Can We Do Better than "One Size Fits All"? OR Models for Screening and Treatment

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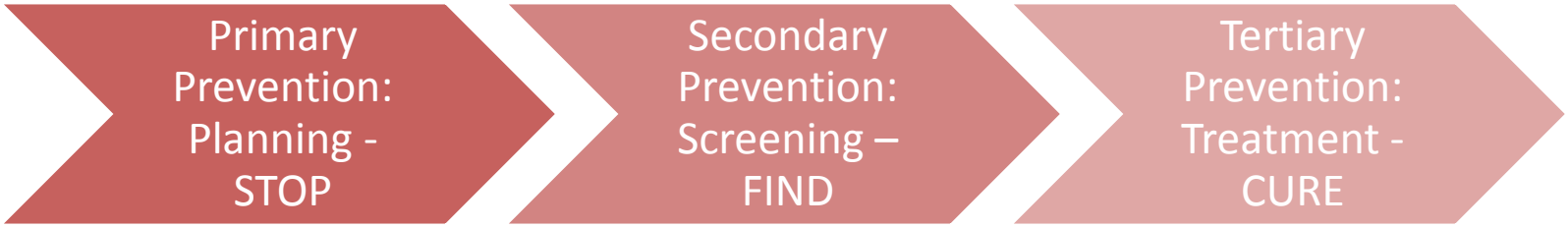
Presentation Agenda

- Prevention – Chronic Disease – Modeling
- Case Study: Breast Cancer Screening
- Background and motivation
- Model formulation
  - Partially observable Markov model
  - Sample path behavior
- Parameter estimation
  - Life-time breast cancer mortality
- Numerical experiments and results
  - Policy evaluation
- Conclusions and future work

An Ounce of Prevention is Worth a Pound of Cure

- "Health maintenance" refers to personal activities intended to *enhance* health or *prevent* disease and disability.



- Chronic Diseases: have a long course of illness, rarely resolve spontaneously and are generally not cured by medication or prevented by vaccine. (http://www.doh.state.fl.us/family/chronicdisease/)
  - Chronic diseases are the leading causes of death and disability in the United States.
  - Chronic diseases are leading cause of mortality in the world: 63% of all deaths. (WHO)
  - Out of the 36 million people who died from chronic disease in 2008, 9 million were under 60 and 90% of these premature deaths occurred in low- and middle-income countries. (WHO)
  - Chronic diseases account for 70% of all deaths in the U.S.: 1.7 million each year. (CDC)
  - These diseases also cause major limitations in daily living for almost 1 out of 10 Americans or about 25 million people. (CDC)

Modeling Chronic Disease

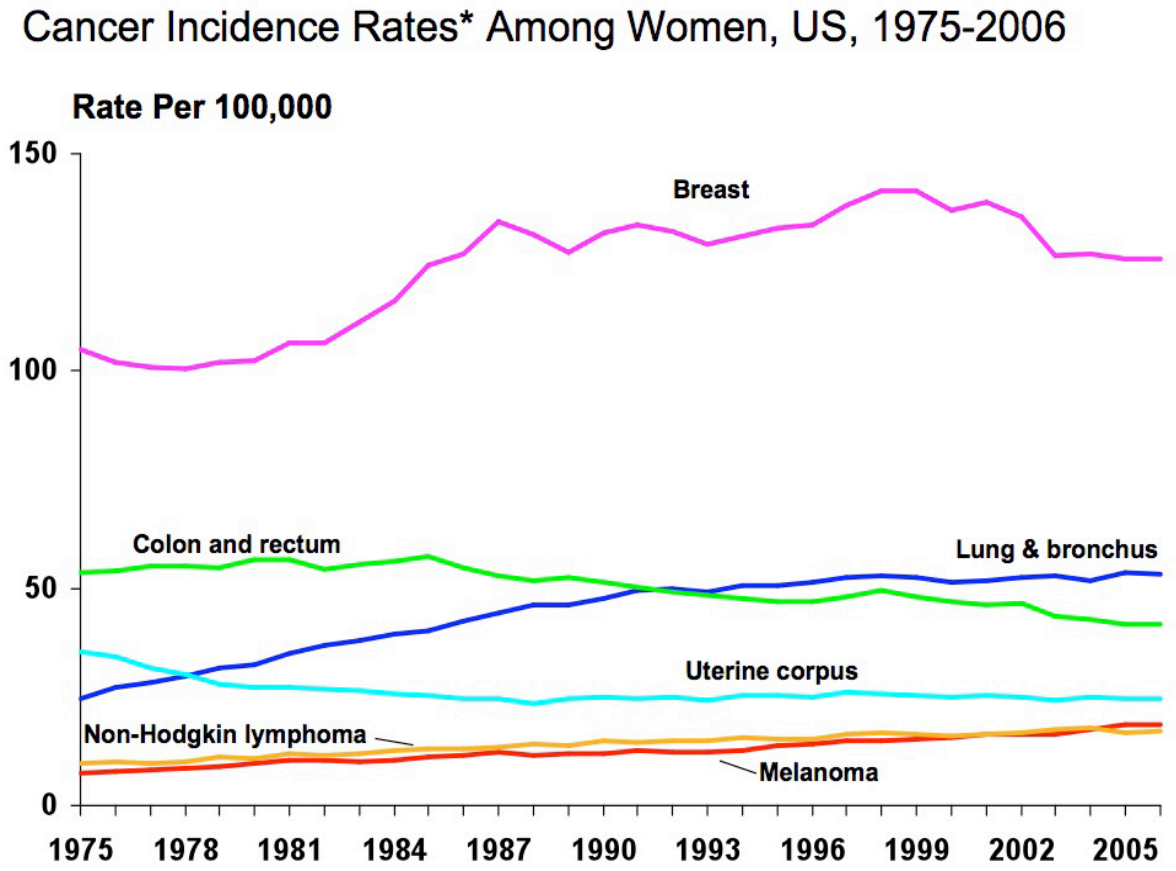
- Common OR Modeling Tools
  - Stochastic Modeling
  - Markov Decision Processes & Partially Observable (Hidden) MDP
  - Multi-agent Models
  - Survival Analysis
- Implicit Requirements for utilizing these modeling tools are:
- Metrics for Measuring a “Good” Decision,
- Methods for Capturing Disease Progression, and
- Methods for Defining and Characterizing the “state”
- Challenges:
  - Behavioral Modeling – Discrete Choice Models – Patient Preference
  - Data Analysis – time series, longitudinal, sparse data, quantitative and qualitative
  - Data from Various Sources

Breast Cancer Case Study

Background

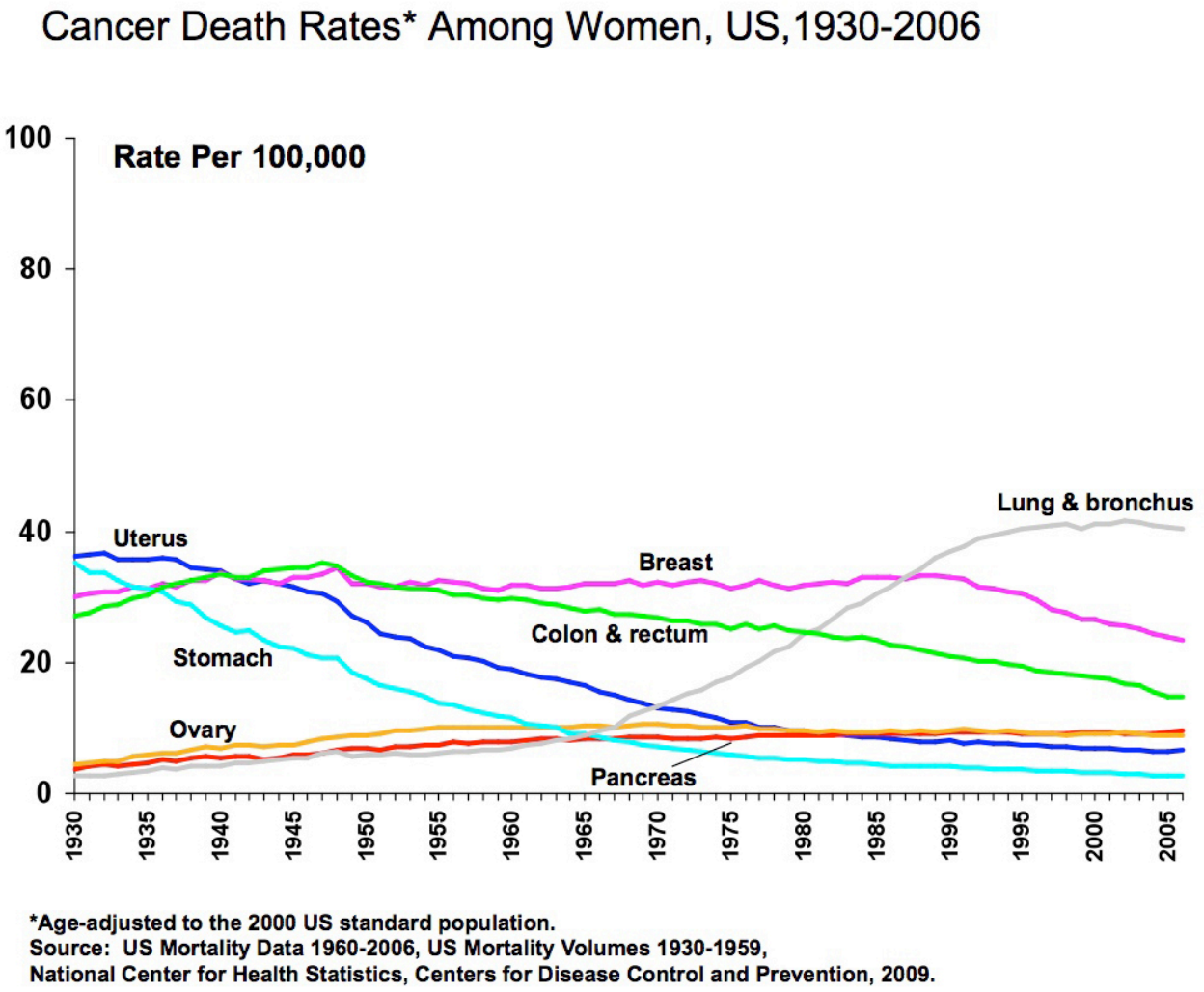
- Breast cancer is the most common noncutaneous cancer in American women (American Cancer Society: ACS)
  - One in eight women
  - 230,480 new cases (both in situ and invasive) estimated in 2011
- High mortality risks
  - Number one cause of cancer death in Hispanic women
  - Second most common cause of cancer death in other races
  - 39,520 breast cancer death in women in 2011
- Mammography
  - Current recommended screening technology
  - Regular screening mammograms help reduce deaths from breast cancer

Background - Statistics



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2006, National Cancer Institute, 2009.

Background - Statistics

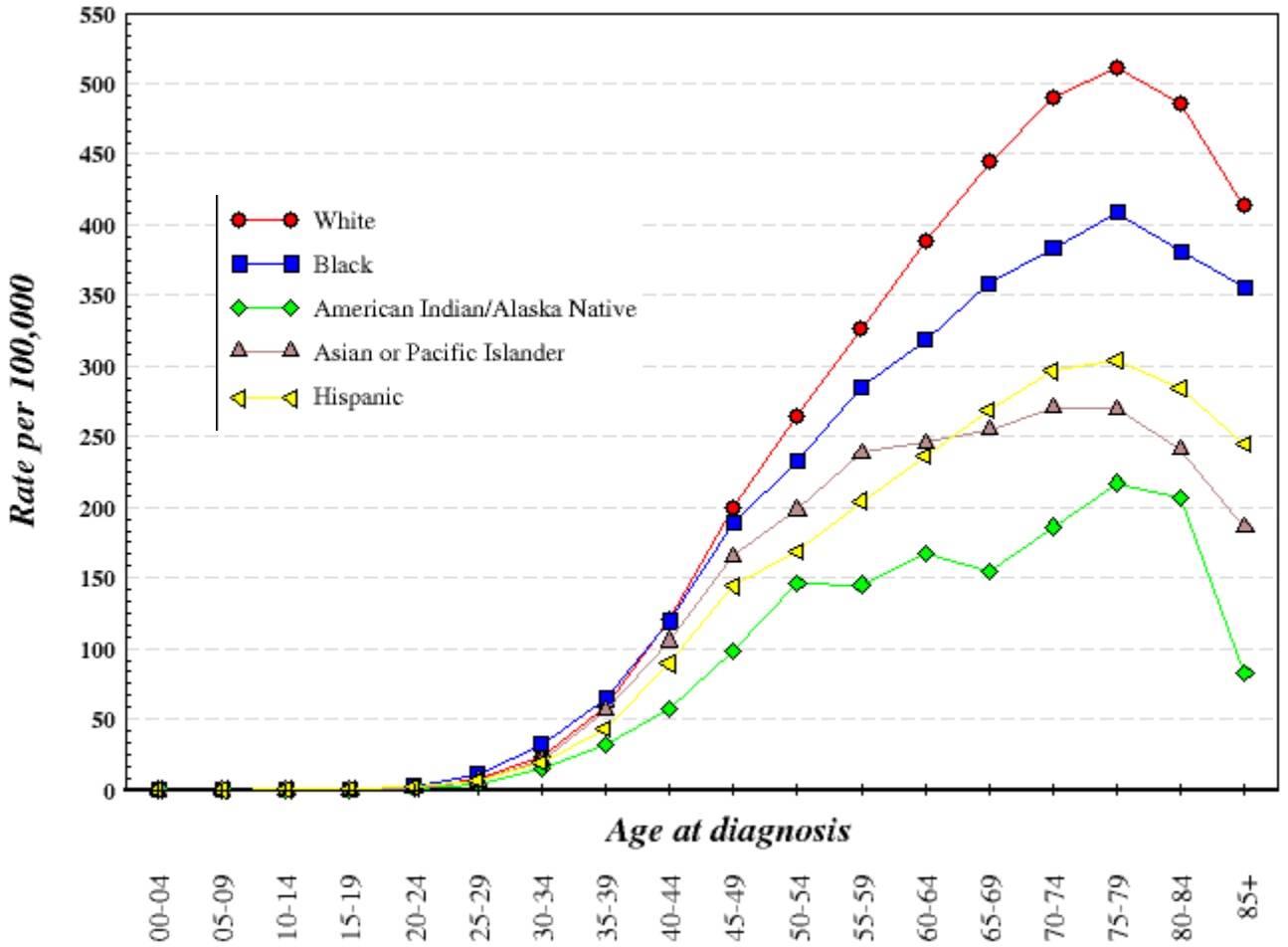


Age Effects

- Incidence
  - increases with age
- Aggression
  - decreases with age
- Mammogram accuracy
  - increases with age
    - due to lower tissue density
- *Survival*
  - *increases with age*
    - *due to more responsive tumors*

Age Effects: Incidence

- By age 25
  - 1 in 19,608
- By age 35
  - 1 in 622
- By age 45
  - 1 in 93
- By age 55
  - 1 in 33
- By age 65
  - 1 in 17
- By age 75
  - 1 in 11
- By age 85
  - 1 in 8



Age Effects: Aggression

- Mean sojourn time of the detectable, preclinical phase
  - 40-49: 2.4 years
  - 50-59: 3.7 years
  - 60-69: 4.2 years
  - 70-79: 4 years
- Median doubling time
  - 40-49: 80 days
  - 50-70: 157 days
  - over 70: 188 days

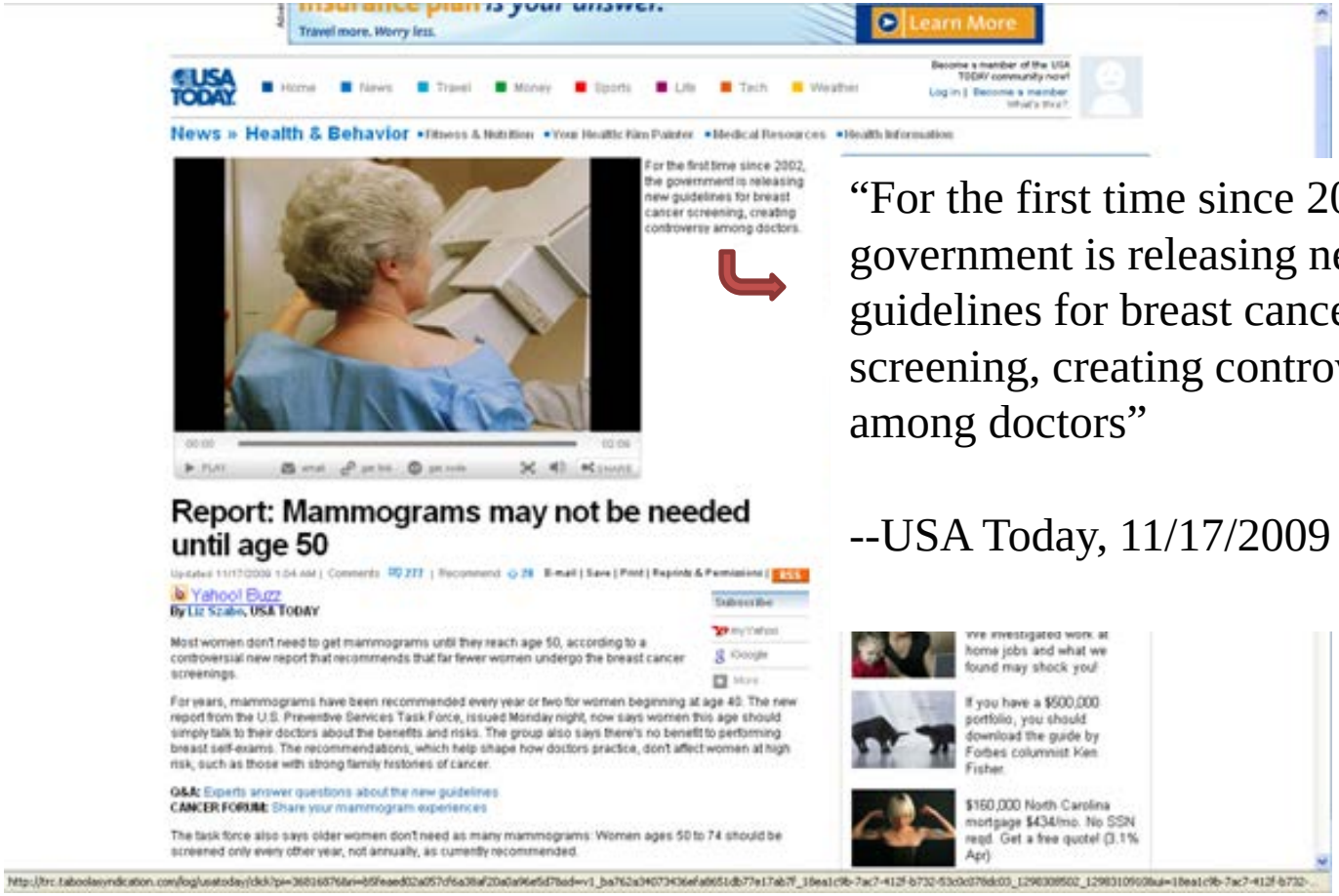
Age Effects: Tumor Responsiveness

- Lifetime survival by stage at detection
  - under 60
    - localized 79%
    - regional 51%
    - distant 19%
  - 60-69
    - localized 82%
    - regional 56%
    - distant 21%
  - over 70
    - localized 86%
    - regional 66%
    - distant 30%

Background - Mammography

- Benefits
  - Small tumors can be detected; more treatment options are available
  - Some type of breast cancer (in situ) can only be detected through mammogram
  - Minimal radiation remains
- Risks
  - A slight chance of cancer from excessive exposure to radiation
  - False positive mammograms
- Major controversies over breast cancer screening guidelines
  - Under-diagnosis – higher mortality
  - Over-diagnosis – unnecessary treatment

Media Report on New Guideline



"For the first time since 2002, the government is releasing new guidelines for breast cancer screening, creating controversy among doctors"

--USA Today, 11/17/2009

Mammography Screening Guidelines

	Agency	Recommendation
US	**American Cancer Society**	**Yearly for women > 40**
	US Preventive Services Task Force (since 2009)	**Every 2 year for women 50-74**
	US Preventive Services Task Force (before 2009)	Every 1-2 year for women 50-69
	American Academy of Family Physicians	Every 1-2 year for women 50-69, counsel women 40-49
	American College of Obstetricians and Gynecologists	Every 1-2 year starting at age 40, yearly after 50
	American Medical Association	Every 1-2 year for women 40-49, yearly beginning at 50
International	Canadian Task Force on Preventive Health Care	Every 1-2 year for women 50-69
	NHS Breast Screening Programme in UK	Every 3 years for women >50
	BreastScreen Australia	Every 2 years for women 50-69

Age Effects: Mammography Accuracy

- Sensitivity (true+)
  - under 40: 54%
  - 40-49: 77%
  - 50-64: 78%
  - older than 64: 81%
- Specificity (true-)
  - 40-49: 92%
  - 50-59: 93%
  - 60-69: 95%
  - 70-79: 96%

Motivation

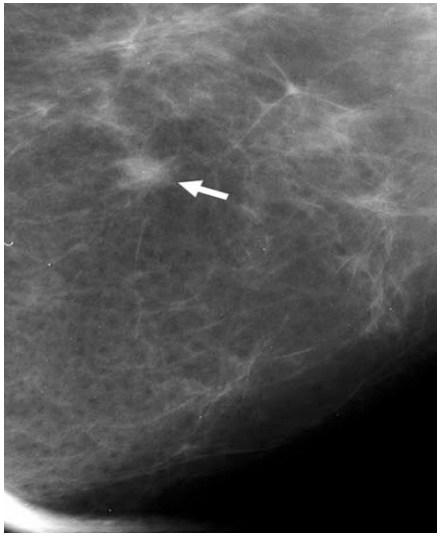
- Average population → Individual
  - Risks or outcomes are not the same
  - Disease is not developed the same way
- Common assumptions on disease modeling and decision making
  - Breast cancer natural progression (ACS definition)
    - Cancer free
    - Ductal carcinoma in situ (noninvasive)
    - Invasive
    - Death from breast cancer and other causes
  - Parameter estimation
- Studies have shown breast cancers may spontaneously regress without treatment

Medical Evidence

- Norwegian mammography study (2008)
  - Zahl et al., Archives of Internal Medicine, 168(21), Vol. 168 No. 21, November 24, 2008
  - Compared breast cancer rates among nearly 120,000 women for 3 mammograms over 6 years with the rates among nearly 110,000 women in a control group that were invited to undergo a 1-time prevalence screen at the end of the observation period
  - Higher incidence rates in the screening group compared to the control group
  - “The study, …, suggested breast cancer screening may be leading to overdiagnosis of cancer, with upwards of *22 percent* of cases likely to resolve themselves without treatment” – CBS news (November 25, 2008)

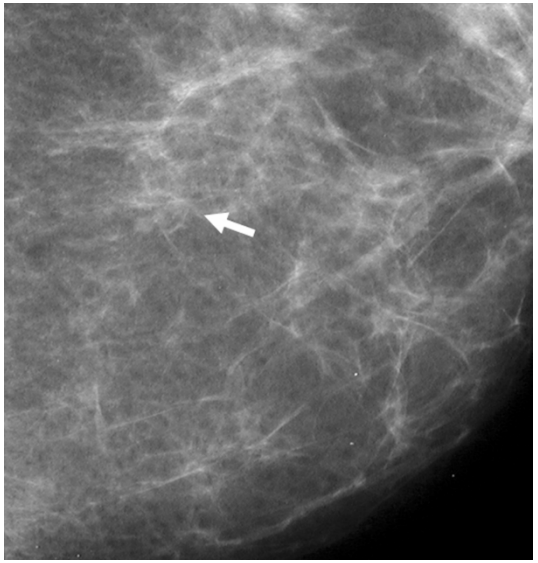
Medical Evidence

- Larsen and Rose (1999)
  - A literature review on spontaneous remission
  - 32 cases were found; phenomenon is rare
- Burnside et al. (2006)
  - An example of regression on imaging



A mass is confirmed on imaging for a 64-year-old asymptomatic female

One year after the initial mammogram, the imaging demonstrate that the mass has disappeared.



Research Objectives

- Propose a Markov model to incorporate breast cancer spontaneous regression
- Find the impact of spontaneous regression rate on the estimate of lifetime breast cancer mortality probability
- Incorporate different treatment decisions in the case of regression
- Select different screening policies and test the impact of regression rate

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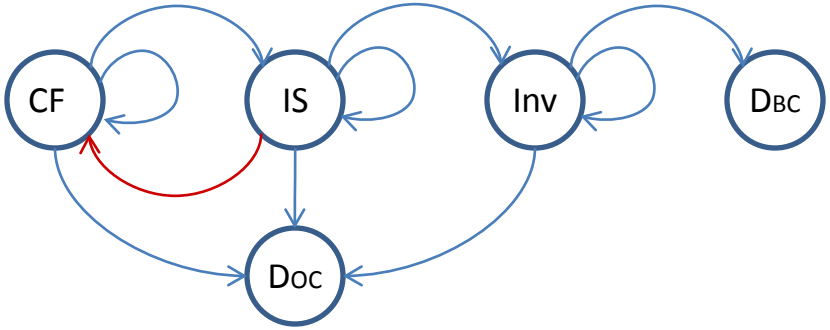
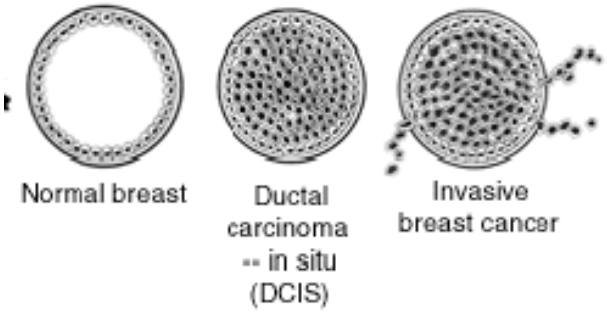
Model Formulation

- Five-state discrete-time Markov chain



State
1: CF – Cancer Free
2: IS – In Situ
3: Inv – Invasive
4: DBC – Death from breast cancer
5: DOC – Death from other causes

- **In situ**: *cancer cells that start in the ducts but have not grown through the duct walls into the nearby tissue*
  - Can only be diagnosed by mammography
- **Invasive**: *cancer that has spread beyond the layer of cells where it first developed and has grown into nearby tissues*
  - Can be seen in a mass



Siteman Cancer Center

Model Formulation

- Age-dependent transition probability matrix

$= T(a_n)$: Transient state transition matrix

$$P(a_n) = \begin{bmatrix} p_{11}(a_n) & p_{12}(a_n) & 0 & 0 & p_5(a_n) \\ p_{21}(a_n) & p_{22}(a_n) & p_{23}(a_n) & 0 & p_5(a_n) \\ 0 & 0 & p_{33}(a_n) & p_{34}(a_n) & p_5(a_n) \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

a_n is the patient age at period n

- Belief State
  - Partially observable $\underline{\pi} = (\pi_1, \pi_2, \pi_3)$
  - Probability distribution of all possible states
  - Disease occupancy

Main Assumptions

- Breast cancer will only regress at in situ stage.
- Mammograms are independent of each other.
- If the screening result is abnormal, a biopsy will always be ordered, and the biopsy is assumed to be perfect.
  - If true positive, go treatment and leave model, or wait (depends on decision rules)
  - If false positive, re-enter at cancer free stage and proceed
- Probability of dying from other causes are the same from each state.

Parameters for Modeling

Parameters	Description
$W_n(\underline{\pi}_n)$	Main outcome measure: Lifetime breast cancer mortality probability
$\underline{\pi}_n=[\pi_{n,1} \quad \pi_{n,2} \quad \pi_{n,3}]$	Disease occupancy distribution at period n (cancer free, in situ, invasive)
$m_j(a_n)$	Probability of getting an abnormal mammogram result given at age a_n and in disease stage j, j=1,2,3
$r_1(a_n)$	Treated life time breast cancer mortality probability if the cancer is detected at in situ
$r_2(a_n)$	Treated life time breast cancer mortality probability if the cancer is detected at invasive

Actions at Period n

- Do nothing

Invasive to BC Death

Die from other causes

Survive to the next period

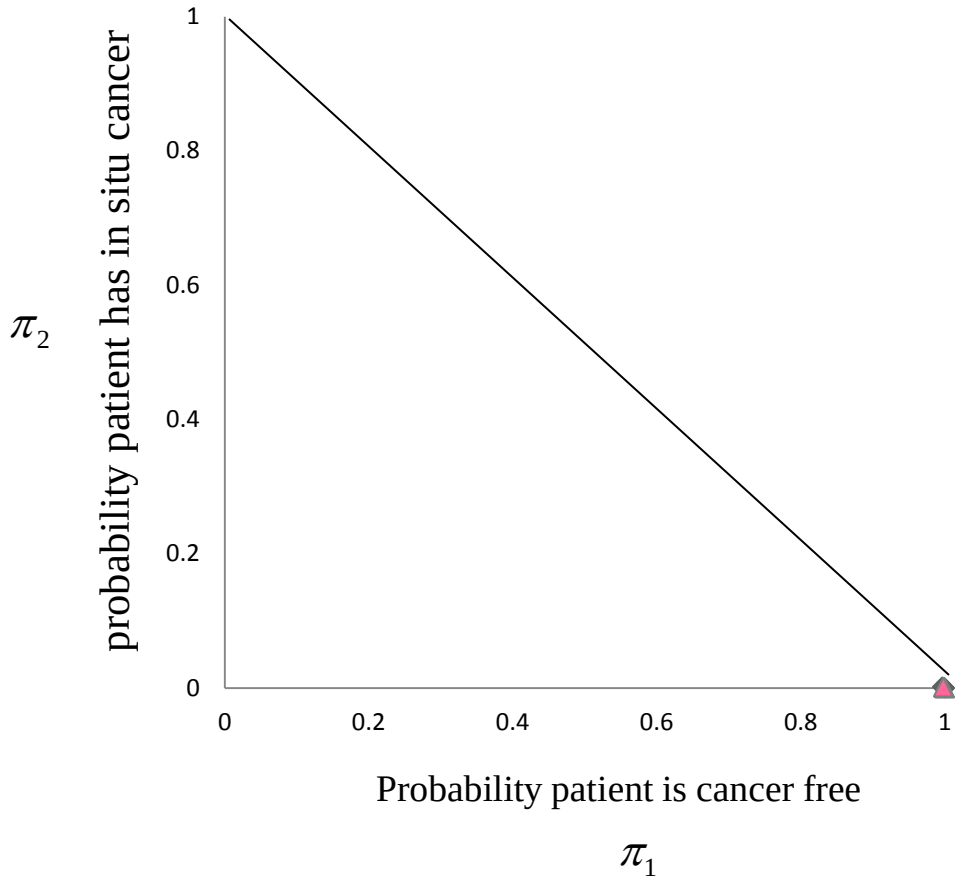
$$W_n(\underline{\pi}_n) = DN_n(\underline{\pi}_n) \equiv \pi_{n,3} p_{34}(a_n) \cdot 1 + (\pi_{n,1} + \pi_{n,2} + \pi_{n,3}) p_5(a_n) \cdot 0$$
$$+ [1 - \pi_{n,3} p_{34}(a_n) - (\pi_{n,1} + \pi_{n,2} + \pi_{n,3}) p_5(a_n)] \cdot W_{n+1}(\underline{\pi}_{n+1})$$
$$= \pi_{n,3} p_{34}(a_n) + [1 - \pi_{n,3} p_{34}(a_n) - p_5(a_n)] \cdot W_{n+1}(\underline{\pi}_{n+1})$$

Update occupancy distribution for next period

$$\underline{\pi}_{n+1} = \frac{\underline{\pi}_n T(a_n)}{1 - \pi_{n,3} p_{34}(a_n) - p_5(a_n)}$$

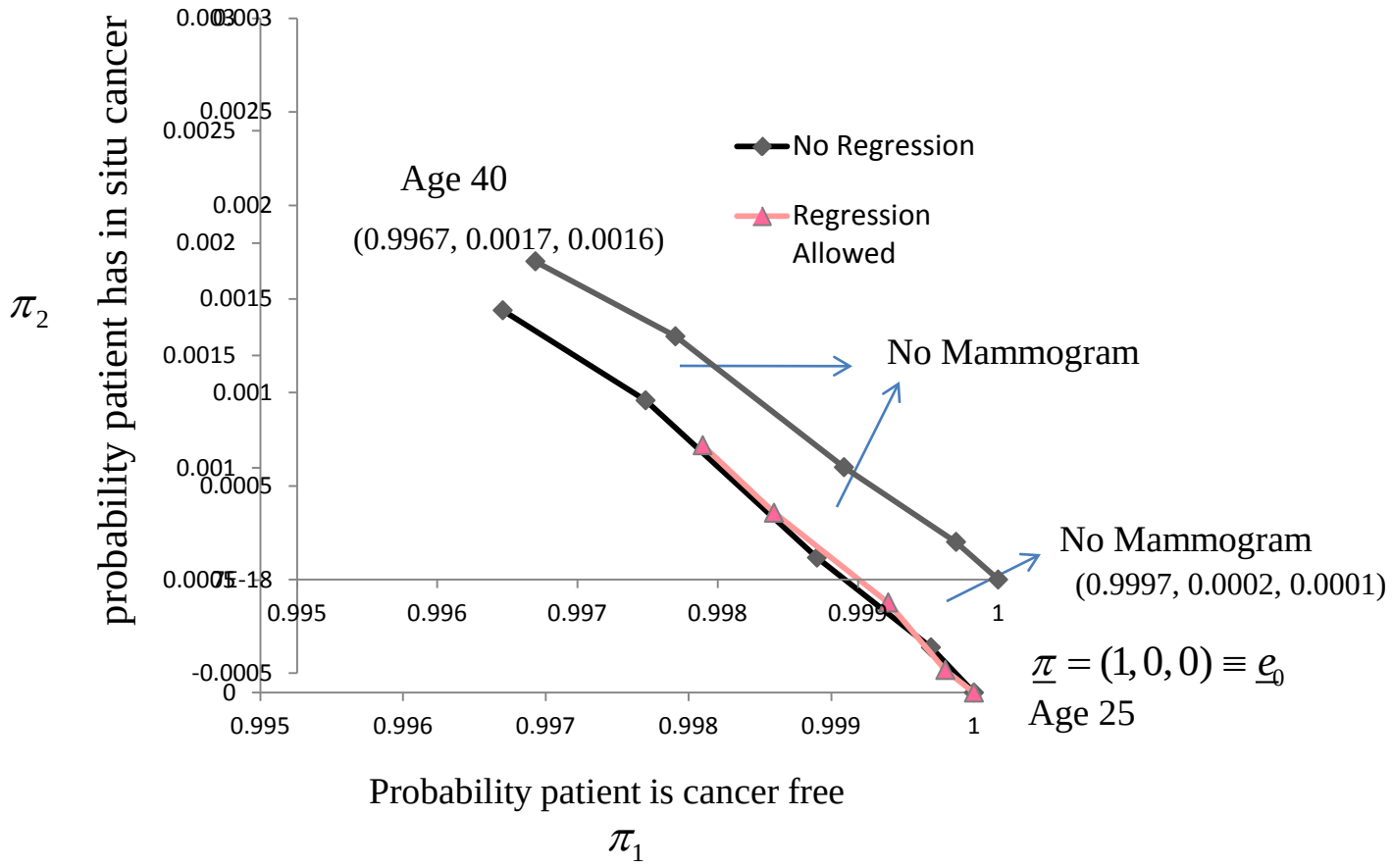
- Mammogram
  - Different treatment decision rules for updating lifetime breast cancer mortality probability
    I. Always treat
    II. Wait till invasive
    III. Wait once

Sample Path Overview



Sample Path Example

$$\underline{\pi}_{n+1} = \frac{\underline{\pi}_n P_{1-3}(a_n)}{1 - \pi_{n,3} p_{34}(a_n) - p_5(a_n)}$$



Decision Rules After Diagnosis

I. Always go to treatment after true diagnosis

False positive — Diagnosed at in situ — Diagnosed at invasive

$$W_n(\underline{\pi}_n) = M_n(\underline{\pi}_n) \equiv \pi_{n,1} m_1(a_n) DN_n(\underline{e}_0) + \pi_{n,2} m_2(a_n) r_1(a_n) + \pi_{n,3} m_3(a_n) r_2(a_n)$$
$$+ [\sum_{i=1}^{3} \pi_{n,i}(1 - m_i(a_n))] \cdot DN_n(\underline{\pi}_n'')$$

Negative screening result, and do nothing

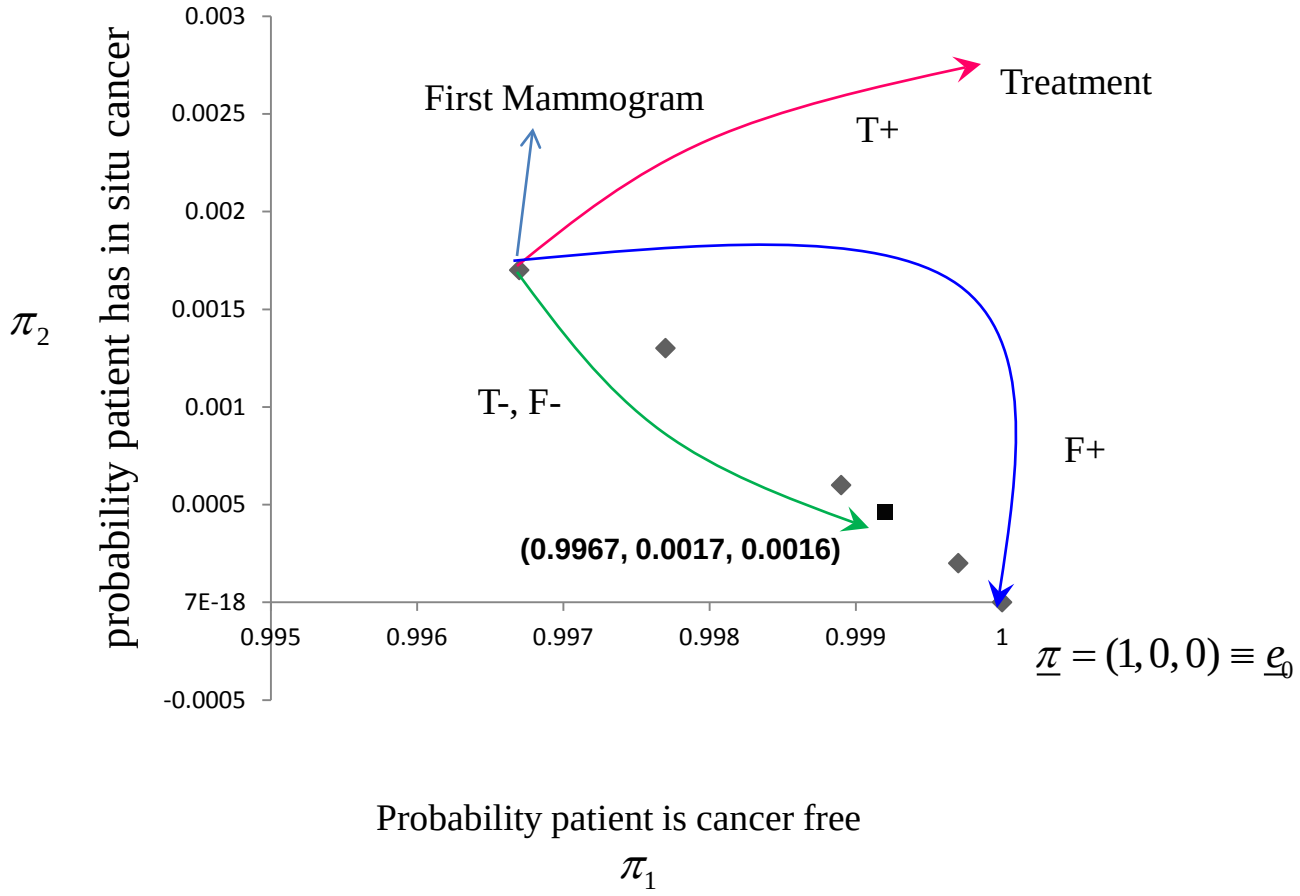
where $\underline{e}_0 = [1 \;\; 0 \;\; 0]$

Update occupancy distribution after normal result

$$\pi''_{n,j} = \frac{\pi_{n,j}(1 - m_j(a_n))}{\sum_{i=1}^{3} \pi_{n,i}(1 - m_i(a_n))}, \quad j = 1, 2, 3$$

Sample Path Example

$$\pi''_{n,j} = \frac{\pi_{n,j}(1-m_j(a_n))}{\sum_{i=1}^{3}\pi_{n,i}(1-m_i(a_n))}$$



Decision Rules After Diagnosis

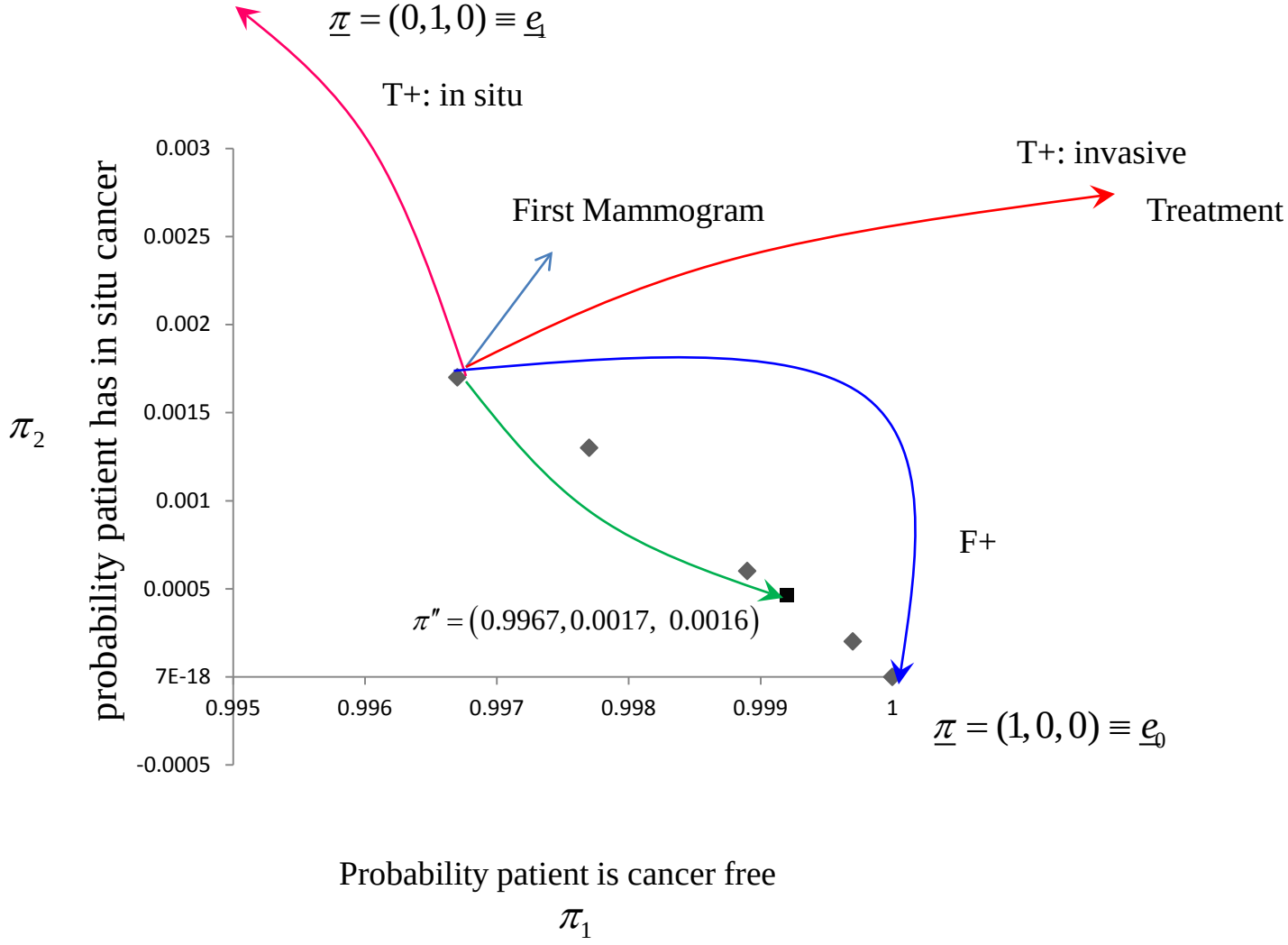
II. Wait and do not treat when diagnosed at in situ stage, continue screening and only treat when diagnosed at invasive stage

Do not treat at in situ

$$W_n(\underline{\pi}_n) = M_n(\underline{\pi}_n) \equiv \pi_{n,1} m_1(a_n) DN_n(\underline{e}_0) + \pi_{n,2} m_2(a_n) DN_n(\underline{e}_1) + \pi_{n,3} m_3(a_n) r_2(a_n)$$
$$+ [\sum_{i=1}^{3} \pi_{n,i}(1 - m_i(a_n))] \cdot DN_n(\underline{\pi}_n'')$$

where $\underline{e}_1 = [0 \;\; 1 \;\; 0]$

Sample Path Example



Decision Rules After Diagnosis

III. If diagnosed at in situ stage for the first time in screening, wait and do not treat until diagnosed again in the next screening

$$W_n(\underline{\pi}_n) = M_n(\underline{\pi}_n) \equiv \pi_1 m_1(a_n) DN_n(\underline{e}_0) + \pi_2 m_2(a_n) DN_n(\underline{e}_1) \cdot \prod_{k=1}^{m-1}(1 - m_2(a_k))$$

$$+ \pi_2 m_2(a_n) r_1(a_m) \cdot [1 - \prod_{k=1}^{m-1}(1 - m_2(a_k))] + \pi_3 m_3(a_n) r_2(a_n)$$

$$+ [\sum_{i=1}^{3} \pi_i (1 - m_i(a_n))] \cdot DN_n(\underline{\pi}_n'')$$

where m is the number of mammograms so far

Boundary Conditions

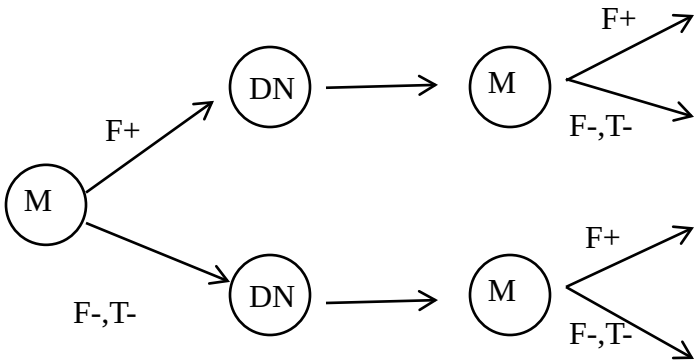
- In the last period N, the patient will die from breast cancer if she is in the cancer states, otherwise she will not die from breast cancer.

$$DN_N(\underline{\pi}) = \pi_2 + \pi_3$$

$$M_N(\underline{\pi}_n) = \pi_{n,2} m_2(a_n) r_1(a_n) + \pi_{n,3} m_3(a_n) r_2(a_n)$$
$$+ [\sum_{i=1}^{3} \pi_{n,i}(1 - m_i(a_n))] \cdot (\pi''_{n,2} + \pi''_{n,3})$$

Complexity

Always Treat

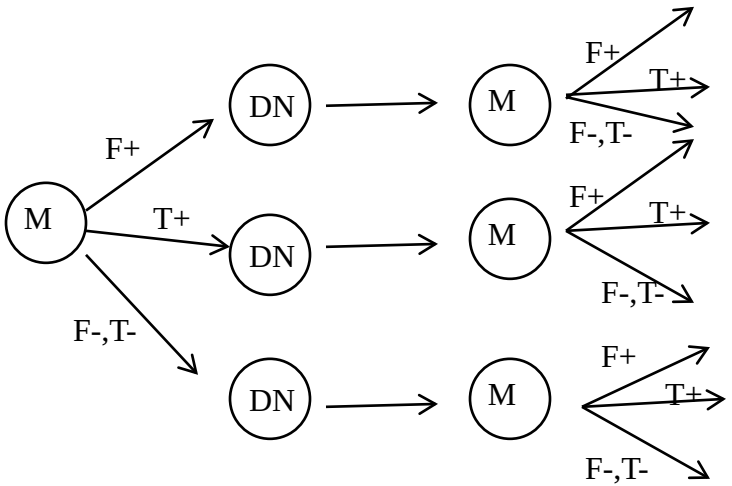


2^m with no T+

↓

2m + 1

Wait till Invasive



3^m with no T+

↓

4m

Numerical Experiment

- Start at age 25 with cancer free, and end at age 100
- Decision epoch, every 6 months
- Transition probability matrix updates every 5 years
- Regression rate can be extracted from either self-loop probability or progression probability

$$p_{21}(a_t) + p_{22}(a_t) + p_{23}(a_t) = 1$$
$$p'_{21}(a_t) = u \cdot p_{22}(a_t) + v \cdot p_{23}(a_t)$$
$$p'_{22}(a_t) = (1-u) \cdot p_{22}(a_t)$$
$$p'_{23}(a_t) = (1-v) \cdot p_{23}(a_t)$$
$$0 \le u, v \le 1$$

Numerical Experiment

- Compare existing screening guidelines
  - American Cancer Society
    - Annual screening from age 40
  - US Preventive Services Task Force
    - Biennial screening from age 50 to 75

Parameter Estimate

Model Parameter	Data Source
Progression rate	Tabar et cl. (2000)
Untreated survival	Bloom et al. (1962)
Death from other causes	CDC Mortality SEER mortality SEER prevalence SEER stage distribution
Incidence	SEER
Specificity	Elmore et al. (1998)
Sensitivity by state	Sibbering et al. (1995)
Treated lifetime breast cancer mortality probability by state	Zhang et al. (2011)

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- Introduction to data
- Method for mortality estimation and variation approximation
- Examples
- Life-time mortality estimation

Introduction to Data

- Unique ID linked three databases in the community-based Carolina Mammography Registry (CMR)
  - Member site of Breast Cancer Surveillance Consortium (BCSC)
  - Screening Data
    -- Patient demographics
  - Diagnosis data
    -- Cancer information
  - Vital Data
    -- Mortality information
- Summary statistics
  - 22,328 breast cancer cases with known age and cancer stage
  - 1,435 death from breast cancer
  - 1,890 death from other causes

Mortality Estimation

- Competing risks analysis
  - More than one cause of death
  - Only one type of death will occur at end point
  - Complement of the Kaplan Meier (KM) estimator is biased

$$S_{KM}(t_j) = \prod_{t \le t_j} \left(1 - \frac{d_t}{n_t}\right)$$

n_t = number of individuals at risk just prior to time t
d_t = number of deaths at time t

- Partially observable
  - Cancer start time is only observed when diagnosed
  - Left censoring
  - Tumor growth model
  - Simulation

Mortality Estimation

- Nonparametric Cumulative Incidence Function

$$F_r(t) = \sum_{j: j \le t} \frac{d_{rj}}{n_j} S_{KM}(t_{j-1})$$

d_{rj} = number of patients who die from cause r at time t_j
$S_{KM}(t_{j-1})$ = Kaplan-Meier Estimate of the overall survival at last time point j-1
n_j = number of patients at risk of mortality at the beginning of time t_j

where $n_j = n - \sum_{k=1}^{j} (d_k + c_k)$

n = number of patients initially at risk
d_k = sum of all causes deaths occurred
c_j = number of patients right censored (death is not observed) at time t_j

Confidence Interval Approximation

- Variance estimator (Marubini and Valsecchi 1995)

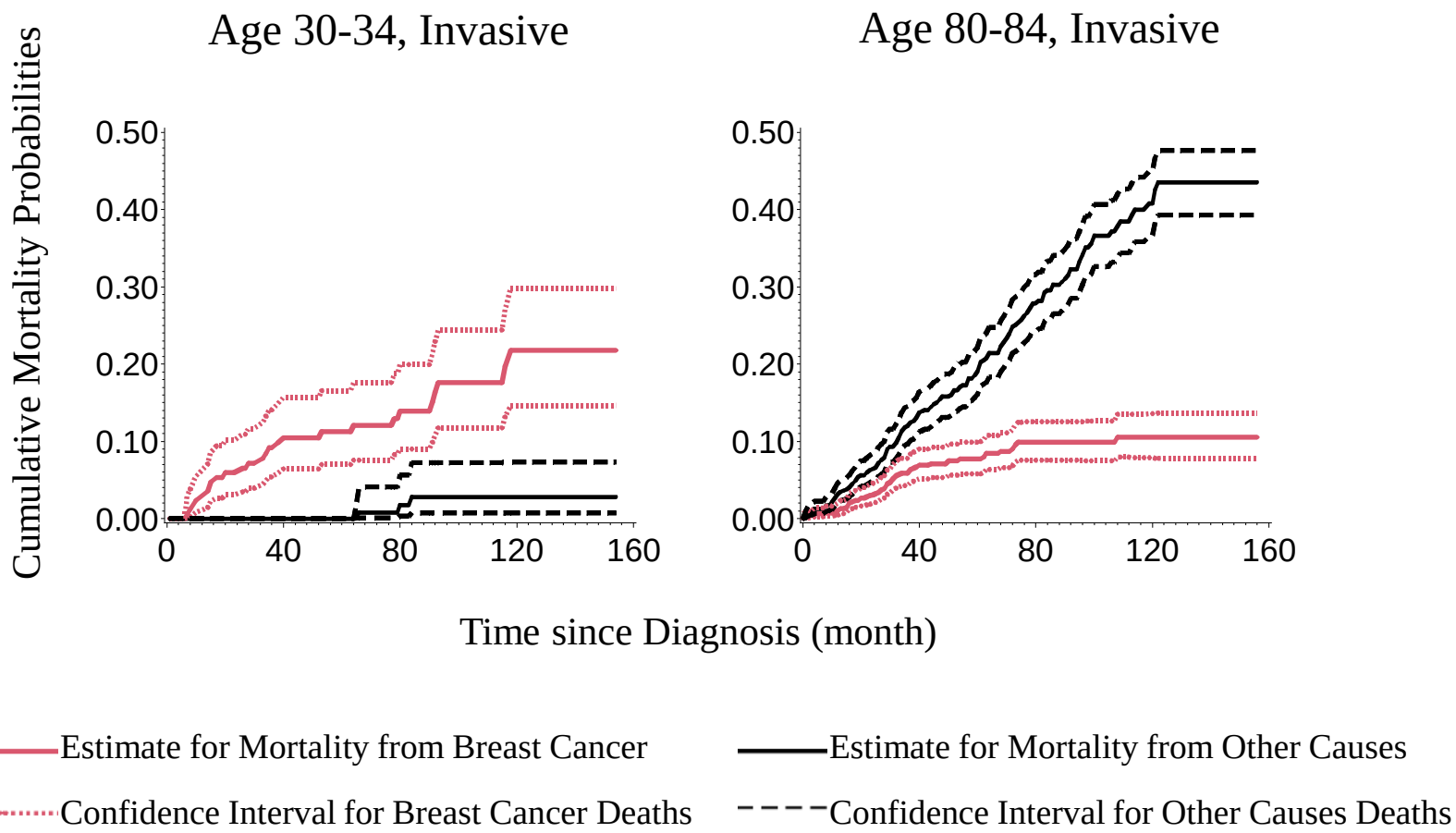
$$Var(\hat{F}_r(t_j)) = \sum_{k=1}^{j} \left\{ \left[\hat{F}_r(t_j) - \hat{F}_r(t_k) \right]^2 \frac{d_k}{n_{k-1}(n_{k-1} - d_k)} \right\} + \sum_{k=1}^{j} S_{KM}{}^2 \frac{(n_{k-1} - d_{rk})}{n_{k-1}} \cdot \frac{d_{rk}}{n_{k-1}^2}$$
$$- 2 \sum_{k=1}^{j} \left[\hat{F}_r(t_j) - \hat{F}_r(t_k) \right] \cdot S_{KM} \cdot \frac{d_{rk}}{n_{k-1}^2}$$

- ln(-ln) transformed bounds for confidence interval (Choudhury 2002)

$$\hat{F}_r(t)^{\exp\left\{ \frac{\pm c_{\alpha/2} \sqrt{Var_r(t)}}{\hat{F}_r(t) \ln(\hat{F}_r(t))} \right\}}$$

where $c_{\alpha/2}$ is the upper α/2 quantile of the standard normal distribution

Mortality Estimation Example



Estimate for Treated Lifetime BC Mortality

- Backward calculation for lifetime mortality
  - Assume patients over 85 years old have the same lifetime breast cancer mortality probability
  - For the age group 85 and over, find the mortality probability at 15 years (life time) with detection at in situ and invasive stage
  - For each age group a_n, lifetime probability

    $r_i(a_n)$ = P(5-year mortality) +[1-P(5-year mortality)]* $r_i(a_{n+1})$

    i = 1, diagnosed at in situ; i = 2, diagnosed at invasive stage

- Range for probability estimate
  - $r_1(25\text{-}29)$ = 0.13657; $r_2(25\text{-}29)$ = 0.6853
  - $r_1(>=85)$ = 0.08200; $r_2(>=85)$ = 0.11600

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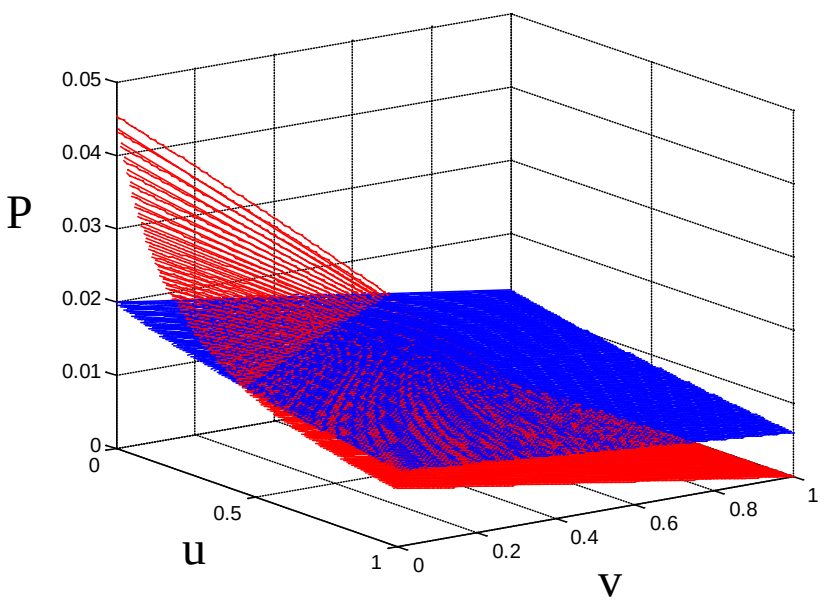
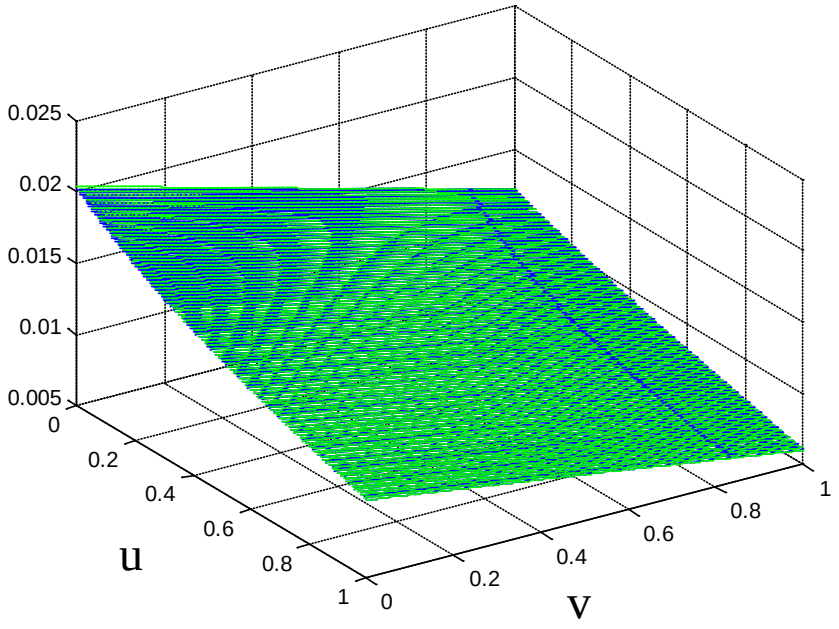
ACS Screening Policy: Annually from 40

X-axis: % from self loop (u) Y-axis: % from progression (v)
Z-axis: Lifetime breast cancer mortality probability

Always treat vs. Wait to Inv

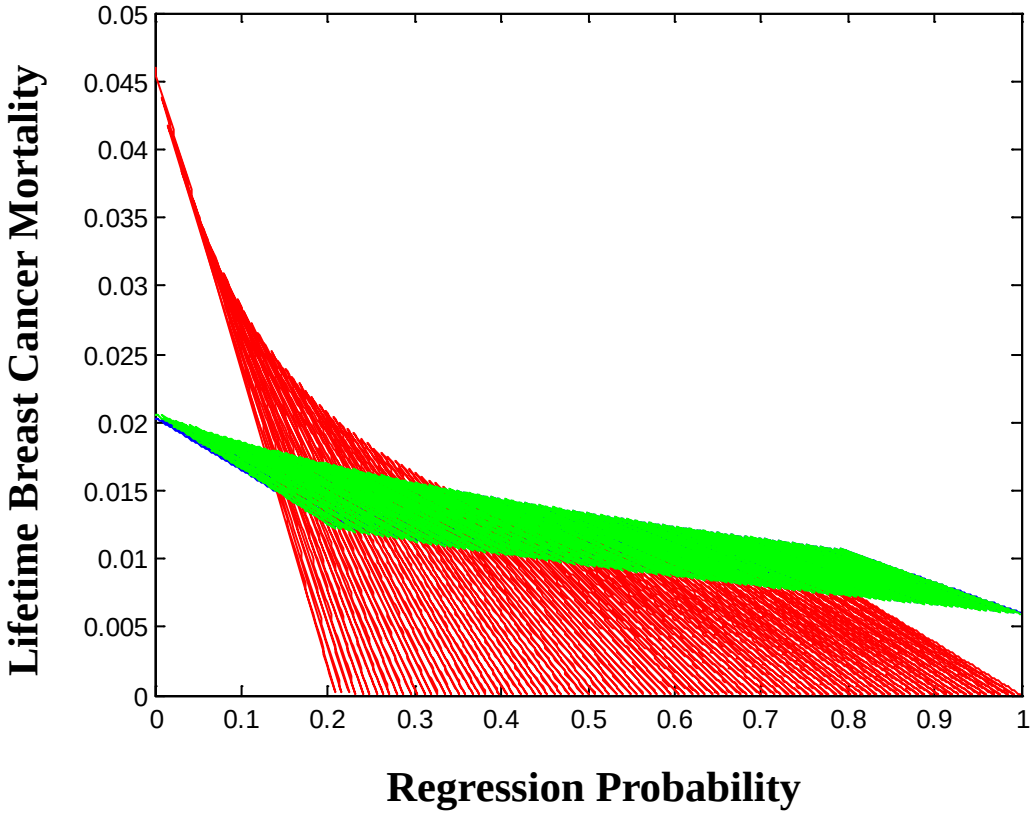


Always treat vs. Wait once



Blue: Treat Red: Wait to Inv Green: Wait once

ACS Screening Policy



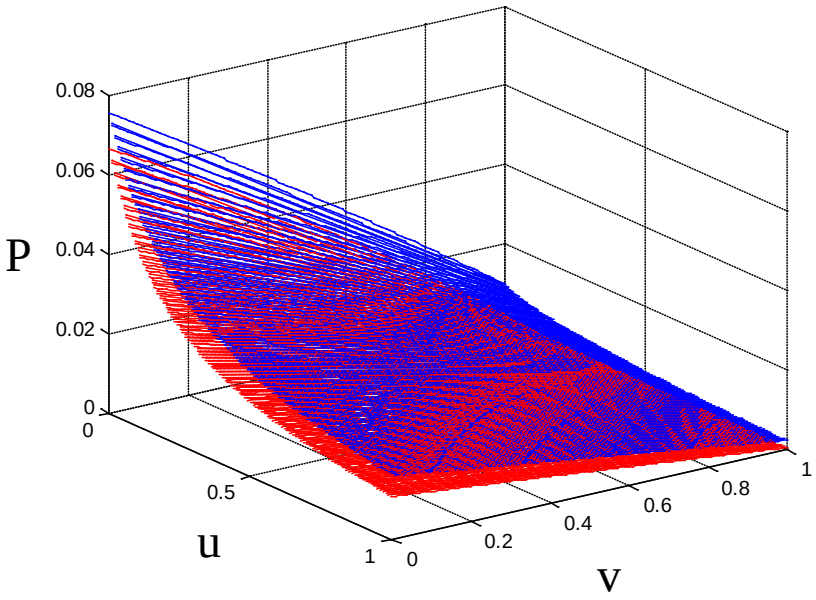
Blue: Treat
Red: Wait to Inv
Green: Wait once

Regression probability is extracted from combinations of progression and self-loop probabilities

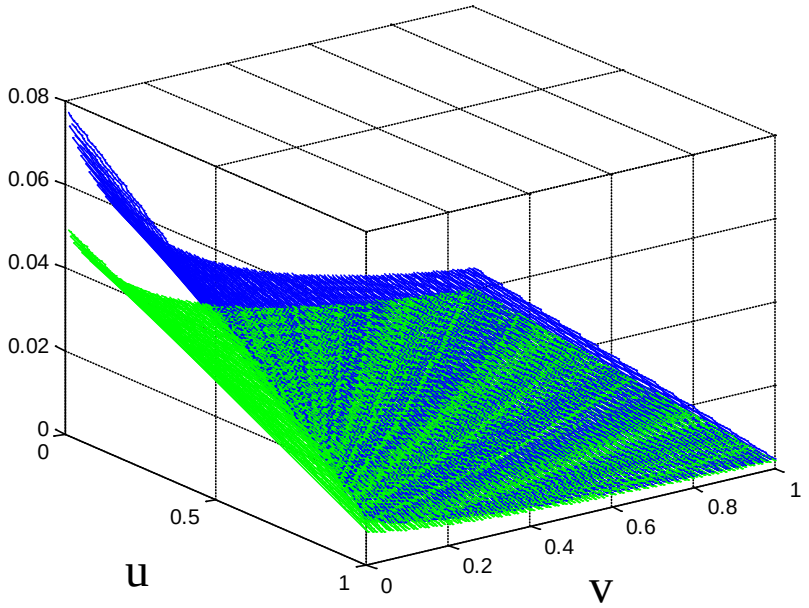
USPSTF Screening Policy: Biennially 50-75

X-axis: % from self loop (u) Y-axis: % from progression (v)
Z-axis: Lifetime breast cancer mortality probability

Always treat vs. Wait to Inv

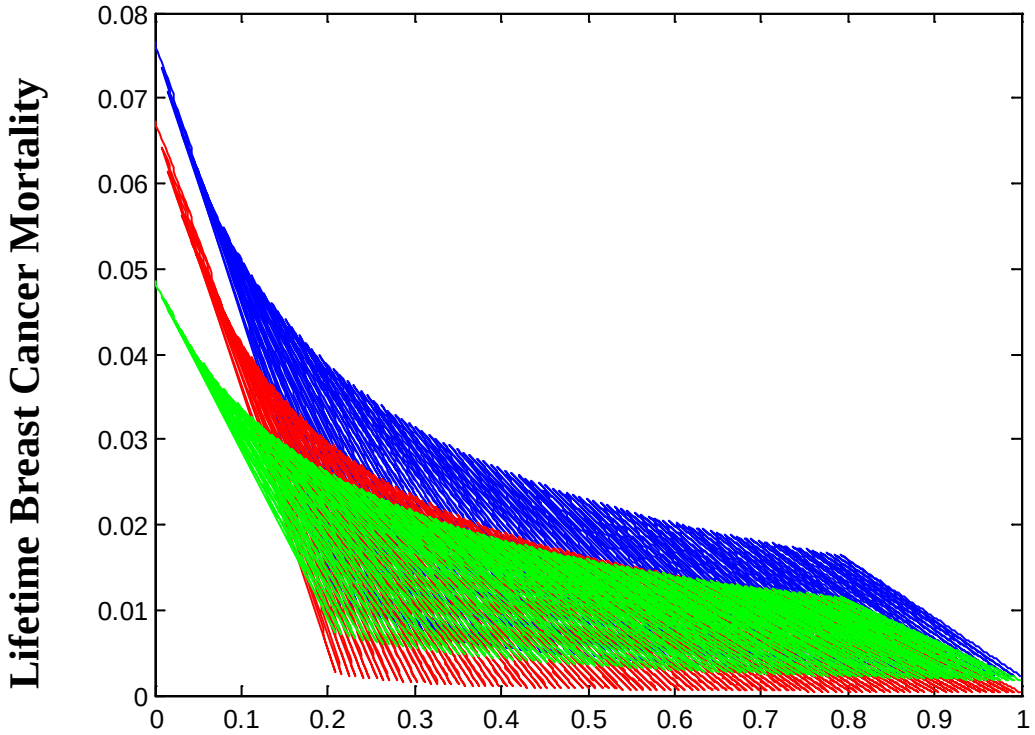


Always treat vs. Wait once



Blue: Treat Red: Wait to Inv Green: Wait once

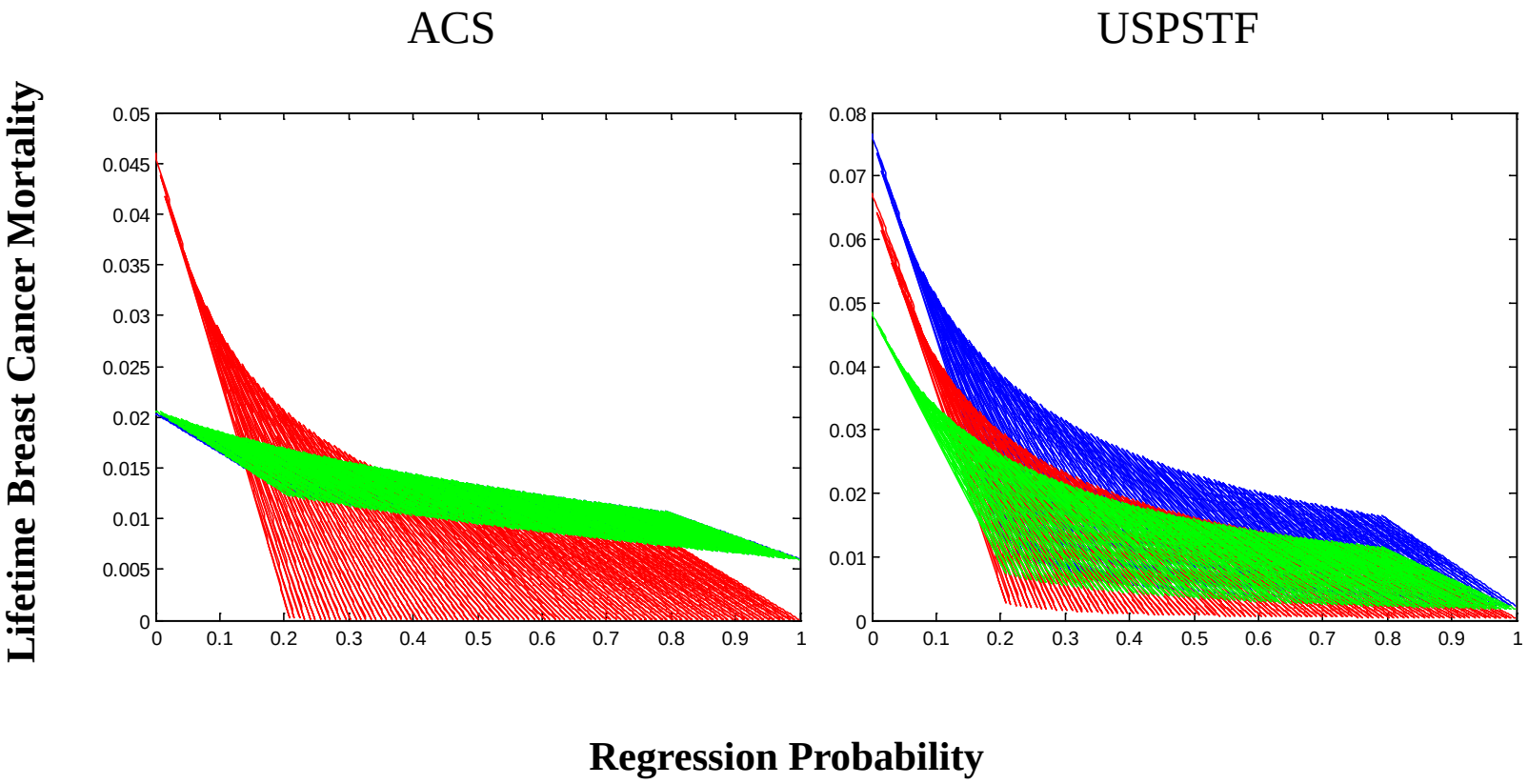
USPSTF Screening Policy



Blue: Treat
Red: Wait to Inv
Green: Wait once

Regression probability is extracted from combinations of progression and self-loop probabilities

ACS vs. USPSTF



Blue: Treat Red: Wait to Inv Green: Wait once

Conclusions

- The possibility of breast cancer regression may impact lifetime breast cancer mortality
  - While regression rate is unknown, screening and treatment decisions will be affected by the rate
  - Although biology of breast cancer regression is uncertain, the results suggest regression should still be considered in breast cancer policy decisions
- Impact varies among screening policies
  - For more frequent screening, when in situ cancer can regress, it may be more beneficial to wait to treat
  - For less frequent screening, waiting has a lower mortality
- Understanding the natural development of breast cancer is important for developing decision models
  - Transition between disease states
  - Screening and treatment decisions may be affected

Limitations and Future Work

- Relax some assumptions
  - Other patient characteristics can be incorporated for estimating breast cancer mortality[1]
  - Biopsy may not be necessary if cancer can regress
- Parameter estimation is a limitation
  - Develop methods for better estimation: transition probabilities, etc.
  - Breast cancer natural development
- Optimal screening & treatment policy
  - More dynamic screening policies
  - Incorporate regression
  - Regression rate may depend on other covariates

[1]Zhang et al. Characterizing the Role of Breast Density on Breast Cancer Patient Mortality, working paper 2011.s

Thank you!

Questions?

Extensions to Personalized Screening Policies:
Role of race, age, risk and comorbidity

Objective

- Long term goal:
  - To develop a model for determining breast cancer screening benefit for a patient given their age, race, breast cancer risk factors, comorbid conditions, and mammography screening program

- For women 65 and older who participate in screening,
  - we propose to develop decision models for evaluating breast cancer screening policies (defined by age-specific screening interval and stopping age) using an estimation of lifetime breast cancer mortality risk as a function of other-cause (non-breast cancer) mortality risk by patient age and race.

Hypothesis

i. Women over 65 with comorbid conditions may benefit from alternative screening strategies
ii. These strategies are most likely dynamic (will change with patient age)
iii. These strategies will differ between individuals and there may be significant differences in the appropriate screening strategy for women by race and other risk factors

Breast Cancer Risk in Elderly

- Aging is one of the single greatest risk factors for the development of new breast cancer
  - Almost 50% of women are 65 or older at time of invasive cancer diagnosis
  - 35% of women are over 70 at time of diagnosis

Age	Risk of Developing New Breast Cancer
Lifetime	1 in 8
39 years and Younger	1 in 210
40 to 59 years	1 in 25
60 to 69 years	1 in 27
70 years and Older	1 in 14

Aging Population

- In 1980, people aged 65 and older represented 11.3% of the total population
- By 2030,
  - this number is anticipated to rise to 20%
  - Within this age group almost 50% will be 75 and older
- Life Expectancy of a 65 year old woman is 17.5 years
- Life expectancy of an 80 year old woman is 8.6 years
- Women over 65 will become the most prevalent patient cohort in the breast cancer population

Screening for the Elderly

- Despite the fact that cancer risk increases with age, experts have been divided over whether to screen those 70 and older

Mammography Screening for the Elderly

- There are limited guidelines for mammography screening for women 70 and over
  - ACS guidelines recommend:
    - Screening decisions in older women should consider their current health status and estimated life expectancy and women should continue screening as long as she is in good health
  - US Preventative Service Task Force Guidelines recommend:
    - Mammography screening to age 74 and after age 74 there is insufficient evidence to assess benefits/harms

Implications for Elderly Women

- Women over 70 remain underrepresented in screening populations and represent a group in which considerable impact might still be made (Homes et al. 2007)

- Older women have been found to be less likely to receive the standard care for their disease which has been linked to higher rates of breast cancer recurrence and mortality (Crivellari et al, 2007)

Aging and Comorbidity

- Aging is an individualized process that correlations poorly with chronological age

- The challenge for the clinician is to estimate an older person's health status which requires assessment of comorbidity
  - Comorbid Condition:
    - Chronic disease in addition to the index condition

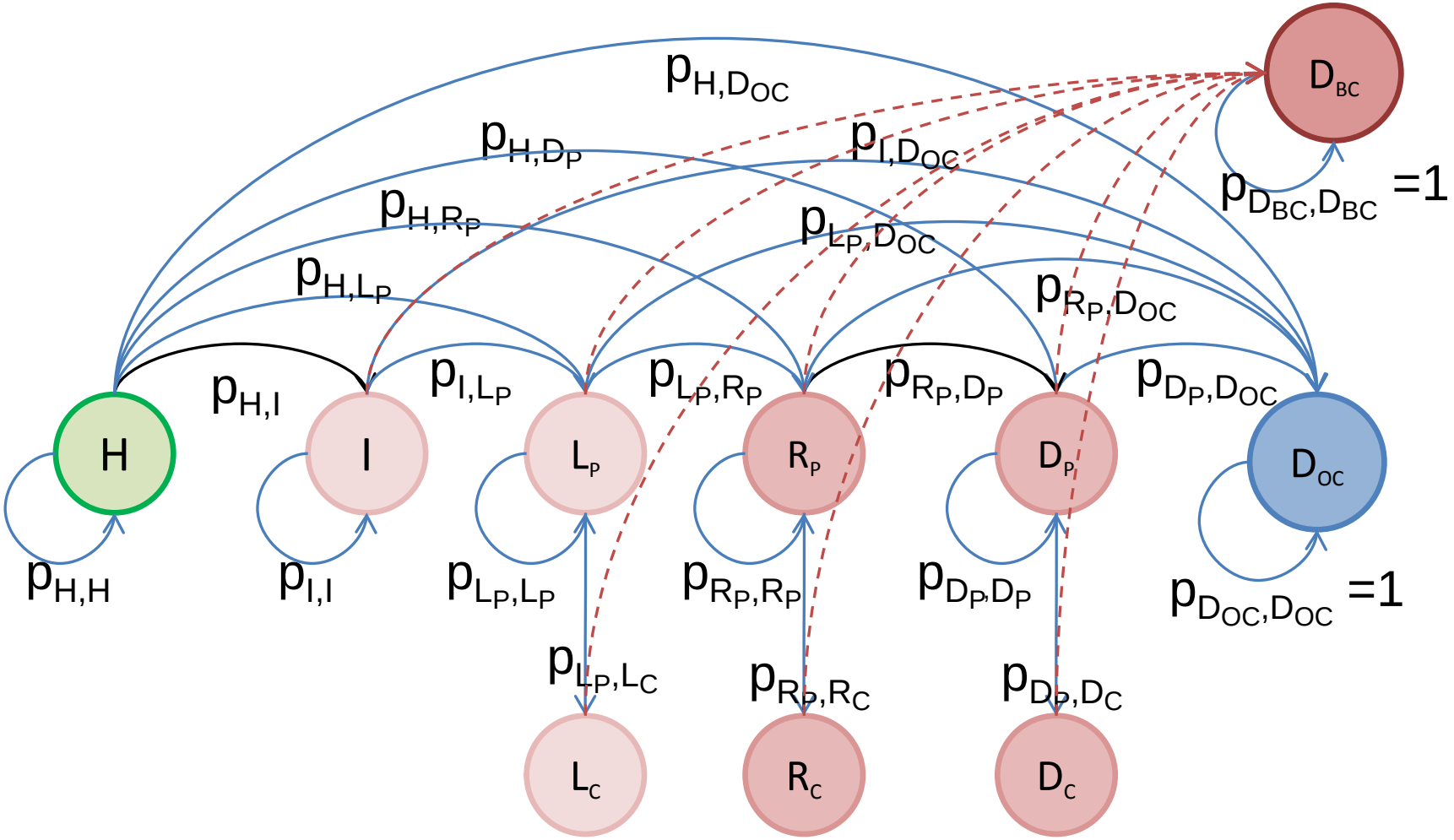
Comorbidity and Breast Cancer

- Presence of 3 or more comorbid conditions has been associated with a
  - Fourfold higher rate of all cause mortality
  - Twentyfold higher rate of mortality from cases other than breast cancer at three years

    (when compared to women with primary breast cancer with no comorbid conditions)

- While there is an extensive literature exploring the effect of age and comorbidity in postmenopausal breast cancer patients, the literature has been limited to exploring the impact of comorbidity on **treatment not screening**

Extended Model Structure



Incorporating Comorbid Disease Diagnosis