

**Cancer Intervention and  
Surveillance Modeling Network:  
Reissuance Concept  
NCI Board of Scientific Advisors  
March 2, 2009**

**Robert T. Croyle, Ph.D.**  
Director, Division of Cancer Control and  
Population Sciences

Concept from Statistical Research and  
Applications Branch, Surveillance  
Research Program, DCCPS

# Purpose of CISNET

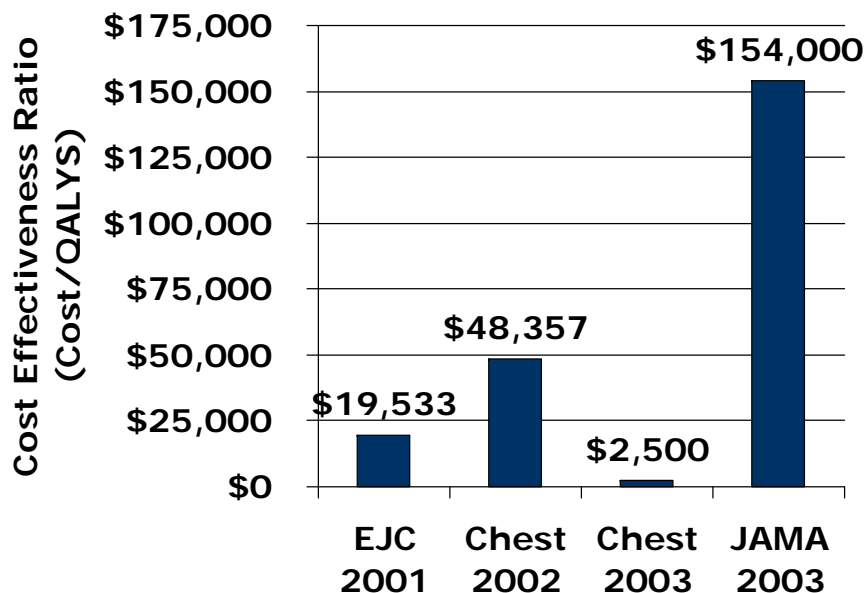


- NCI Sponsored Collaborative Consortium (U01) of Modelers in Breast, Prostate, Colorectal and Lung Cancer
- Focused on bringing the most sophisticated evidence-based decision tools to:
  - ◆ Understand the impact of cancer control Interventions (screening, treatment, prevention) on current and future trends in incidence and mortality
  - ◆ Extrapolate evidence from RCT's, epidemiologic, and observational studies to determine the most efficient and cost-effective strategies for implementing technologies in the population
  - ◆ Be responsive to challenges due to the increased pace of technology, by helping to determine which new technologies are the most promising when scaled up to the population level

# Comparative Modeling Approach



## Older Approach: 4 Independent Studies of the Cost-Effectiveness Of CT Screening for Lung Cancer



Differences in target population, screening frequency, stage shift, assumptions about lead time and overdiagnosis, sensitivity

## Approach Innovated by CISNET: Systematic Comparative Modeling

- Central questions to be addressed by groups collaboratively with a common set of inputs and outputs
  - ◆ Reproducibility across models adds credibility to results
  - ◆ Differences points out areas for further study in a systematic way
- Encourages cooperation instead of competition between modelers

# Examples of Questions Addressed by CISNET



Landmark paper: What are the contributions of screening and adjuvant therapy on declines in breast cancer mortality?



– *US Preventive Services Task Force*

What are the optimal starting and stopping ages, periodicity, and combination of screening modalities to be recommended for colorectal and breast cancer screening?



National Coverage Determinations for colorectal cancer screening tests – What should CMS reimburse for new more effective screening technologies?

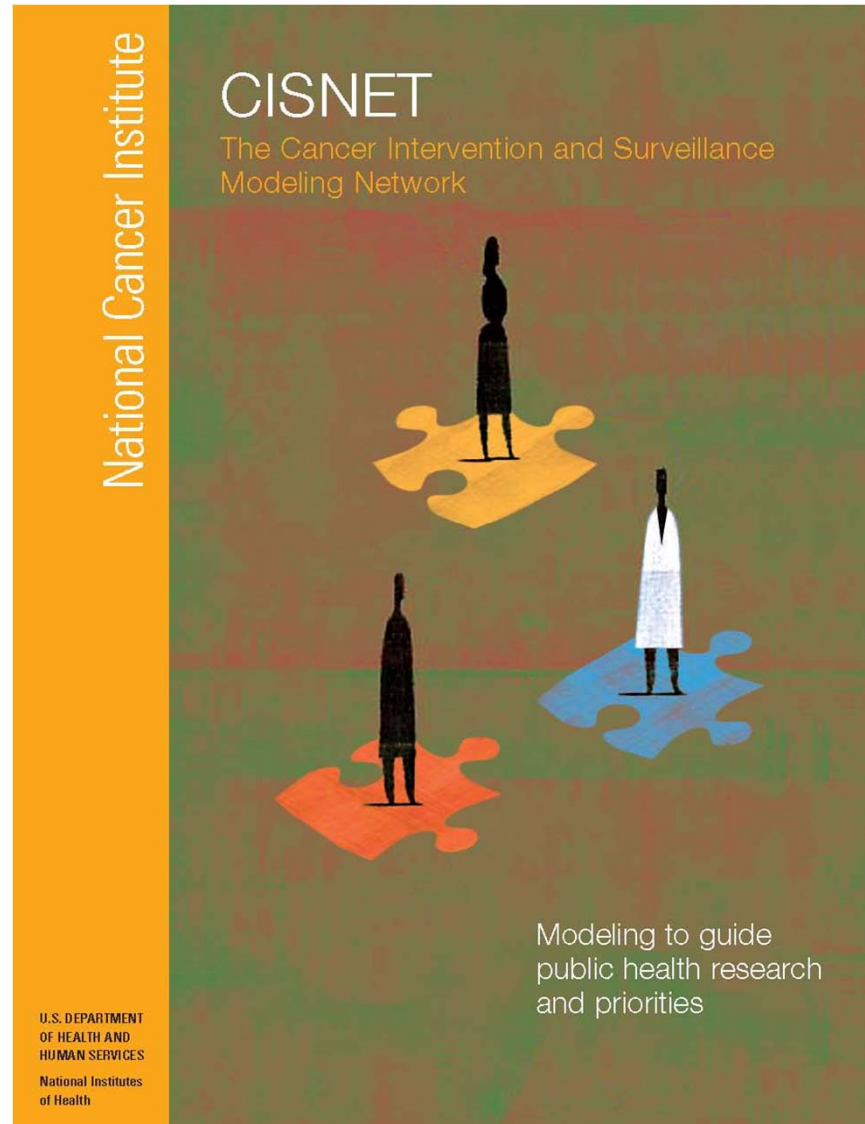


What are the number of lung cancer deaths averted due to tobacco control efforts in the last half century?



Do prostate cancers dedifferentiate (change Gleason's score) during their screen-detectable preclinical phase?

# For More Details on Accomplishments

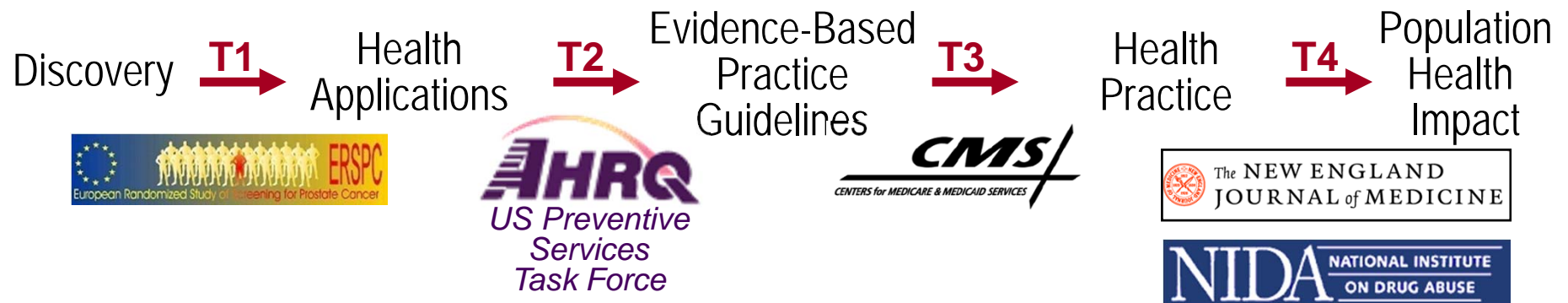


# Continued Scientific Need



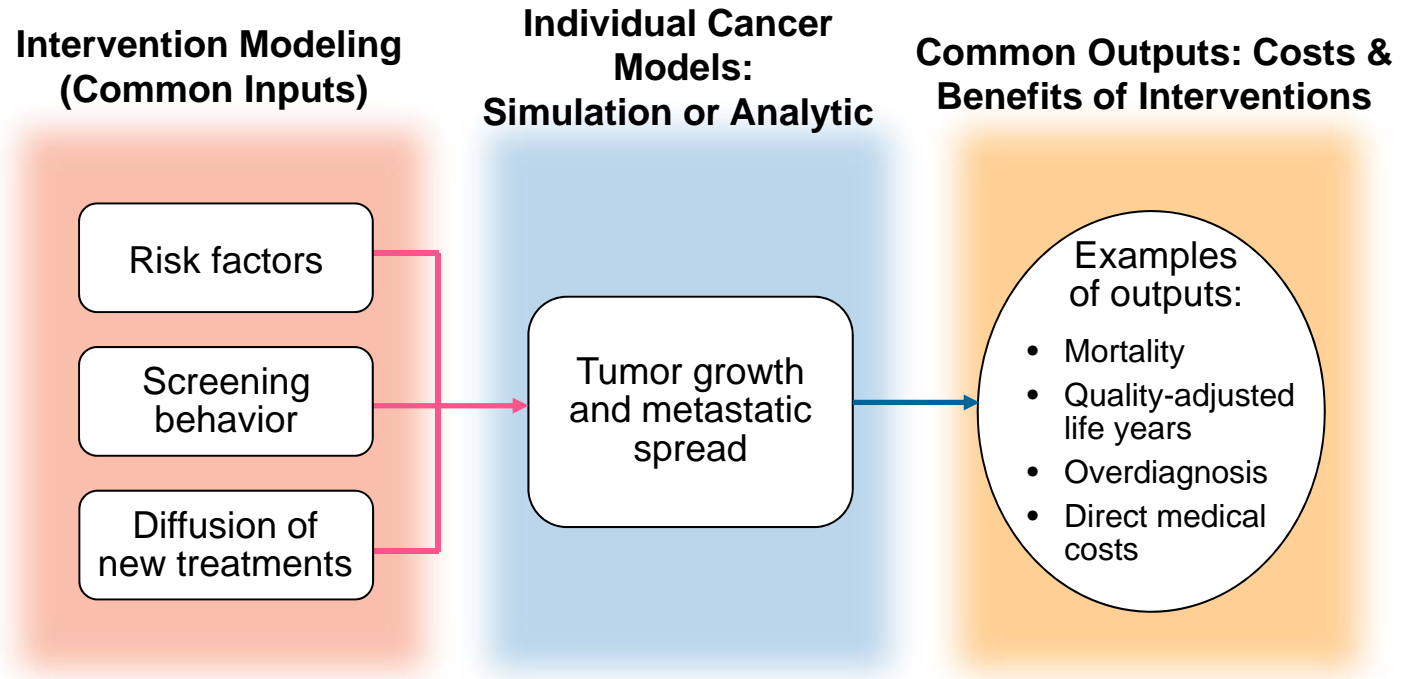
- Formidable and growing gap between the rapid pace of innovation in biomedicine and our ability to harness it to improve public health
  - ◆ “There is no capacity or infrastructure to meet the tsunami of basic research discoveries and move these discoveries rationally into clinical application.”
    - Kathy Hudson, director of Genetics and Public Policy Center, Johns Hopkins (Health Affairs, 2008)
  
- Maturation of modeling in cancer sites beyond the “top 4”
  - ◆ Cervical
  - ◆ Ovarian
  - ◆ Esophagus

# Schema for the Translation of Medical Research



- CISNET models provide a platform for evaluating the downstream consequences of decisions and strategies that are made in earlier phases.
- New Areas for Exploration (with special emphasis on connecting from earlier phases)

# Current Schema for CISNET Modeling





# Upstream Modeling



## Upstream Modeling

## Intervention Modeling

## Cancer Modeling

## Common Outputs: Costs & Benefits of Interventions

Social, economic, and other determinants of usage of screening, treatment & risk behavior

Risk factors

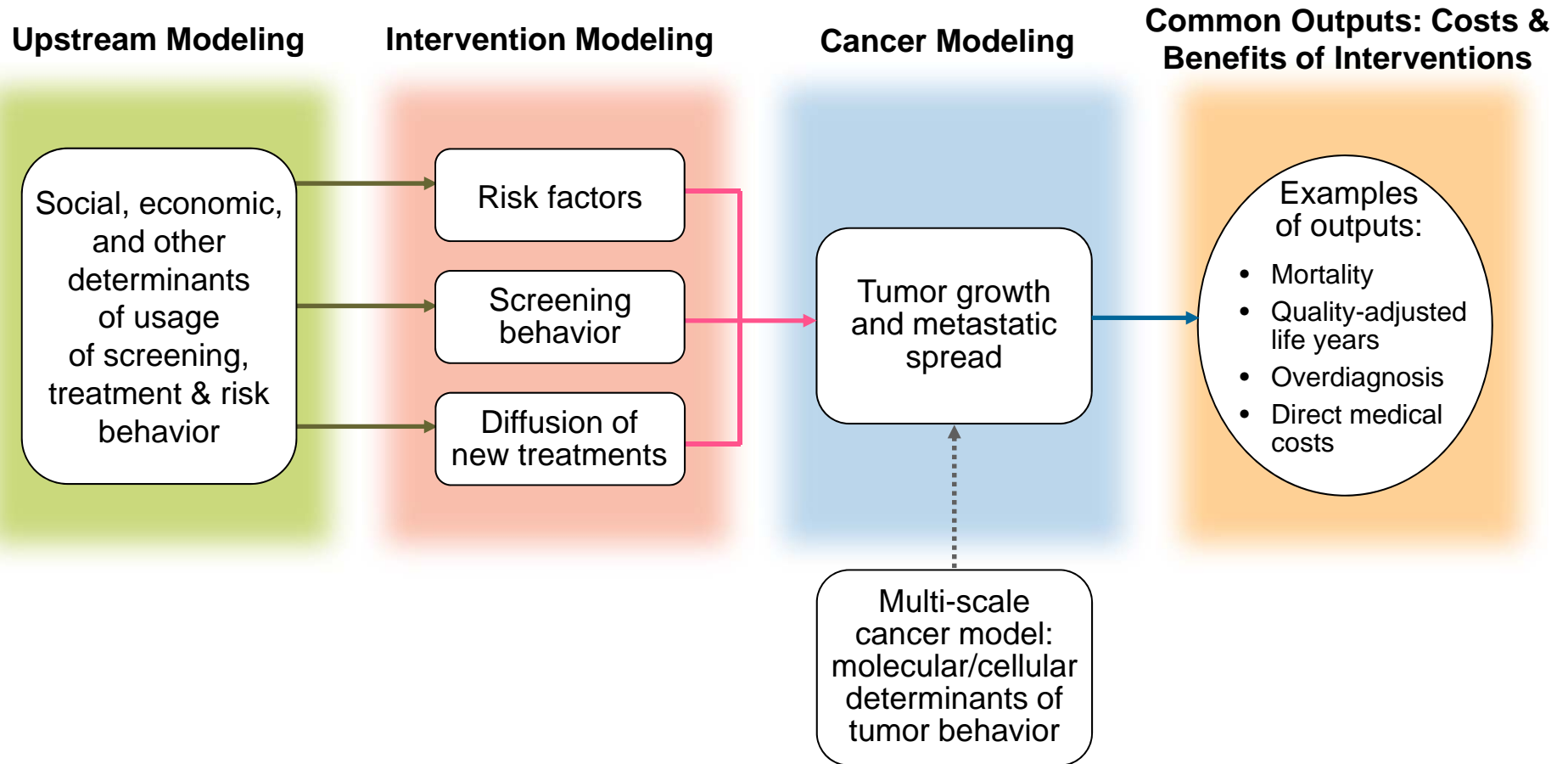
Screening behavior

Diffusion of new treatments

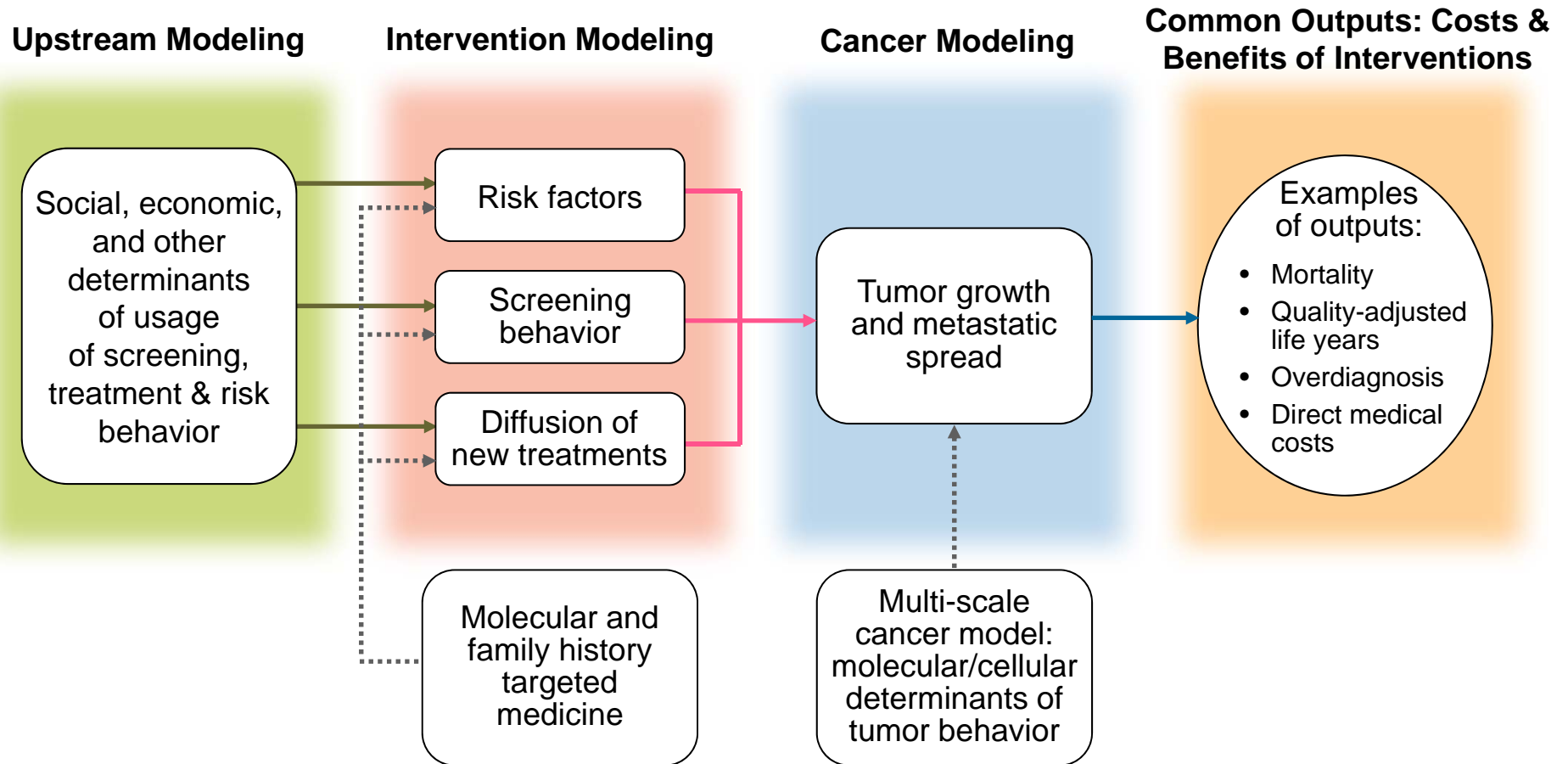
Tumor growth and metastatic spread

- Examples of outputs:
- Mortality
  - Quality-adjusted life years
  - Overdiagnosis
  - Direct medical costs

# Multi-Scale Modeling



# Incorporating Genomic and Family History Risk Profiles



# Optimizing Biomarker Development Strategies



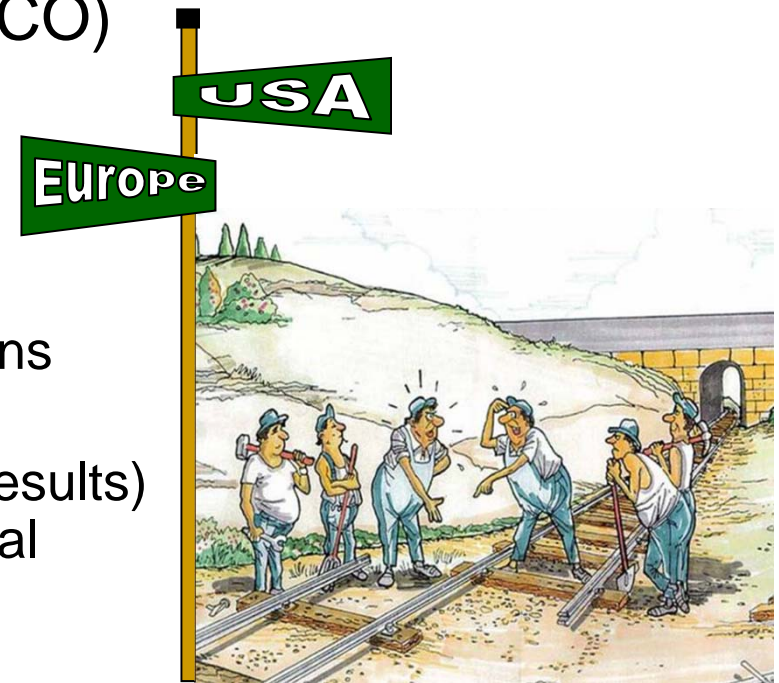
CISNET models can provide a set of tools for EDRN investigators to:

- Project the likely impact of screening tests of given sensitivity on disease-specific deaths
- Investigate how early in the preclinical period the test needs to become sensitive in order to produce a target benefit in terms of lives saved
- Given specified test characteristics, project benefits and costs associated with different regimens of screening

# Translation of Trial Results into Clinical Guidelines and Public Health Policy



- European (ERSPC) and US (PLCO) prostate cancer screening trials differ with respect to:
  - ◆ Screening protocols, test positive criteria, compliance with biopsy recommendations, treatment patterns
  - ◆ ERSPC (efficacy trial – established protocol for follow-up of abnormal results)  
PLCO (effectiveness trial – individual physicians determine follow-up)

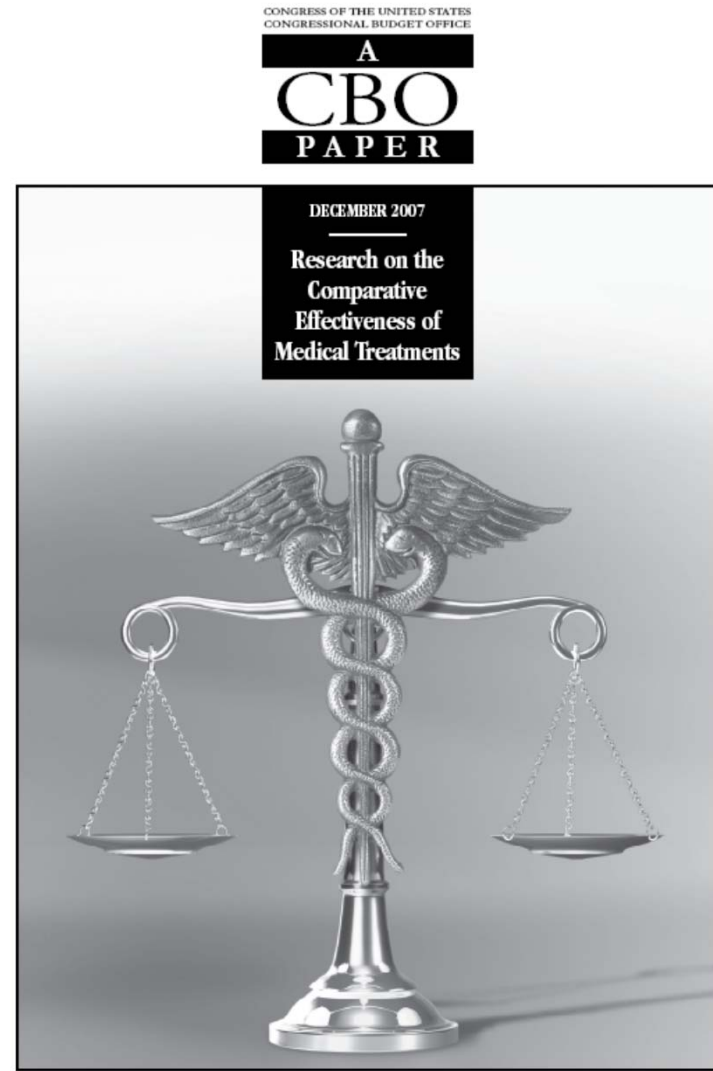


- Probable co-existence of overdiagnosis for some and mortality benefits for others will further complicate guidelines.

# Comparative Effectiveness Research



- “... a rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients.” CBO, 2007
  
- Modeling can integrate evidence, extend available evidence from intermediate to long term outcomes, and balance trade-offs
  - ◆ E.g. Radical prostatectomy vs. conservative management for prostate cancer (survival benefit vs. urinary and sexual dysfunction)



## Other Areas



- Modeling to suggest optimal routes to reduce health disparities
- Development of interactive decision tools
- Evaluation of diagnostic tests

# Budget



- Up to 6 linked cancer-site specific groups of awards
  - ◆ 2-5 collaborating modelers within each group
  - ◆ Average of \$900K total cost per year for each linked group of awards
  - ◆ 5 year awards
  
- Collaborative Study Funds
  - ◆ \$600K per year in Years 2-5
  - ◆ Set up to provide a systematic mechanism to facilitate collaborations (either with gov't or non-gov't) who bring timely cancer control issues amenable to modeling
  - ◆ Funds would pay for time of collaborators, time of CISNET investigators, data acquisition, etc.



# Budget Summary



	<b>FY10</b>	<b>FY11</b>	<b>FY12</b>	<b>FY13</b>	<b>FY14</b>
<b>Grant funds</b>	<b>\$5.40M</b>	<b>\$5.40M</b>	<b>\$5.40M</b>	<b>\$5.40M</b>	<b>\$5.40M</b>
<b>Collaborative Study Funds</b>	_____	<b>\$0.60 M</b>	<b>\$0.60M</b>	<b>\$0.60M</b>	<b>\$0.60M</b>
<b>Total</b>	<b>\$5.40M</b>	<b>\$6.00M</b>	<b>\$6.00M</b>	<b>\$6.00M</b>	<b>\$6.00M</b>

# Responses to Subcommittee Questions

# What is the rationale for the increase in the budget?



## ➤ Budget

- ◆ Current budget: about \$3.75M per year
- ◆ Proposed: Year 1: \$5.4M, Years 2-5: \$6M per year

## ➤ Three reasons for increase:

- ◆ (1) increase from original 4 to up to 6 cancer sites
- ◆ (2) slightly larger awards to individual PI's to accommodate:
  - (a) adding various model components – possibly through subcontracts with specialized modelers (e.g. multi-scale modelers, up-stream modelers)
  - (b) adding more multi-disciplinary expertise
- ◆ (3) \$0.6M collaborative study funds in years 2-5

## Accomplishments in terms of the full initiative: # of models, # of model applications, cross- over of models among cancer sites



- 18 models (5 lung, 7 breast, 3 colorectal, 3 prostate)
  - ◆ Affiliate members (2 lung, 1 colorectal)
  
- Model applications: 90 papers
  
- No cross over models per se, since model development for each cancer is unique with respect to the biology of the cancer, the data sources, and the state of RCT evidence
  - ◆ Methodologic advances do have broad applicability across cancer sites:
    - 48 methodology papers

# Status of Implementing External Review Recommendations (Especially Pilot Studies in New Areas)



- Pilot Studies in New Areas
  - ◆ Multi-Scale Modeling
    - 2 pilot studies in breast and lung cancer with ICBP
  - ◆ Incorporating Genomic and Family History Risk Profiles
    - Formulating plans for possible use of stimulus money to fund pilot projects in this area
  - ◆ Health Disparities
    - Pilot project with ACS to model the factors underlying divergent patterns of colorectal cancer mortality rates for blacks and whites
  
- Use of Modeling to Evaluate Diagnostic Tests
  - ◆ New area suggested by external review and added to concept
  - ◆ Initiated discussions with Diagnostic Imaging Branch, DCTD
  - ◆ Have applied for stimulus package funds on comparative effectiveness research in this and other areas

## Future Expectations in Terms of New Model Development vs. Model Application



- No new models developed from scratch (even in newly added cancer sites)
  
- Emphasis on:
  - ◆ Updating models based on new evidence
  - ◆ Model applications
  - ◆ Adding modules to existing CISNET models to allow expansion into new areas



# Suggesting Optimal Routes to Reduce Health Disparities



- Moving beyond standard racial/ethnic characterizations
  - ◆ Education/Income
  - ◆ Insurance Status
  - ◆ Geographic Disparities
  
- Search for the largest leverage points to reduce disparities in mortality rates as a function of:
  - ◆ Risk Factors: smoking rates, obesity, other risk factors
  - ◆ Screening rates, follow-up to abnormal screening
  - ◆ Treatment, quality of care



# Interactive Policy-Level Decision Tools



## Colorectal Cancer Mortality Projections Website

National Cancer Institute | U.S. National Institutes of Health | www.cancer.gov

### Colorectal Cancer Mortality Projections

**Modeling the impact of cancer control efforts on US colorectal cancer mortality**

Our purpose is to inform cancer control planning and public policy discussion.

The NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) developed this Web site to help cancer control planners, program staff and policy makers consider the impact of risk factor reduction, increased early detection, and increased access to optimal treatment on future colorectal cancer mortality rates.

This site shows the results of simulation modeling—computer simulations of colorectal disease progression in a population with the characteristics of the US population. Use this information to:

- see how policy options to increase cancer prevention, screening, and access to state-of-the-science treatment can affect future mortality trends.
- help determine cancer control program priority areas for new intervention investments.
- identify research questions and opportunities.

To get started:

- Watch and listen to our [Introductory Tutorial](#) (Flash - 1:10 min.).
- View [Key Findings](#) to answer important questions about how best to reduce CRC mortality.
- Explore the [Interactive Graphs](#) to view and compare results of the simulation models.

**Suggested Citation:** Colorectal Cancer Mortality Projections, National Cancer Institute, NIH, DHHS, Bethesda, MD, December 2007, <http://cisnet.cancer.gov/projections/colorectal/>.

All material in this report is in the public domain and may be reproduced or copied without permission. Citation as to source, however, is appreciated.

For a printable summary of the Colorectal Cancer Mortality Projections Web Site, download the [Fact Sheet \(PDF\)](#).

Last modified: January 03, 2008

Accessibility | Privacy Policies

➤ Allow cancer control planners and policy makers to explore the impact of varying key parameters involved in their decision making.

## Mock-Up of Prostate Cancer Policy Assessment Calculator

### Prostate Cancer Screening and Treatment Guidelines Assessment Calculator

This calculator interface is to project the impact of candidate decision-to-biopsy and decision-to-treat policies. By providing reliable outcomes and cost/benefit measures associated with these policies, this calculator will become a useful tool for policy-makers and will ultimately advance the process by which guidelines for prostate cancer screening and treatment are developed. A complete user's manual is available [here](#), and a step-by-step tutorial is [here](#).

The Prostate Cancer Screening and Treatment Guidelines Assessment Calculator is currently under development. Please direct questions or comments to [rgulati@nih.gov](mailto:rgulati@nih.gov).

Simulation		Screening Policy		Outcomes	
Parameter	Value	Parameter	Value	Outcome	Format
Population size	10000000	Min screening age	45	Correct treatment rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
Random seed	47194	Max screening age	84	Curable stage detections	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
		Screens per year	1.0 <input type="button" value="Editor"/>	Deaths prevented	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
		PSA level	4.0 <input type="button" value="Editor"/>	False positive rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
		PSA velocity	0.5 <input type="button" value="Editor"/>	Mean lead time	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
		Biopsy frequency	0.4 <input type="button" value="Editor"/>	Number needed to harm	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
		Biopsy sensitivity	0.9 <input type="button" value="Editor"/>	Number needed to screen	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Number needed to treat	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Overdiagnosis rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Overtreatment rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				PSA sensitivity	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				PSA testing rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Positive predictive value	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Stage shifted rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Underdiagnosis rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Undertreatment rate	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot
				Years of life saved	<input checked="" type="checkbox"/> Table <input type="checkbox"/> Plot

Economic Costs		Treatment Policy	
Parameter	Value	Parameter	Value
Cost per PSA test	65 <input type="button" value="Editor"/>	PSA velocity	0.5 <input type="button" value="Editor"/>
Cost per biopsy	1500 <input type="button" value="Editor"/>	Treatment efficacy	0.56 <input type="button" value="Editor"/>
Cost of treatment	15000 <input type="button" value="Editor"/>	AJCC Stage	72 <input type="button" value="Editor"/>
PSA failure rate	0.4 <input type="button" value="Editor"/>	PSA level	4.0 <input type="button" value="Editor"/>
Expected ADT courses	2.1 <input type="button" value="Editor"/>	Gleason grade	5 <input type="button" value="Editor"/>
Cost of ADT course	600 <input type="button" value="Editor"/>	Adjuvant ADT efficacy	0.44 <input type="button" value="Editor"/>
Terminal costs	12000 <input type="button" value="Editor"/>		

Calculate outcomes | Reset

➤ Ensure that the tools are understandable and relevant for target audiences.

# Evaluation of Diagnostic Tests



- A large number of diagnostic tests (conducted for symptoms or for known disease) are not supported by empirical studies showing that they affect patient outcomes
  
- Example: Assistance to CMS in making coverage decisions about indications for using PET imaging
  - ◆ Which cancers
  - ◆ Diagnosis, staging, restaging and monitoring response to treatment

## Use of the Collaborative Linked Mechanism



- Group proposals will incorporate plans for joint collaborative analyses, rather than having to change plans after the award
- The group as a whole would coordinate to provide coverage of the new areas (with some groups specializing in specific areas)
  - ◆ Groups could bring in and share specialized modeling expertise (e.g. upstream modelers, multi-scale modelers)
- Since groups could decide who they want to work with, it would reward PI's who are perceived as collaborative
- Coordination of group activities would be built into the application, rather than funding it separately

# Cooperative Agreement Mechanism (U01)



- Facilitate comparative modeling
- Allow access to a broader array of data resources and multi-disciplinary expertise
- Provide a forum for discussion of validation and other methodologic issues
- Collaboration with NCI staff will assist in:
  - ◆ Ensuring responsiveness of the consortium to evolving surveillance and cancer control issues
  - ◆ Attaining research goals and catalyzing collaborations with outside groups who often approach NCI seeking assistance
  - ◆ Knowledge of and access to potential data resources

# Status of Implementing External Review Recommendations



- More Comparative Modeling Aimed at Understanding Model Differences
  - ◆ Joint modeling work
    - Some focused on large policy questions (e.g. role of screening and adjuvant therapy on the decline in breast cancer mortality)
    - Others focused on hypothetical exercises aimed at understanding model differences (e.g. how long after a single colonoscopy at age 50 does it take for age-specific CRC incidence rates to return to background levels)
  - ◆ Model Profiler – on-line templated model documentation to aid in model transparency
  - ◆ Publications on model differences

# Funding History



- Originally funded in two phased in rounds (FY00 and FY02)
- Refunded in FY05 – total of 15 grants funded in breast, prostate, colorectal and lung cancer
- 8 Affiliate Members (Funded through other mechanisms – joined CISNET collaboration)

# Optimizing Biomarker Development Strategies



---

<i>Preclinical Exploratory</i>	<b>PHASE 1</b>	<i>Promising directions identified</i>
<i>Clinical Assay and Validation</i>	<b>PHASE 2</b>	<i>Clinical assay detects established disease</i>
<i>Retrospective Longitudinal</i>	<b>PHASE 3</b>	<i>Biomarker detects preclinical disease and a "screen positive" rule defined</i>
<i>Prospective Screening</i>	<b>PHASE 4</b>	<i>Extent and characteristics of disease detected by the test and the false referral rate are identified</i>
<i>Cancer Control</i>	<b>PHASE 5</b>	<i>Impact of screening on reducing burden of disease on population is quantified</i>

---

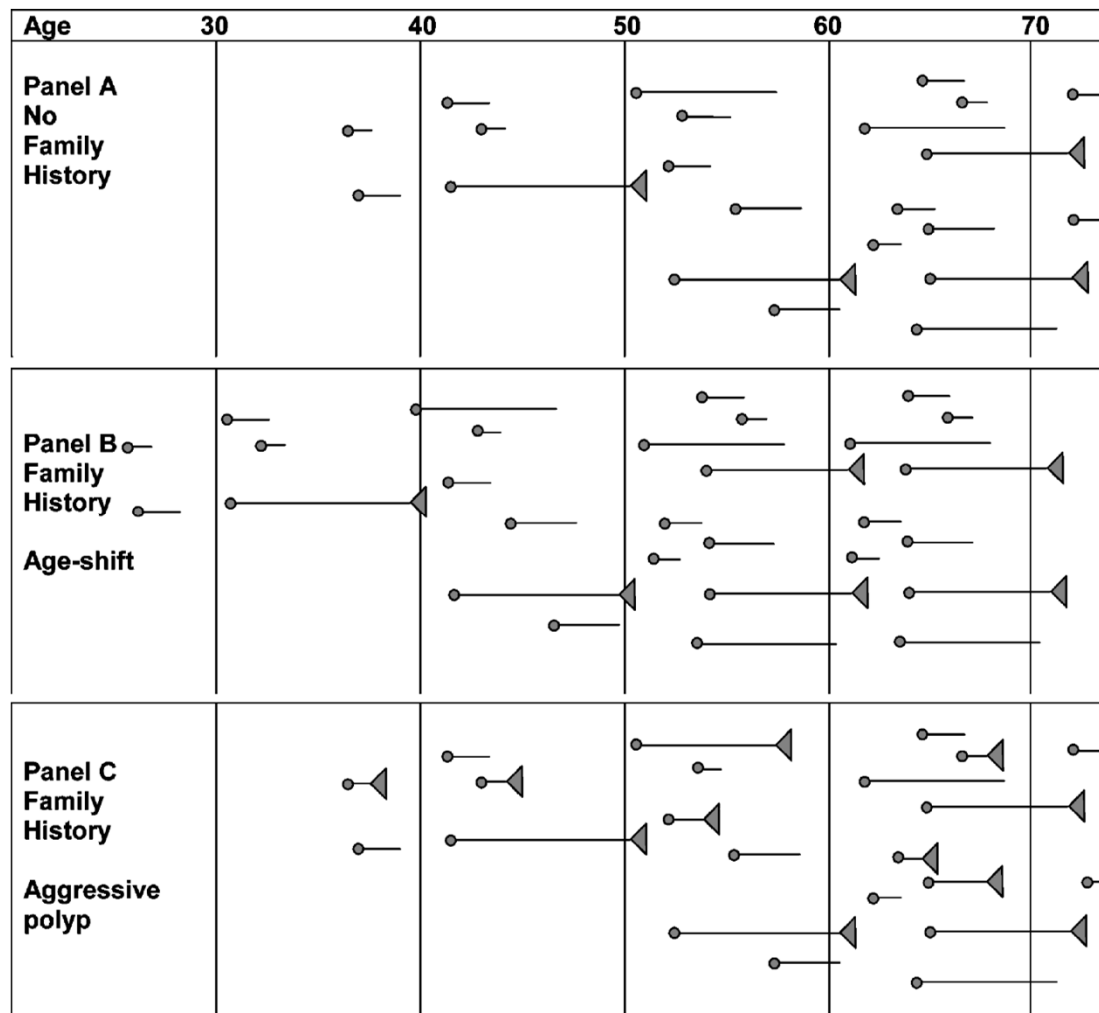
# Building Capacity and a Unique Approach to Modeling



- Flexible-Broad Based Disease Models
  - ◆ Able to incorporate the full range of cancer control interventions
- Multiple-Birth Cohort Modeling
  - ◆ Construct the actual US experience rather than a single hypothetical birth cohort
- Comparative Modeling
  - ◆ Central questions to be addressed by all groups with a common set of inputs and outputs
    - Reproducibility across model adds credibility to results
    - Differences points out areas for further study in a systematic way
- Transparency in Modeling Structure and Assumptions
  - ◆ Standardized web-based documentation across models



# How Should Screening Schedules for Colorectal Cancer be Modified for Individual with A Family History?



Ramsey et al. Cancer Epidemiol Biomarkers Prev, 2005