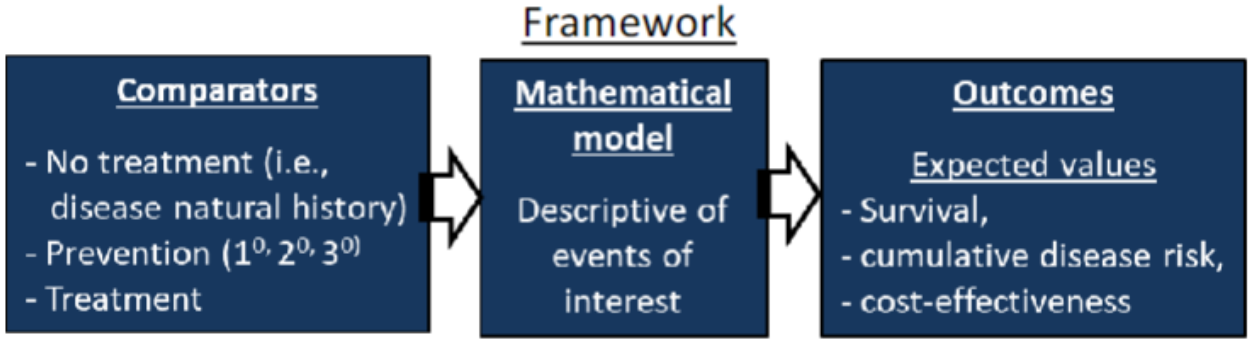
The cost-effectiveness of screening ranges from $23,000 for a 65-69 year old with average health to $100,000 for a 85+ year old woman with major co-morbidity.

CEA Review (Again)

- 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 Review Again

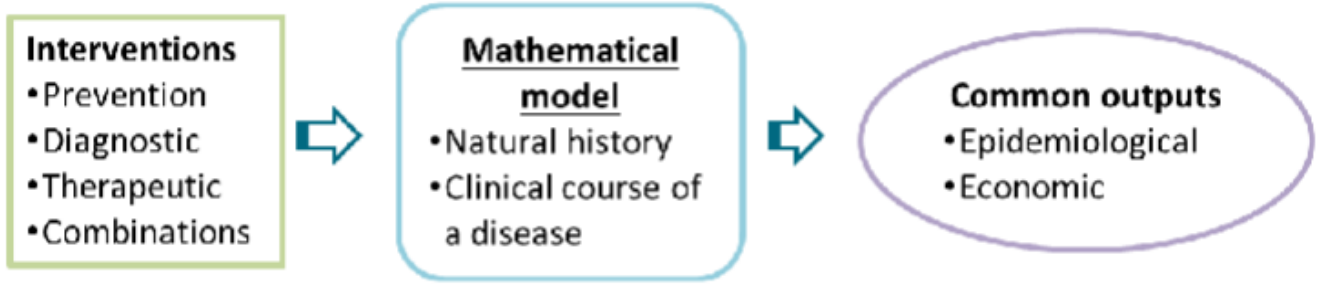
- A quantitative method for evaluating decisions between multiple alternatives under conditions of uncertainty
  - Is this like real life?



- 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 Review Again

- 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 Analytic Modeling Review

- 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