

# Simulation Models to Inform Health Policy: Colorectal Cancer Screening



GroupHealth

**Carolyn Rutter, PhD**  
**[rutter.c@ghc.org](mailto:rutter.c@ghc.org)**

**Group Health Research Institute**



**Supported by NCI U01 CA52959**  
**<http://cisnet.cancer.gov>**

# Models for Mammography



On Nov 16, the United States Preventive Services Task Force (USPSTF) revised its recommendations for screening mammography, indicating that most women should start regular breast cancer screening at age 50, not 40, and women should test every other year instead of every year.

The change was made in light of:

**New data**, including a very large study of mammography initiated at 40 from England (~1.5 million)

**New focus on harms**, including work-up following a false positive test and over diagnosis and treatment of cancer that would not otherwise have been detected in a woman's lifetime.

## **Results from disease models (CISNET)**

The models did not provide consistent results about over-diagnosis, with estimates that ranged from 6% to 50% of breast cancers.

However, there was agreement that mammograms every two years give the nearly the same benefit as annual ones but confer half the risk of harms, and that there was little benefit to screening women in their 40's.

(Paraphrasing Don Berry)

November 2008: The USPSTF used microsimulation models to guide recommendations for colorectal cancer screening.

Both models supported a range of screening strategies, starting at age 50 up to age 75:

- colonoscopy every 10 years
- annual FOBT
- flexible sigmoidoscopy every 5 years with a mid-interval FOBT

Zauber, Lansdorp-Vogelaar, Knudsen, et al 2008

January 2009: The Medicare Evidence & Discovery Coverage Advisory Committee considered coverage of CT colonography for colorectal cancer screening, based on:

- Operating characteristics & risks of different tests (systematic review)
- Expert Testimony
- Model Predictions

Knudsen, Lansdorp-Vogelaar, Rutter, et al 2010

Recommendation: Insufficient Evidence to support CTC for screening

[www.cms.hhs.gov/mcd/index\\_list.asp?list\\_type=mcac](http://www.cms.hhs.gov/mcd/index_list.asp?list_type=mcac)

Microsimulation models simulate outcomes in a population of interest by ***simulating individual event history trajectories***.

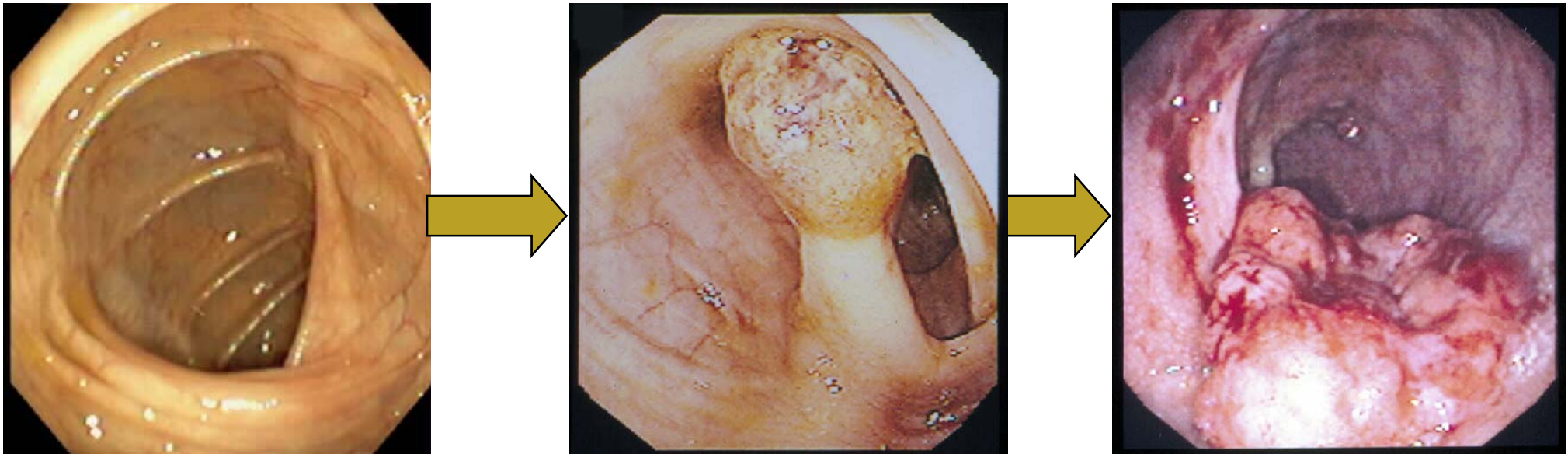
A ***natural history model*** refers to the mathematical formulae that describe these individual histories.

The natural history model is combined with a ***screening or treatment model*** to project population-level effects of treatment.

Existing models describe:

- Cancers: prostate, breast, lung, colorectal, esophageal, cervical
- Cardiovascular disease, diabetes

# Adenoma to Carcinoma Pathway



**Normal  
Epithelium**

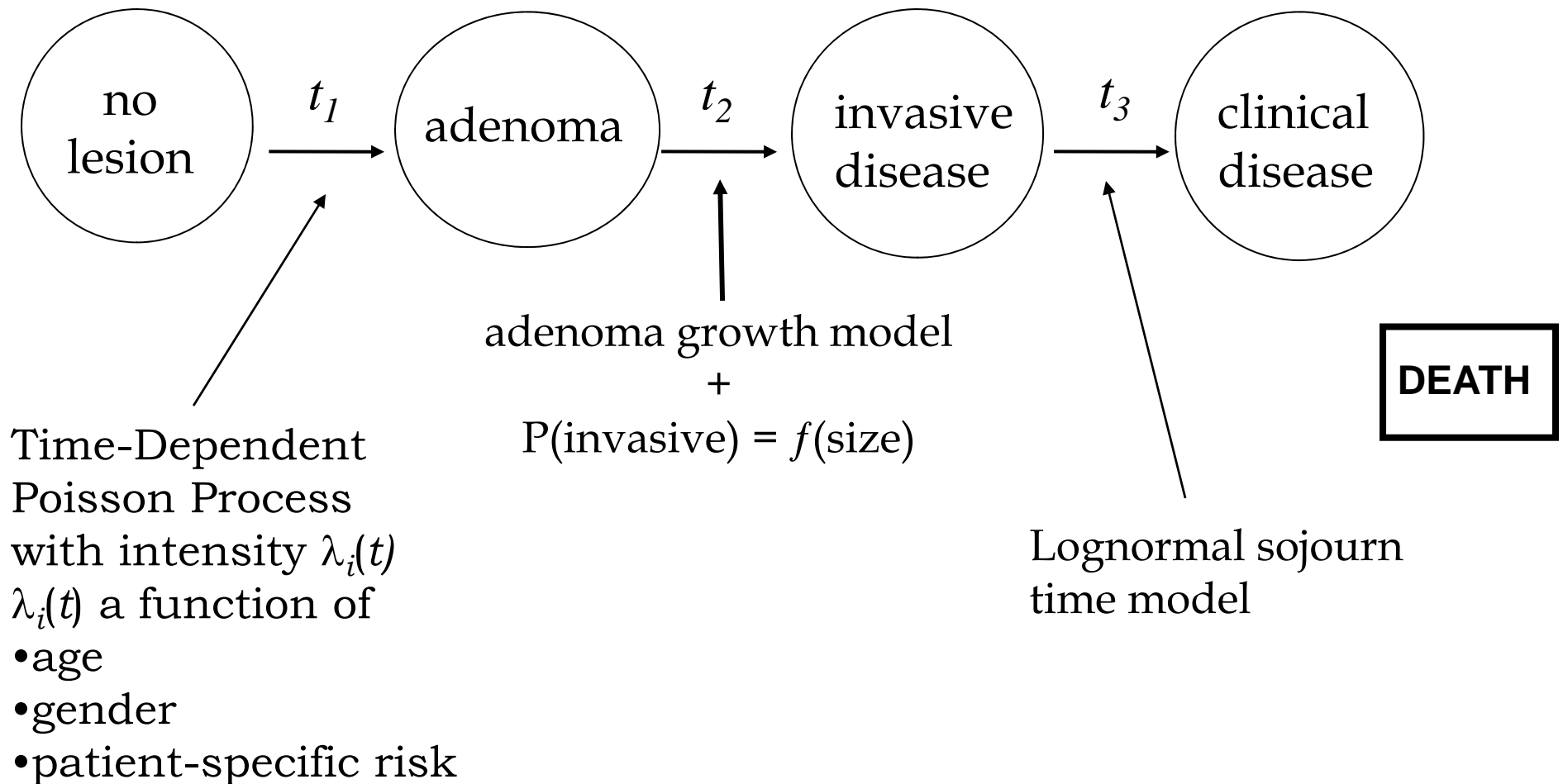
**Small  
Adenoma**

**Advanced  
Adenoma**

**Colorectal  
Cancer**

Thanks to Ann Ann Zauber!

## ColoRectal Cancer Simulated Population model for Incidence and Natural history



Rutter & Savarino, Cancer Epidemiology Biomarkers & Prevention, 2010

# CRC-SPIN model for colorectal cancer

## Model Summary



### 1. Adenoma Risk Model (7 parameters):

$$\psi_i(t) = \exp\left(\alpha_{0i} + \alpha_1 \text{sex}_i + \sum_{k=1}^4 \delta(A_k < \text{age}_i(t) \leq A_{k+1}) \left\{ \text{age}_i(t) \alpha_{2k} + \sum_{j=2}^k A_j (\alpha_{2j-1} - \alpha_{2j}) \right\}\right)$$

$$\alpha_{0i} \sim \text{Normal}(\alpha_0, \sigma_\alpha)$$

$$\delta(y) = 1 \text{ if } y \text{ is true; } 0 \text{ otherwise}$$

### 2. Adenoma Growth Model: Time to 10mm (4 parameters)

$$d_{ij}(t) = d_\infty - (d_\infty - d_0)e^{-\lambda_{ij}t}$$

Reparameterize and write in terms of the time to reach 10mm,  $t_{10mm} = \sqrt{-\frac{1}{\lambda} \ln\left(\frac{d_\infty - 10}{d_\infty - d_0}\right)}$

Assume that  $t_{10mm}$  has a Type 2 Extreme Value distribution,  $F(t) = \exp\left(-\left(\frac{t}{\beta_1}\right)^{-\beta_2}\right)$

### 3. Adenoma Transition Model (8 parameters)

$$\xi_*(\text{size}|\text{age}) = \Phi(\{\ln(\gamma_{1*} \text{size}) + \gamma_{2*}(\text{age} - 50)\})$$

\* indicates 1 of 4 strata, colon/rectum  $\times$  male/female

### 4. Sojourn Time Model (4 parameters)

$$\log(ST_{ij}(c)) \sim \text{Normal}(\xi_c, \nu_c)$$

$$ST_{ij}(c) \sim \text{LogNormal}[\mu_c, \tau_c \mu_c]$$

$$\mu_c = \exp(\xi_c + \frac{1}{2}\nu_c^2)$$

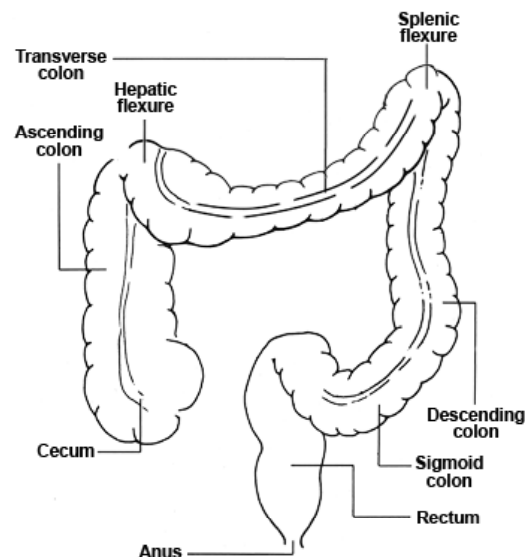
$$\tau_c = \sqrt{\exp(\nu_c^2) + 1}$$

**23 parameters**

# CRC-SPIN model for colorectal cancer

**Adenoma Location:** Multinomial distribution, informed by 9 autopsy studies (and similar to a recent colonoscopy study) :

P(cecum)	=	0.08
P(ascending colon)	=	0.23
P(transverse colon)	=	0.24
P(sigmoid colon)	=	0.24
P(descending colon)	=	0.12
P(rectum)	=	0.09



## CRC Survival:

Assign CRC survival using survival curves estimated SEER survival data from 1975 to 1979, stratified by location (colon or rectum) and AJCC stage with age and sex included as covariates.

## Other Cause Survival:

Assign other-cause mortality using product-limit estimates for age and birth-year cohorts from the National Center for Health Statistics Databases.

**0 parameters**

“Calibration is a form of evidence synthesis in which observations on observable quantities are used to draw inference about unobservable quantities, such as latent rates of disease progression, remission or mutation.”

Milt Weinstein, *Pharmacoeconomics*, 2006

“Calibration is a process of varying the unobservable parameters until model outputs closely match existing clinical and epidemiological data.”

Kong, McMahon, Gazelle, *Value in Health*, 2009

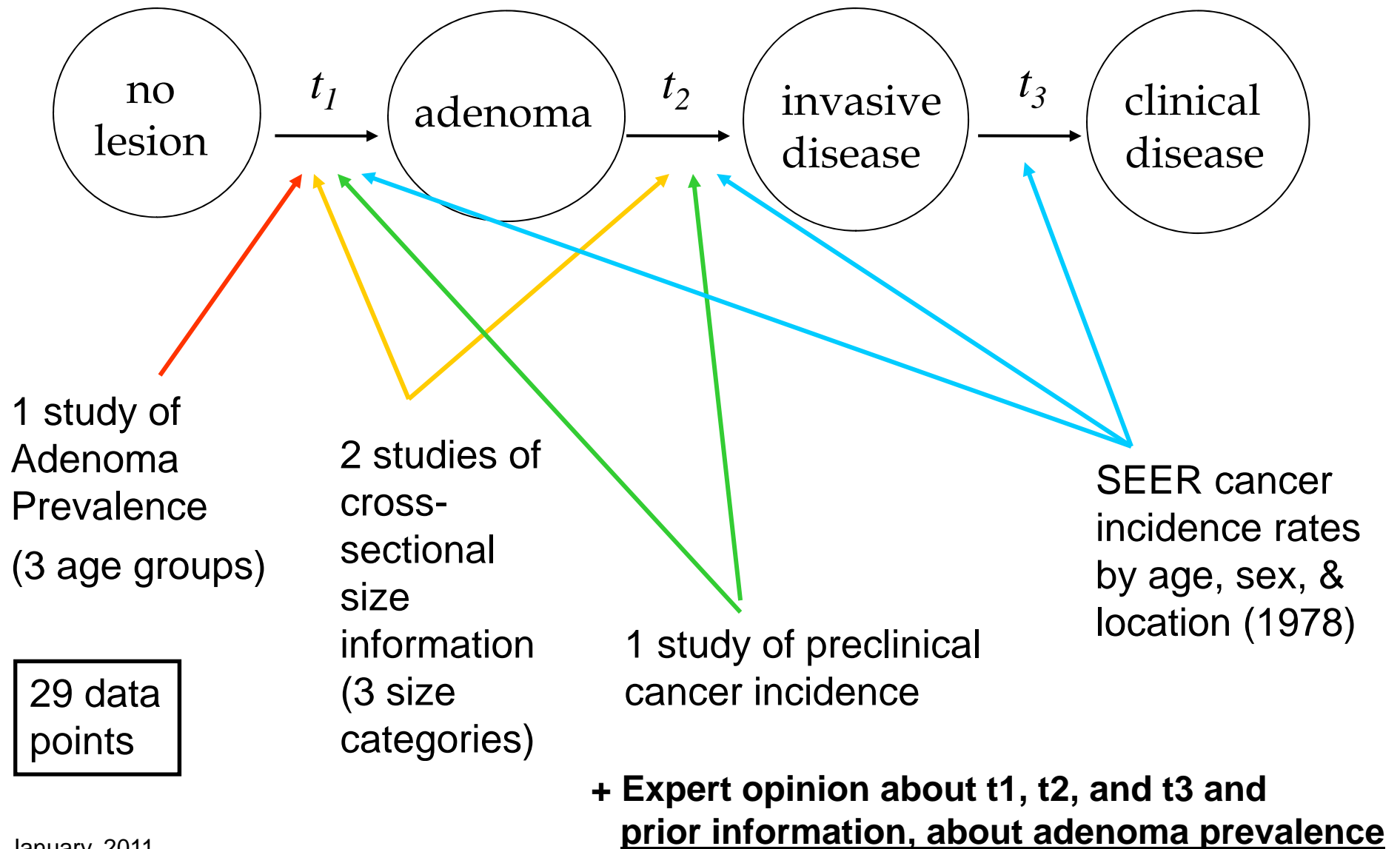
“...calibration involves selecting parameter values that are consistent with observed data and expected findings.”

Rutter, Miglioretti, Savarino, 2009

**“Parameter Estimation”**

# Example: Calibration of CRC-SPIN

## 23 Parameters



# Microsimulation Model Calibration: Published Approaches

- One-at-a-time parameter perturbation, with subjective judgment
- One-at-a-time parameter perturbation, with chi-square or deviance statistics
- Grid Search using objective functions (e.g., likelihood)
  - Undirected: evaluate objective function at each node or at a random set of parameter values.  
Not computationally feasible for highly parameterized models, dense grids can miss maxima.
  - Directed: move through the parameter space toward improved goodness of fit to calibration data.  
Fewer evaluations of the likelihood, but can converge to local maxima.  
A key challenge is numeric approximation of derivatives.
- Likelihood approaches
  - Bayesian estimation (MCMC, other approaches are possible)
  - Simplify the likelihood to allow usual estimation approaches.  
The simplified model needs to be flexible enough to be useful for prediction
  - Active area of research among CISNET group members

- A 2009 review by Stout and colleagues (*Pharmacoeconomics*) found:
- Most modeling analyses did not describe calibration approaches
  - Those that did generally used either undirected or directed grid searches.

**Big problem: lack of information about *precision*.**

Grid searches generally provide point predictions, with no measures of uncertainty for either estimated parameters or resulting model predictions.

- A few ad hoc approaches have been proposed, for example:
- ‘uncertainty intervals’ based on sampling parameters over a specified range
  - Provide a range of predictions based on parameters that provide equally good fit to observed data.

## **Bayesian calibration approach:**

- Place priors on model parameters (allows explicit incorporation of expert opinion)
- Use simulation-based estimation (Markov chain Monte Carlo or sampling importance resampling)

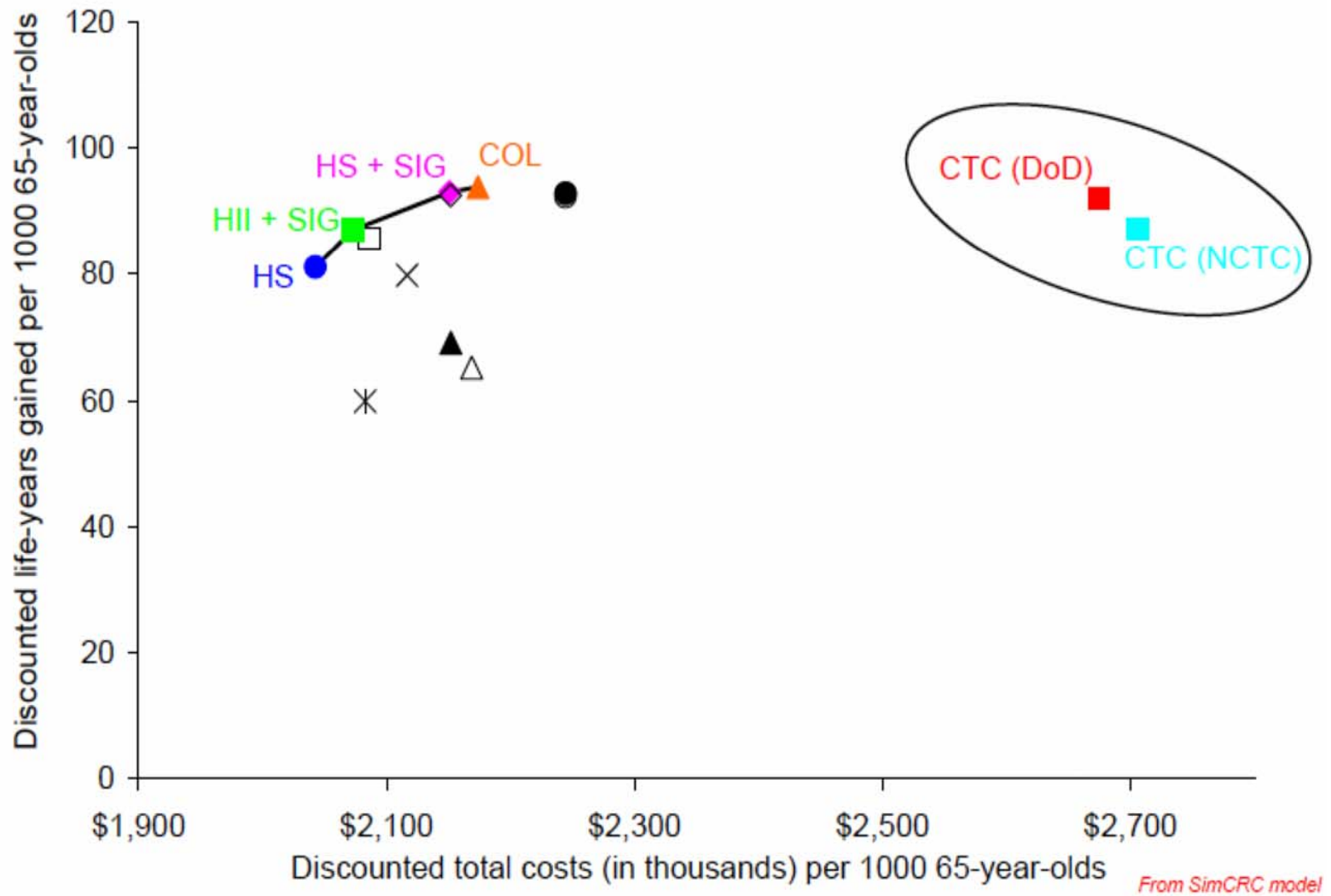
## **Advantages:**

- Interval estimation
- Posterior predicted values for calibration data (goodness of fit)
- Can compare prior and posterior distributions to gain insight about parameter identifiability (Garrett & Zeger, *Biometrics* 2000)

# Example of a Modeling Analysis

**Table 8C.** Undiscounted costs by type, number of life-years gained, and number of cases of CRC per 1000 65 year olds, by screening scenario – SIMCRC

Scenario	Screening Costs	Total Costs	LYG	Symptomatic CRC	Screen-Det CRC
No Screening	0	\$3.5M	0	60	0
SENSA	\$122K	\$2.8M	151	8	18
FIT	\$248K	\$2.6M	148	8	19
FSIG+SENSA	\$444K	\$2.7M	170	5	13
FSIG+FIT	\$638K	\$2.8M	170	5	14
CSPY	\$783K	\$2.7M	171	6	11
CTC(1)	\$1.1M	\$3.3M	168	6	12
CTC(2)	\$1.2M	\$3.3M	160	7	12



# Example of a Modeling Analysis

**Table 8C.** Undiscounted costs by type, number of life-years gained, and number of cases of CRC per 1000 65 year olds, by screening scenario – CRC-SPIN

Scenario	Screening Costs	Total Costs	LYG	Symptomatic CRC	Screen-Det CRC
No Screening	0	\$2.9M	0	53	0
SENSA	\$135K	\$2.0M	155	7	11
FIT	\$267K	\$2.1M	150	8	11
FSIG+SENSA	\$426K	\$2.0M	177	4	7
FSIG+FIT	\$568K	\$2.1M	176	5	7
CSPY	\$822K	\$2.0M	185	3	5
CTC(1)	\$1.2M	\$2.6M	178	5	5
CTC(2)	\$1.3M	\$2.7M	172	6	5

## Comparative effectiveness studies of CT colonography

### Literature review:

- 1 decision tree model
- 6 cohort models
- 3 microsimulation models

Similar overall disease processes (adenoma-carcinoma), similar “calibration” data, but different levels of detail.

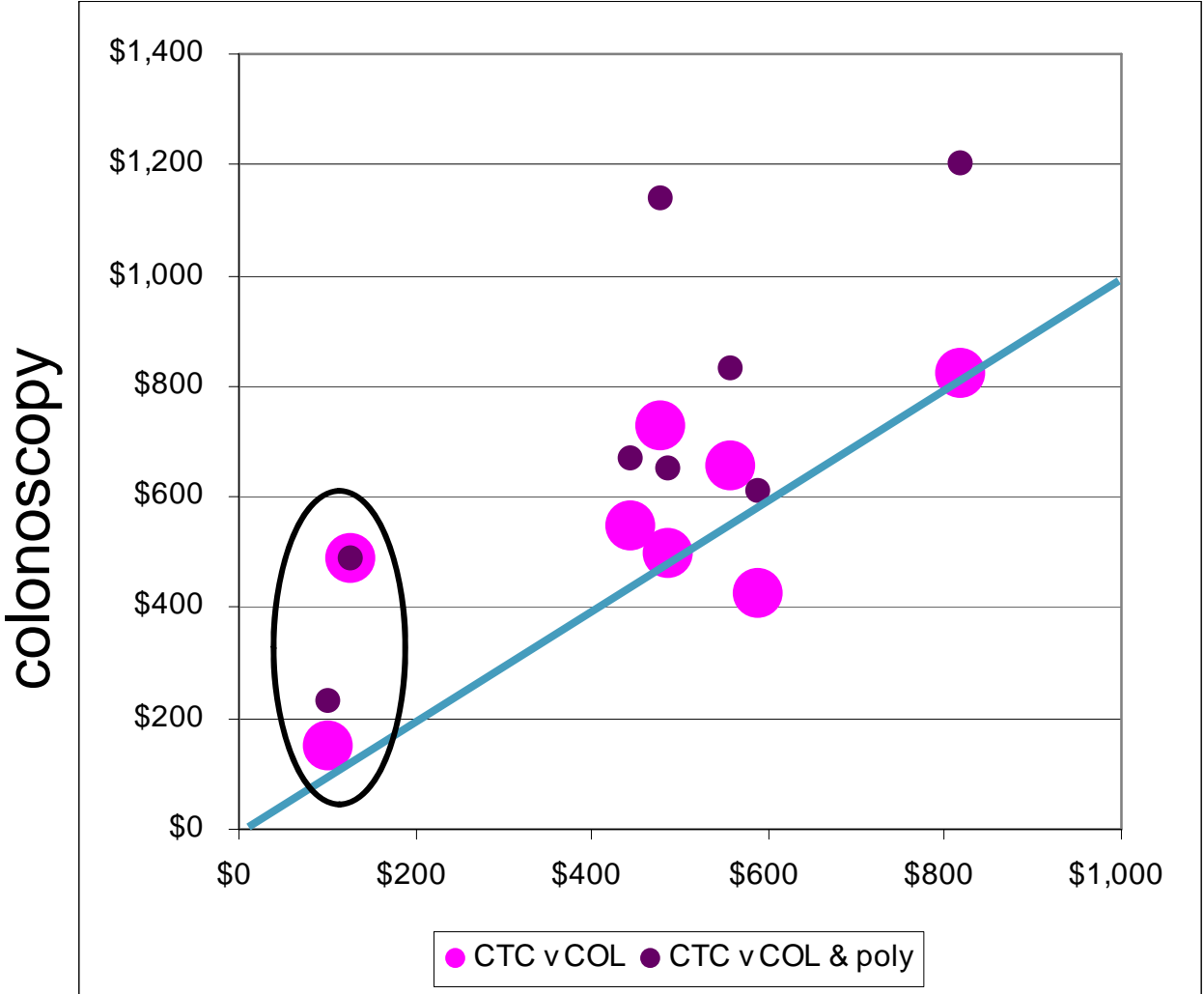
**Microsimulation models:** multiple adenomas, of different sizes and in different (& detailed) locations in the colorectum

**Cohort / decision tree models:** most with one adenoma, one with two in either the proximal or distal colon.

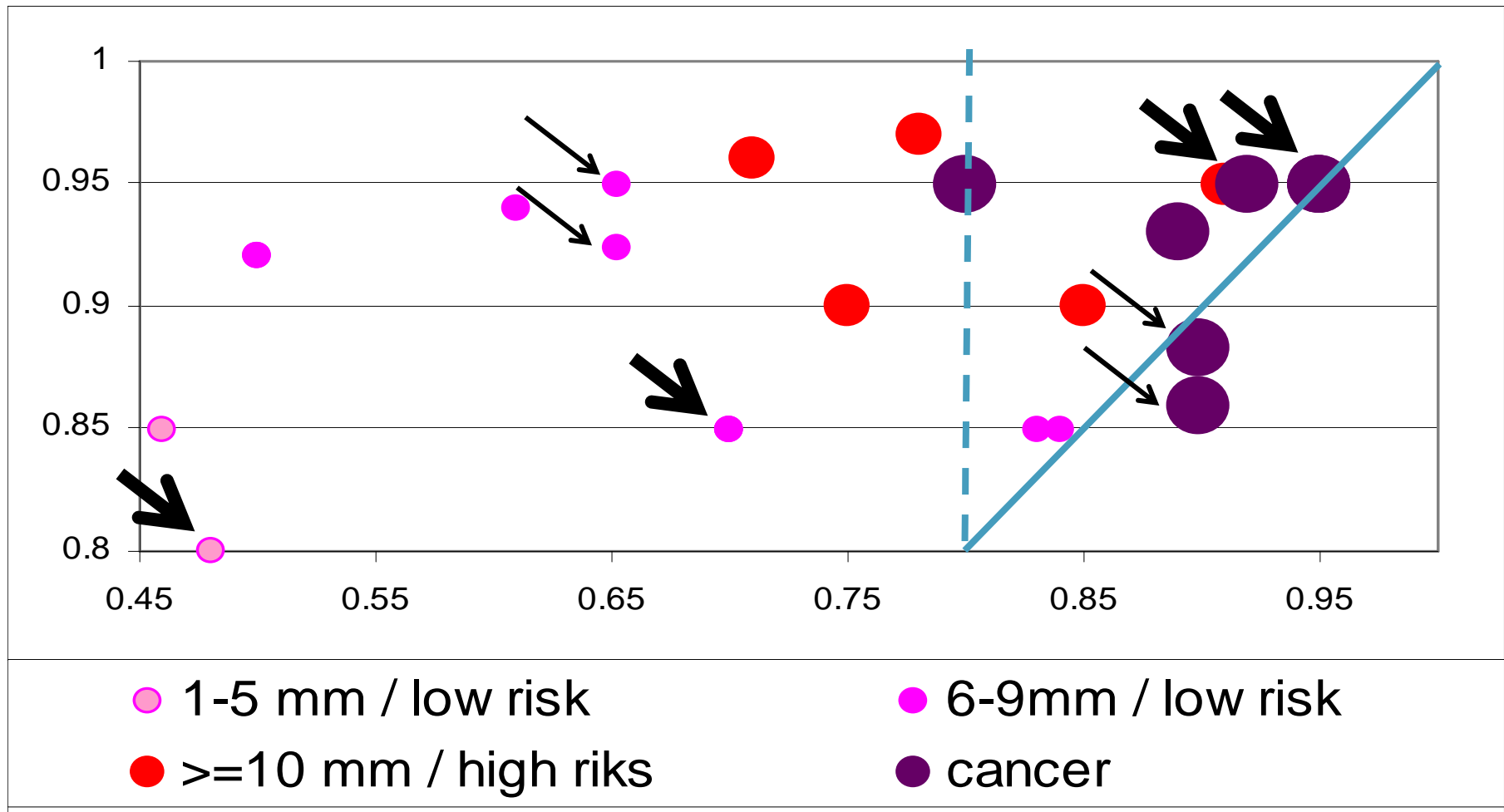
# Simpler models, similar answers

First Author	Year	Model Type	Most Effective	Least Costly	Most Cost-Effective
Heitman	2005	Decision Tree	CSPY	CSPY	CSPY
Sonnenberg	1999	Cohort	CSPY	CTC	CSPY
Ladabaum	2004	Cohort	CSPY	CSPY	CSPY
Vijan	2007	Cohort	CSPY	CSPY	CSPY
Hassan	2007	Cohort	CSPY	CTC	CTC
Lee	2010	Cohort	CSPY	CTC	CTC & CSPY
Telford	2010	Cohort	CSPY	CSPY	CSPY
Knudsen	2010	Microsim	CSPY	CSPY	CSPY

# CTC



## Accuracy of CTC v Colonoscopy



- **Simulation models are increasingly being used to inform health policy**
- **Useful tool, with some shortcomings**
  - Many are complex (when do simpler models make sense?)
  - Few methods for estimating the precision of model estimates
  - Few (no?) models are “public use”
- **Potential for other applications**
  - Study design