

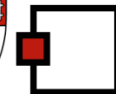
# Inefficiencies and High-Value Improvements in Current US Cervical Cancer Screening Practice

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Department of Health Policy and Management



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# Roadmap

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- Overview of cervical cancer and HPV
- General decision-analytic approach
- Applied example
- Related work

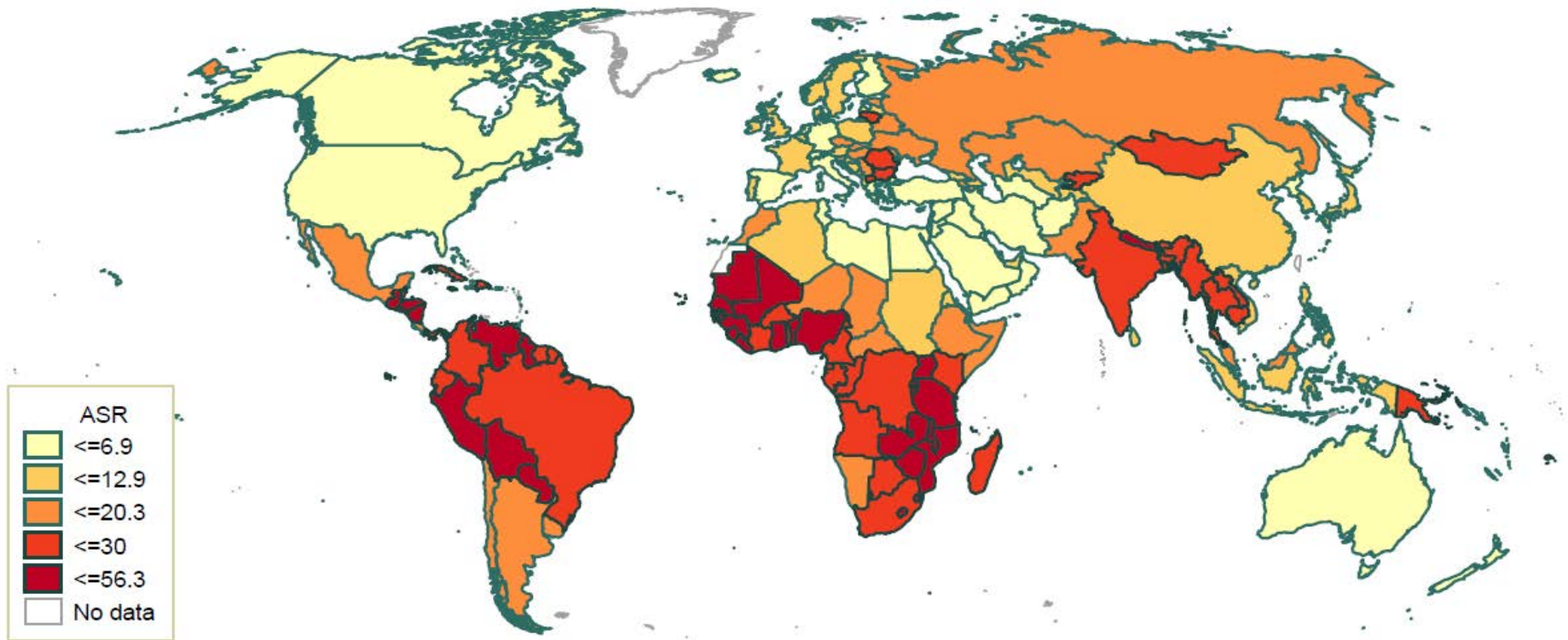
# Why Cervical Cancer?

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- In U.S., screening since the 1960s, but inefficient
- Over 50 million Pap tests conducted annually
  - some women get screened too much; some never
  - loss-to-follow-up of women with abnormal results
  - \$6B in screening-related costs annually
- Over 12,000 new cases and 4,000 deaths per year

# Global Burden of Cervical Cancer

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\* ASR, age-standardized incidence rates per 100,000 women per year; HPV Information Centre ([www.who.int/hpvcentre](http://www.who.int/hpvcentre))

# Human Papillomavirus (HPV)

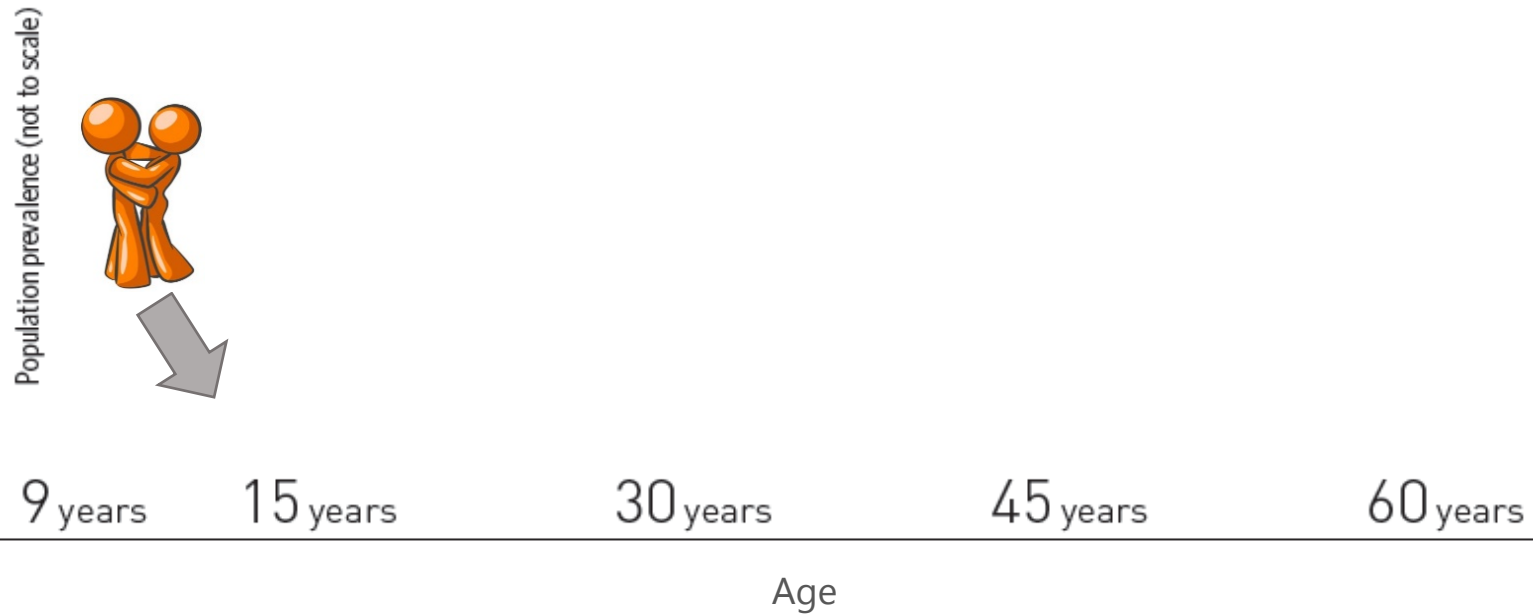
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- HPV is a necessary cause of cervical cancer
  - most common sexually-transmitted infection
  - 80% lifetime cumulative incidence
  - 40 known types; 15 are considered “high-risk” (carcinogenic)
- **High-risk** HPV responsible for cancers of the cervix, anus, vulva, vagina, penis, and oropharynx
  - > HPV-16,-18 are most common
- **Low-risk** HPV associated with >90% genital warts and juvenile onset recurrent respiratory papillomatosis (JORRP)
  - > HPV-6,-11 are most common

# HPV Natural History\*

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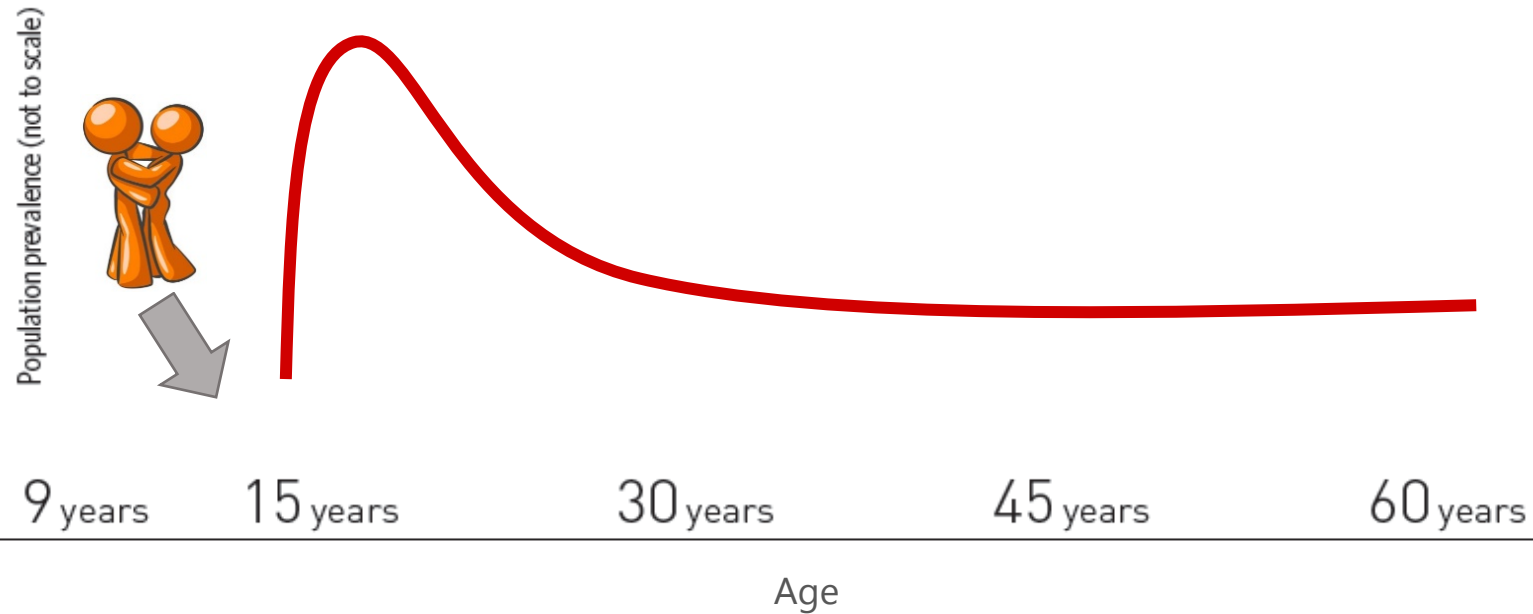
**No  
infection**



\* Adapted from Schiffman and Castle (NEJM 2005); World Health Organization (WHO) Cervical Cancer Guidance Note (2013)

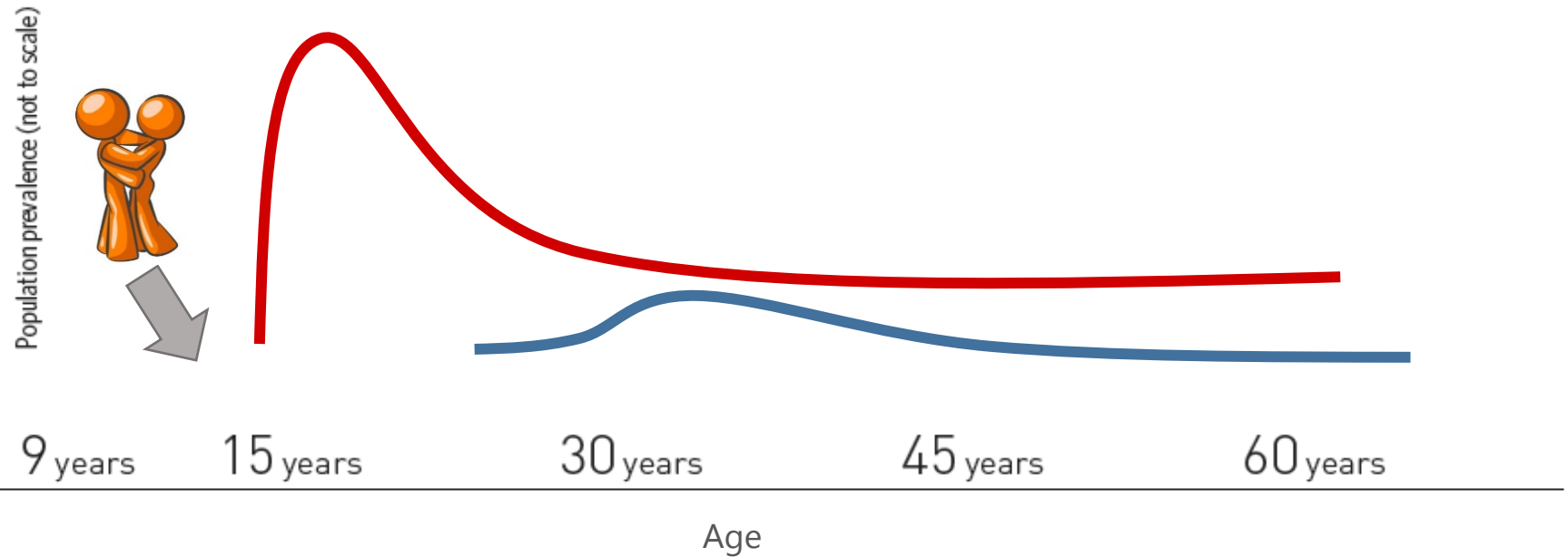
# HPV Natural History\*

No infection ↔ HPV infection



\* Adapted from Schiffman and Castle (NEJM 2005); World Health Organization (WHO) Cervical Cancer Guidance Note (2013)

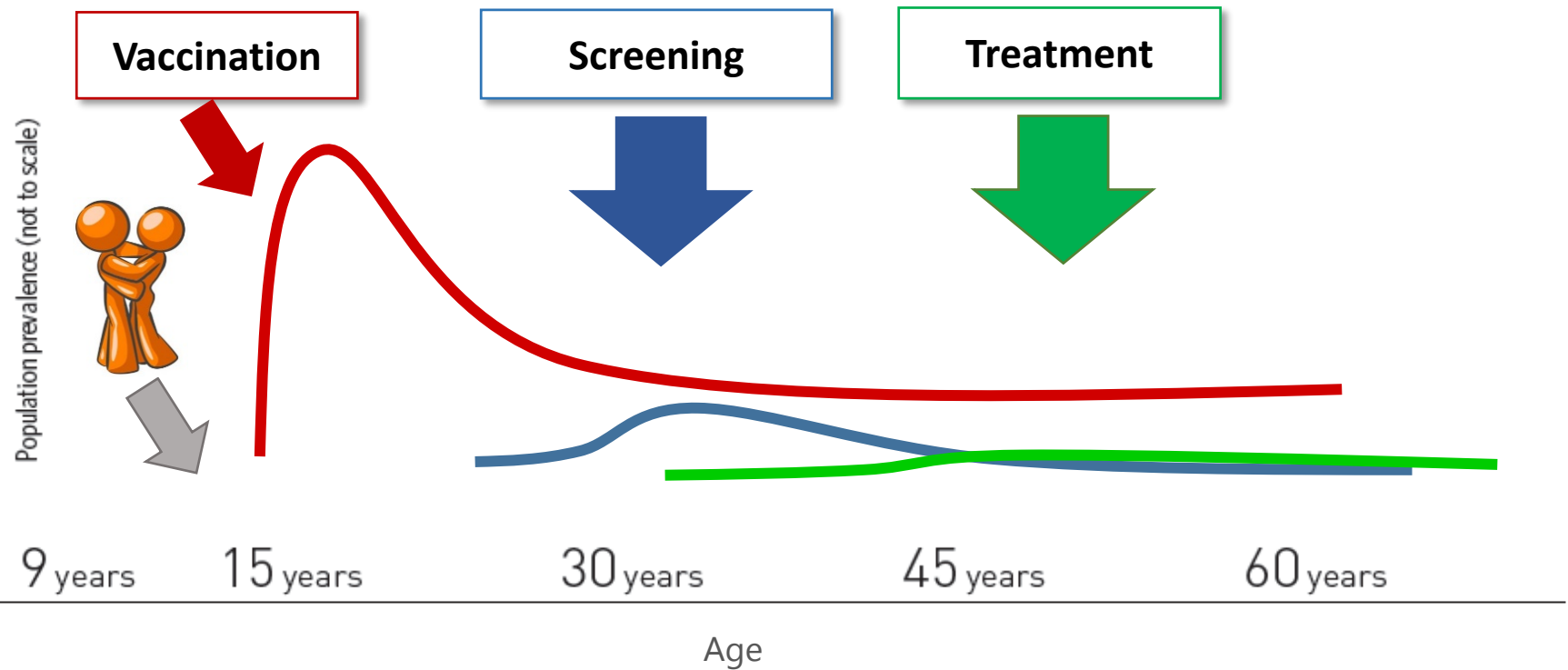
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# Vaccination and Screening

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- **Prophylactic HPV vaccines**
  - Bivalent (2v): HPV 16/18
  - Quadrivalent (4v): HPV 16/18/6/11
  - Nonavalent (9v): HPV 16/18/31/33/45/52/58/6/11
- **Screening technologies**
  - Conventional: Pap test, Pap+HPV “cotest” ages 30+
    - Pap every 3-years with/out switch to cotest every 5-years
  - New: HPV-16/18 test for women ages 25+
  - Newer: mRNA test, viral load, p16/Ki67, methylation

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# Challenges for Decision-Making

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- Diseases that afflict multiple populations and age groups
- Transmissible infection (HPV) and chronic condition (cancer)
- Complex strategies that target different points along disease pathway and different ages
- Clinical trials of all preventive approaches not feasible
- Reliance on surrogate markers and intermediate endpoints
- Emerging, costly technologies

# Decision Analysis

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- Explicit, quantitative and systematic approach to decision making under *uncertainty*.
- Identify, measure, and value the *consequences* of decisions as well as the uncertainty and risk that exist when the decision needs to be made.
- Elements are incorporated into a *model* to structure the decision problem over time, and used to compare the expected value of different options or interventions.

# General Analytic Framework

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## 1. Develop a model

a. Parameterization

b. Calibration

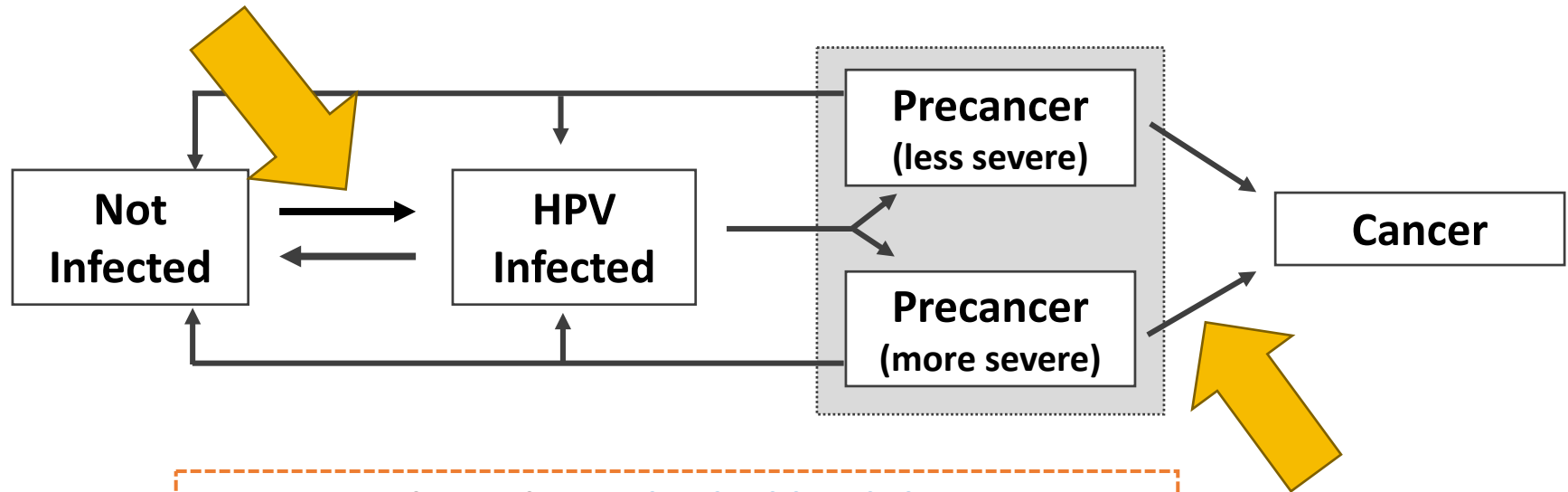
c. Validation

## 2. Simulate strategies

## 3. Explore uncertainties

- To capture key elements of disease process in population of interest
- To synthesize existing evidence and data
- To reflect knowledge and uncertainty about model inputs and assumptions
- To ensure projected outcomes consistent with empirical data
- To project short- and long-term population health and cost outcomes
- To explore the influence of critical uncertainties, alternative scenarios on results

# Model Schematic

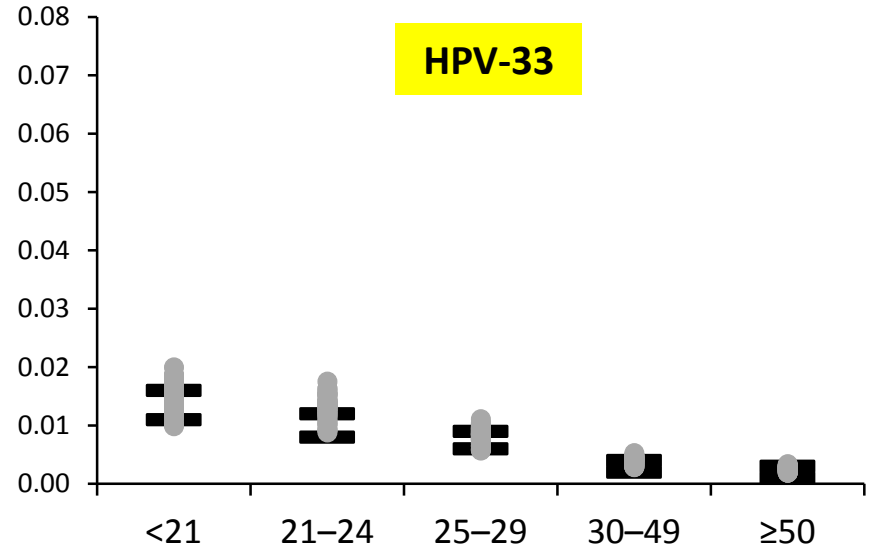
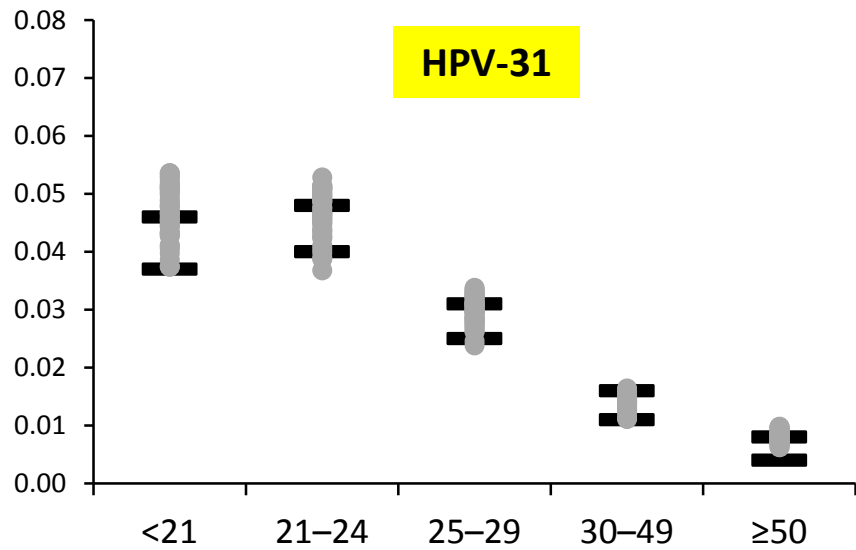
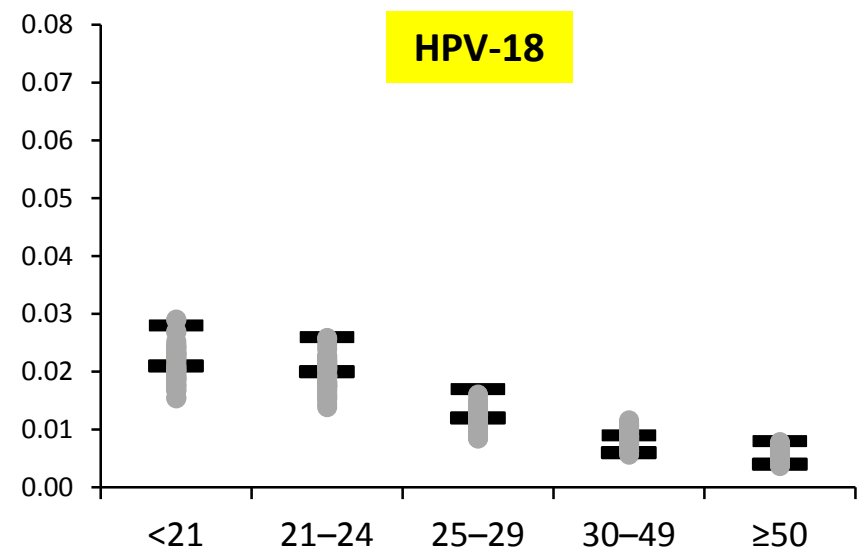
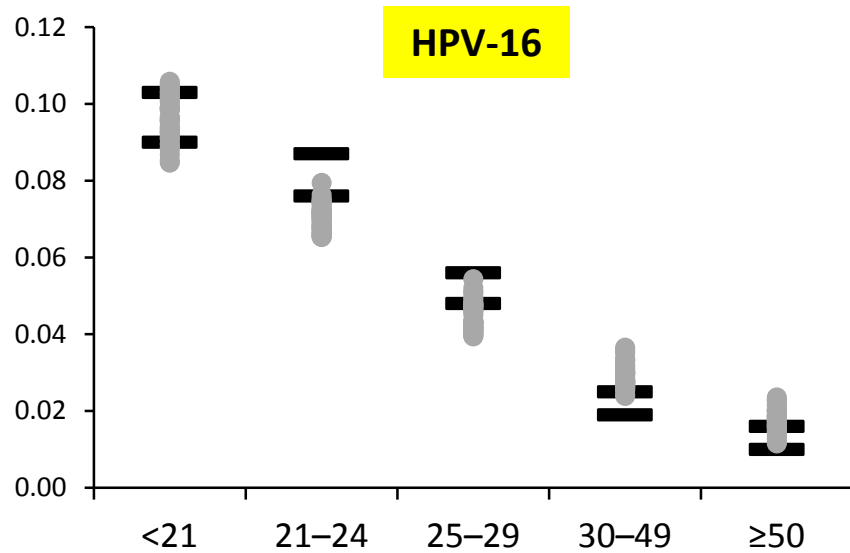


Transitions depend on **individual-level characteristics**

- age
- HPV type (16/18/31/33/45/52/58/other HR/LR)
- HPV persistence
- prior HPV infection
- screening and treatment history

# Calibration Examples

## HPV Prevalence

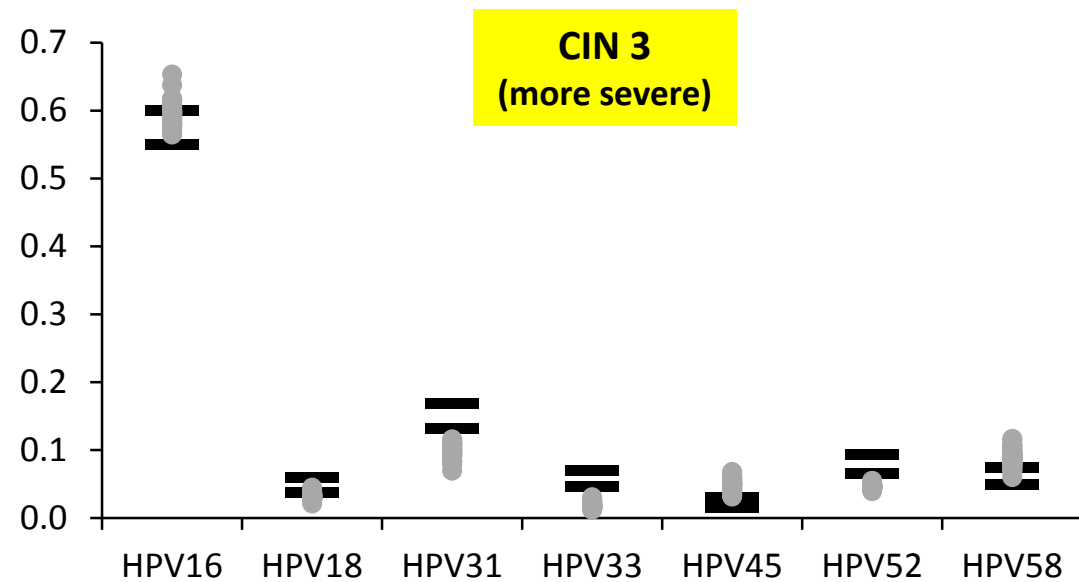
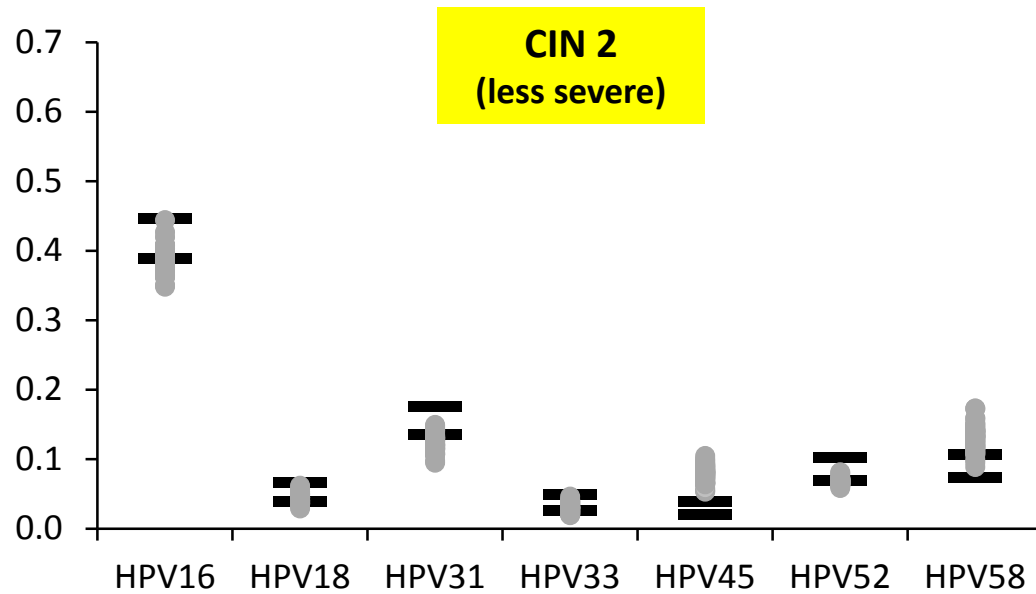




# Calibration Examples

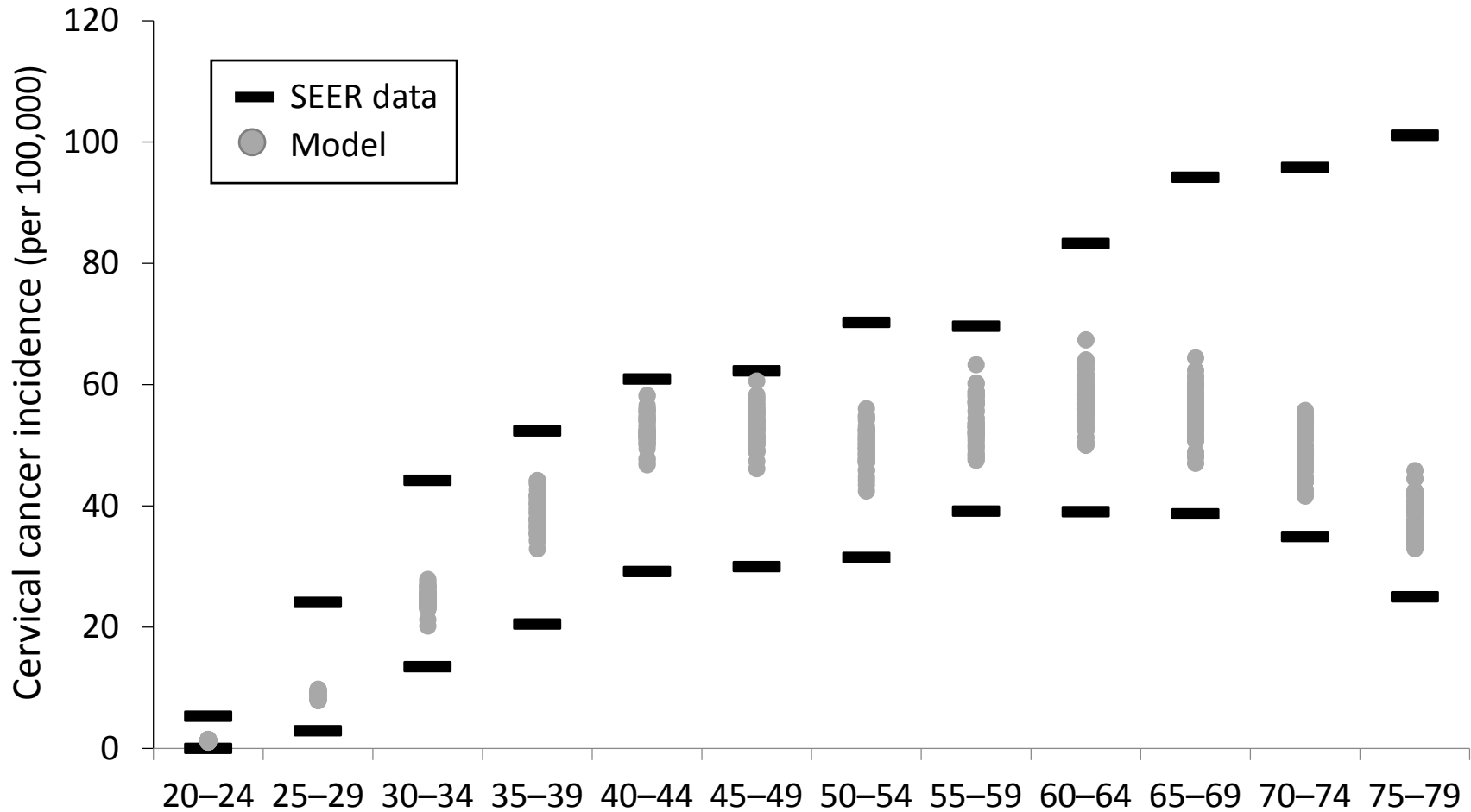
## HPV Type Distribution

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# Validation Example

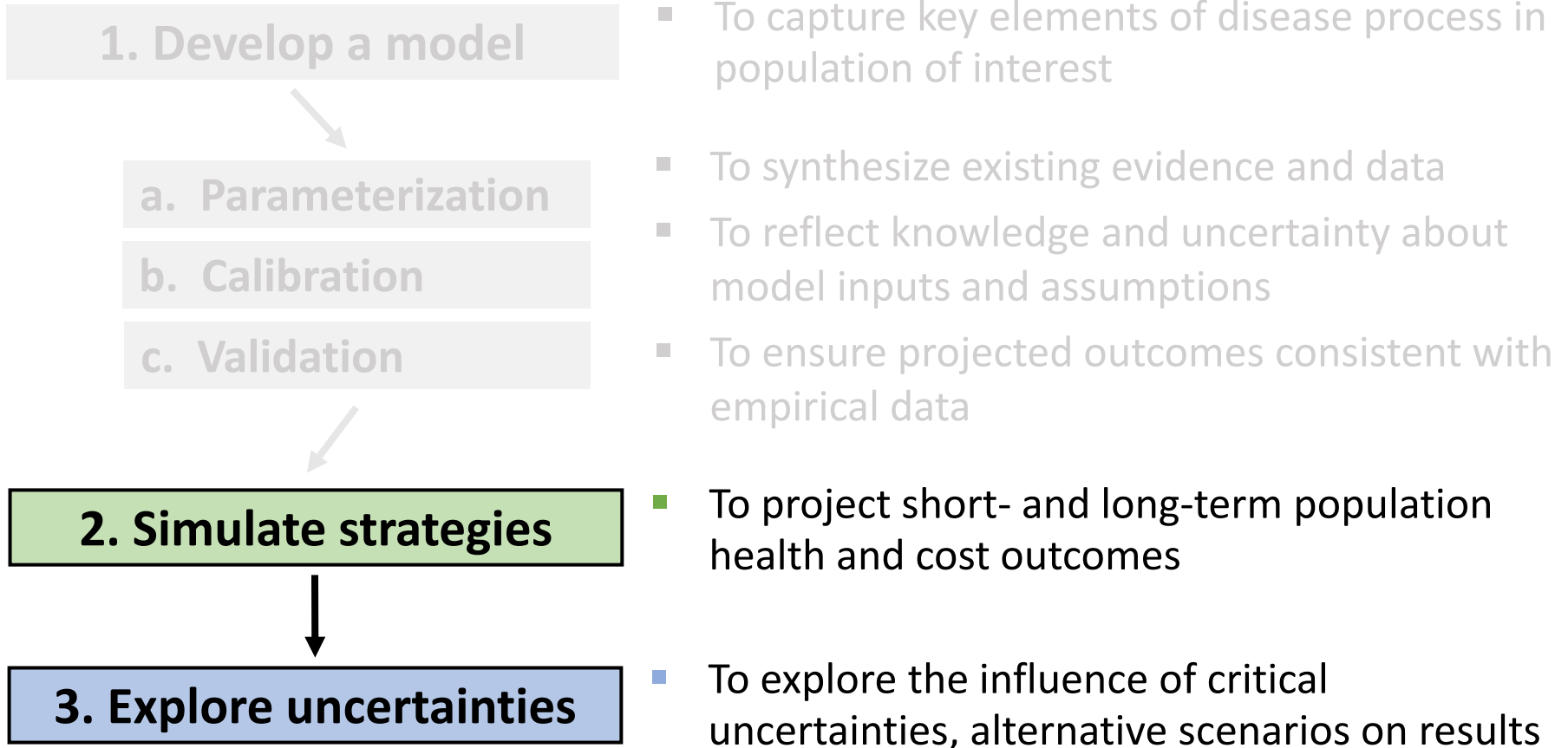
## Cervical Cancer Incidence (pre-screening)\*



\* Parkin et al. (CI5C, vol I-VIII); Campos et al (Am J Epidemiol 2014)

# General Analytic Framework

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# Inefficiencies and High-Value Improvements in U.S. Cervical Cancer Screening Practice

## A Cost-Effectiveness Analysis

Jane J. Kim, PhD; Nicole G. Campos, PhD; Stephen Sy, MS; Emily A. Burger, PhD; Jack Cuzick, PhD; Philip E. Castle, PhD, MPH; William C. Hunt, MS; Alan Waxman, MD, MPH; and Cosette M. Wheeler, PhD, on behalf of the New Mexico HPV Pap Registry Steering Committee\*

**Background:** Studies suggest that cervical cancer screening practice in the United States is inefficient. The cost and health implications of nonadherence in the screening process compared with recommended guidelines are uncertain.

**Objective:** To estimate the benefits, costs, and cost-effectiveness of current cervical cancer screening practice and assess the value of screening improvements.

**Design:** Model-based cost-effectiveness analysis.

**Data Sources:** New Mexico HPV Pap Registry; medical literature.

**Target Population:** Cohort of women eligible for routine screening.

effective relative to guidelines-based strategies. Improvements in the screening process were associated with higher QALYs and small changes in costs. Perfect adherence to screening every 3 years with cytologic testing and adherence to colposcopy/biopsy referrals were associated with the highest INMBs (\$759 and \$741, respectively, at a willingness-to-pay threshold of \$100 000 per QALY gained); together, the INMB increased to \$1645.

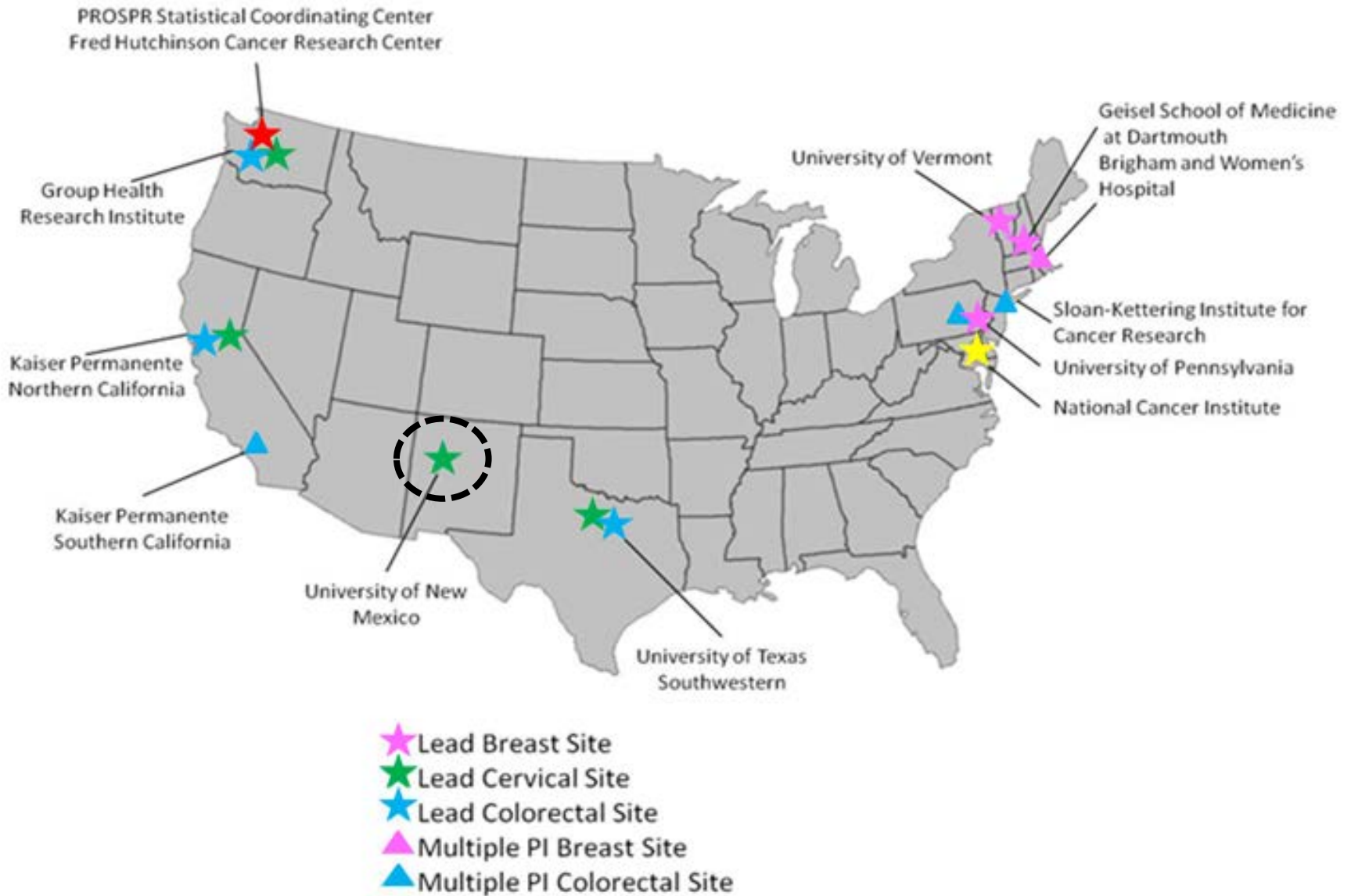
**Results of Sensitivity Analysis:** Current screening practice was inefficient in 100% of simulations. The rank ordering of screening improvements according to INMBs was stable over a range of screening inputs and willingness-to-pay thresholds.

**Limitation:** The effect of human papillomavirus vaccination was not considered.

Funded by the US National Cancer Institute through a cooperative agreement (U54 CA164336), part of the Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR) consortium.

# PROSPR

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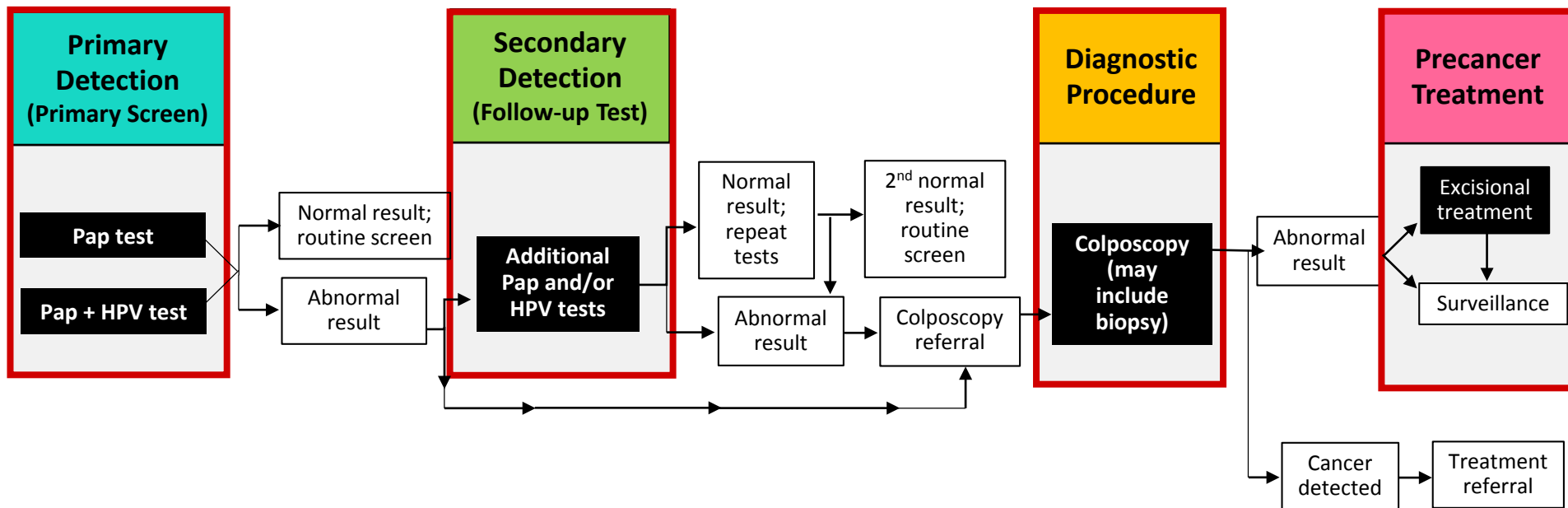
# HPV Pap Registry

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- HPV Pap Registry is a public health surveillance unit that serves as the only existing population-based cervical cancer screening registry in the US
  - Receives data on all cervical cancer screening services
  - Enables linkages of clinical and laboratory records at the individual level on the full spectrum of cervical cancer preventive care

# Cancer Screening Process\*

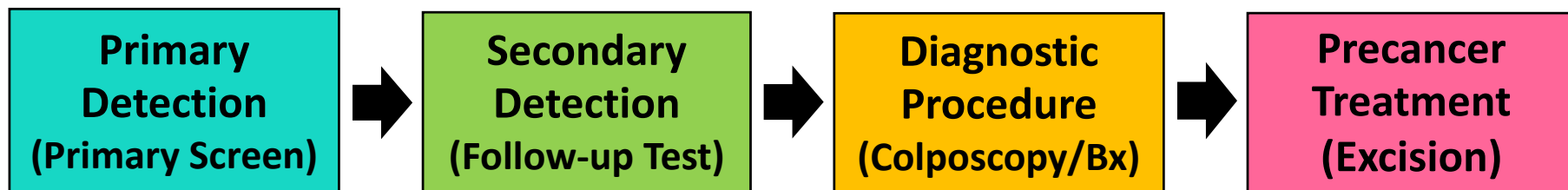
“Screening is a cascade of events rather than a single test”\*\*



\* Beaber et al (JNCI 2015); \*\* Harris et al (Ann Intern Med 2015)

# Cancer Screening Process

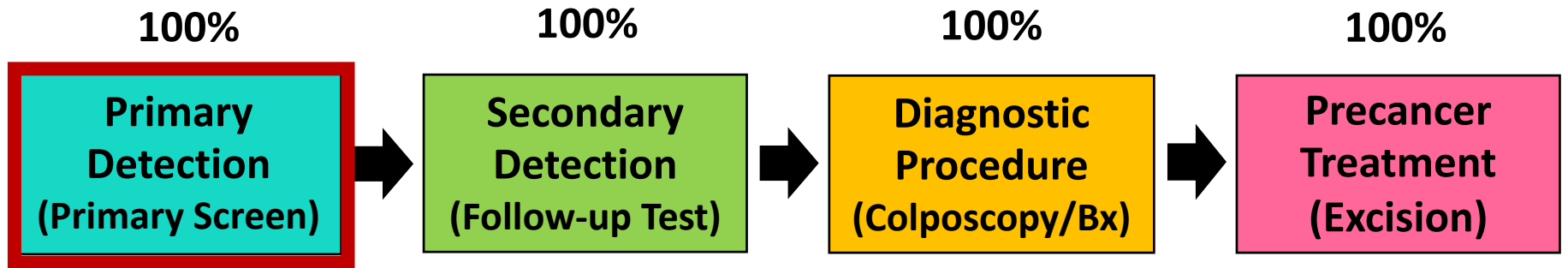
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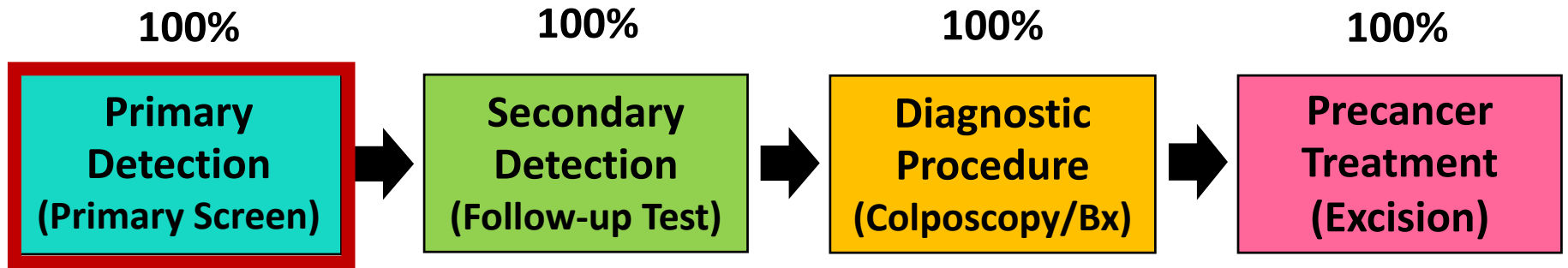
# Cancer Screening Process

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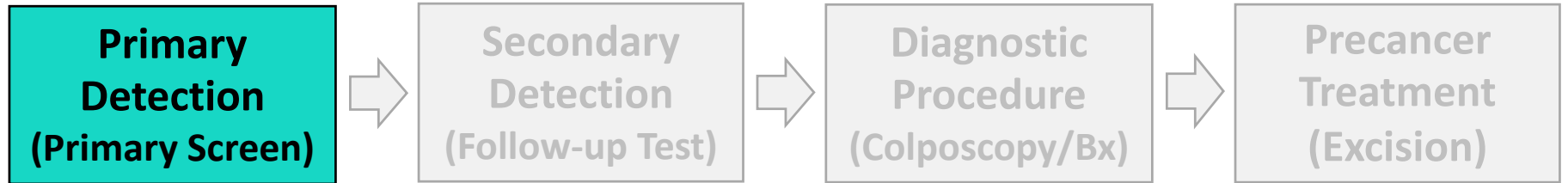


## Objectives:

1. To project outcomes associated with “current practice”
2. To explore improvements in the screening process

# Cancer Screening Process

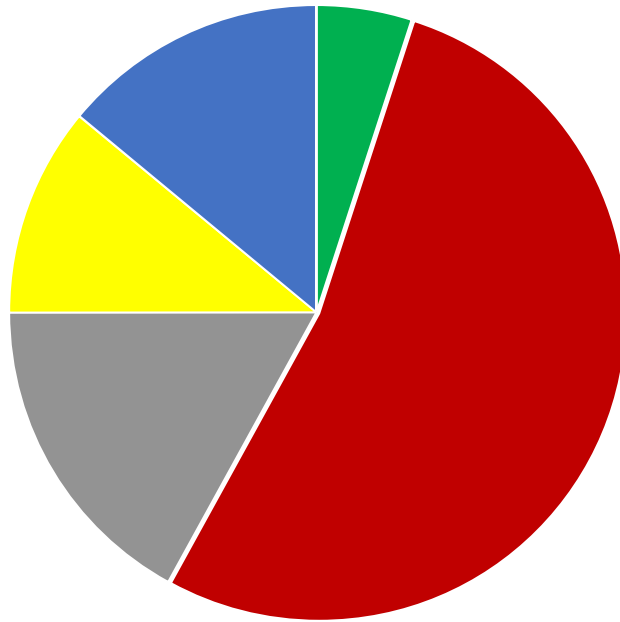
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# Primary Screening Interval

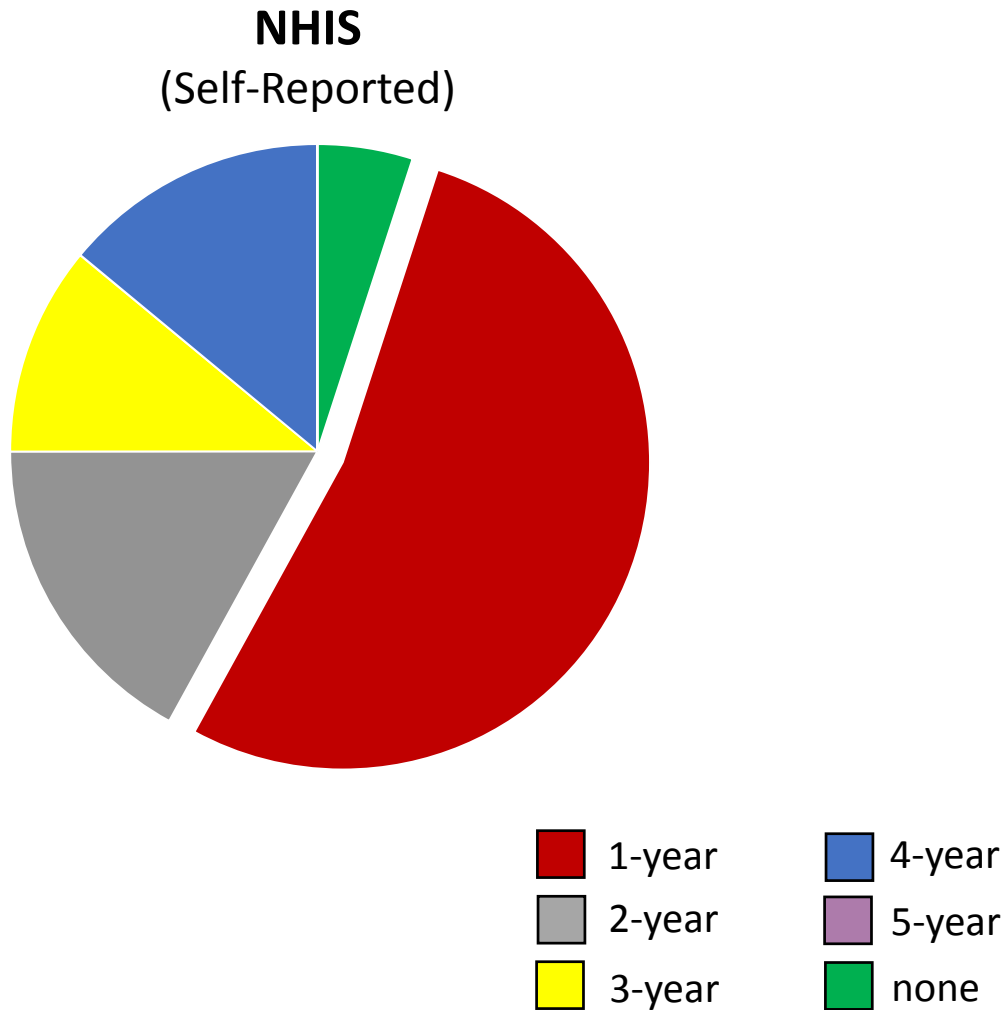
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**NHIS**  
(Self-Reported)



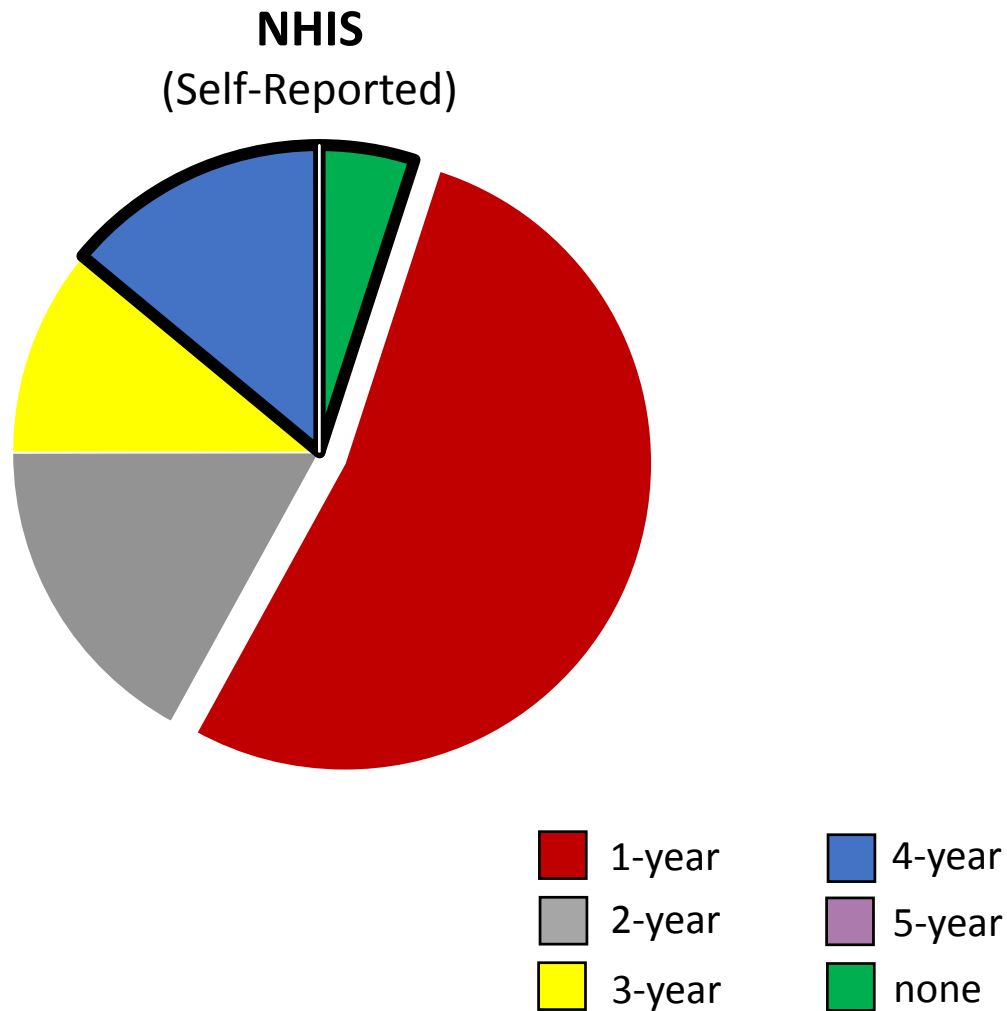
# Primary Screening Interval

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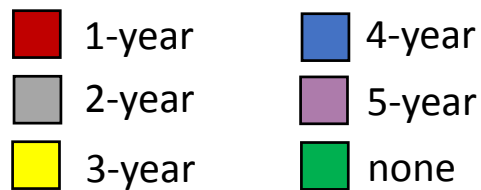
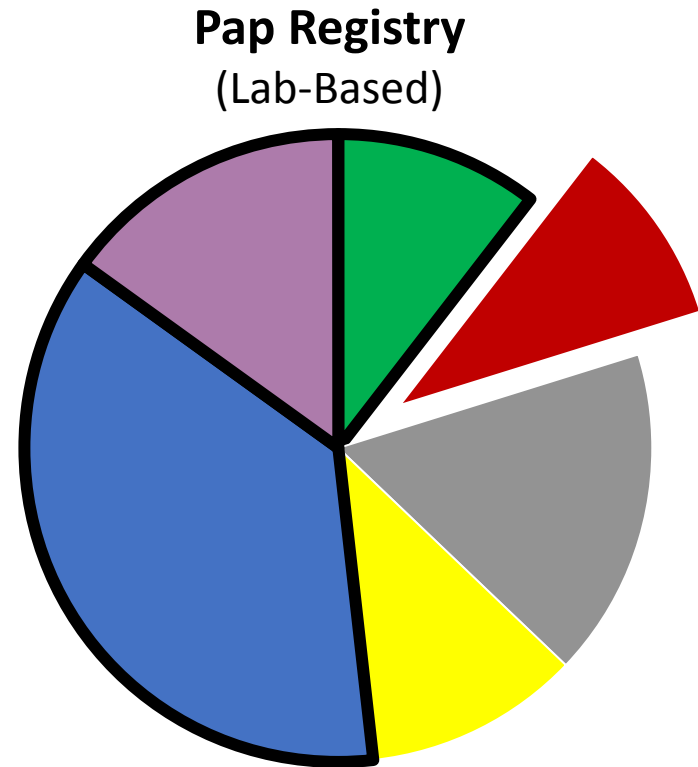
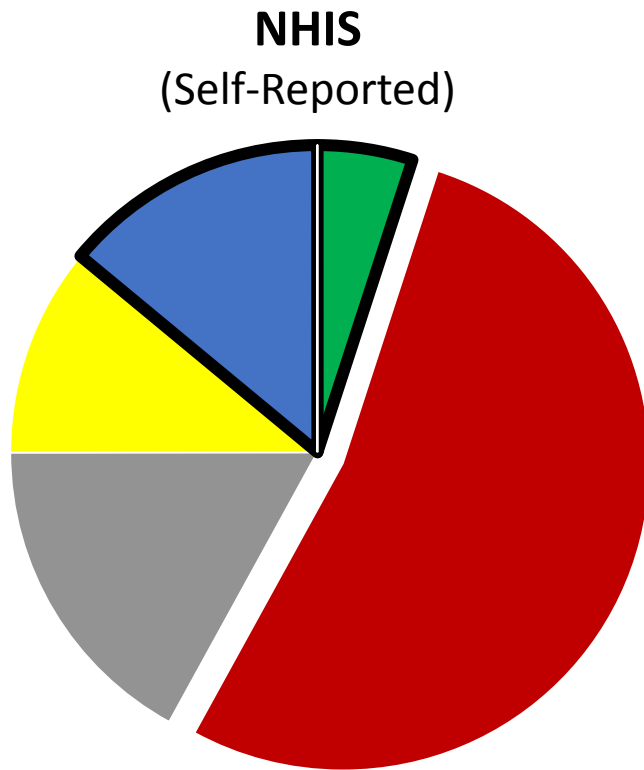
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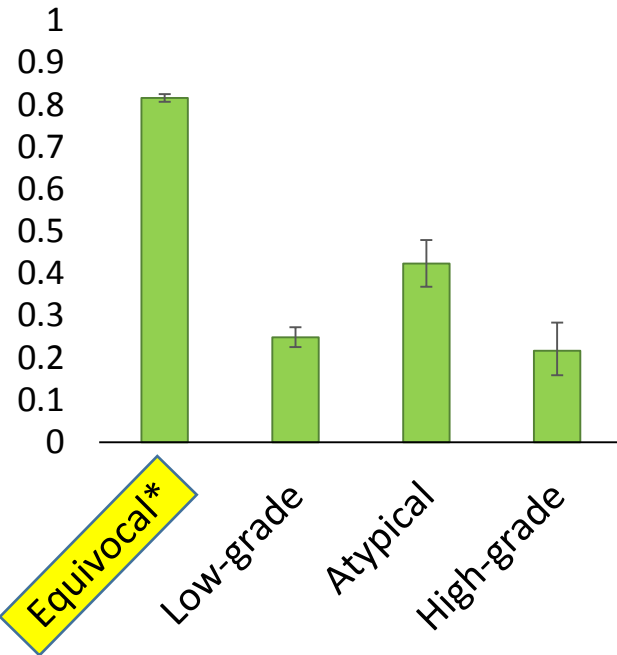
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# Adherence to Clinical Management

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**Detection  
(Follow-up test)**



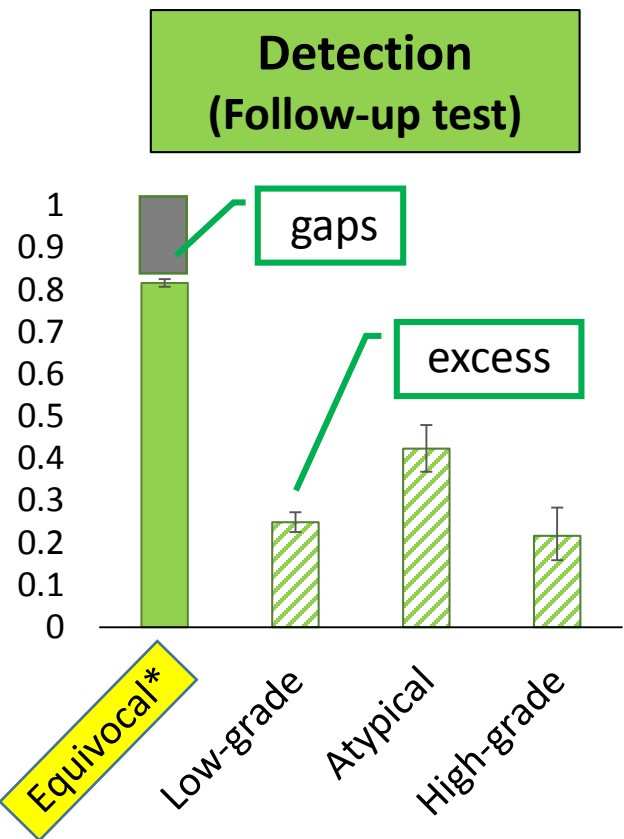
**% women receiving  
HPV triage test**

\* should receive procedure, according to guidelines



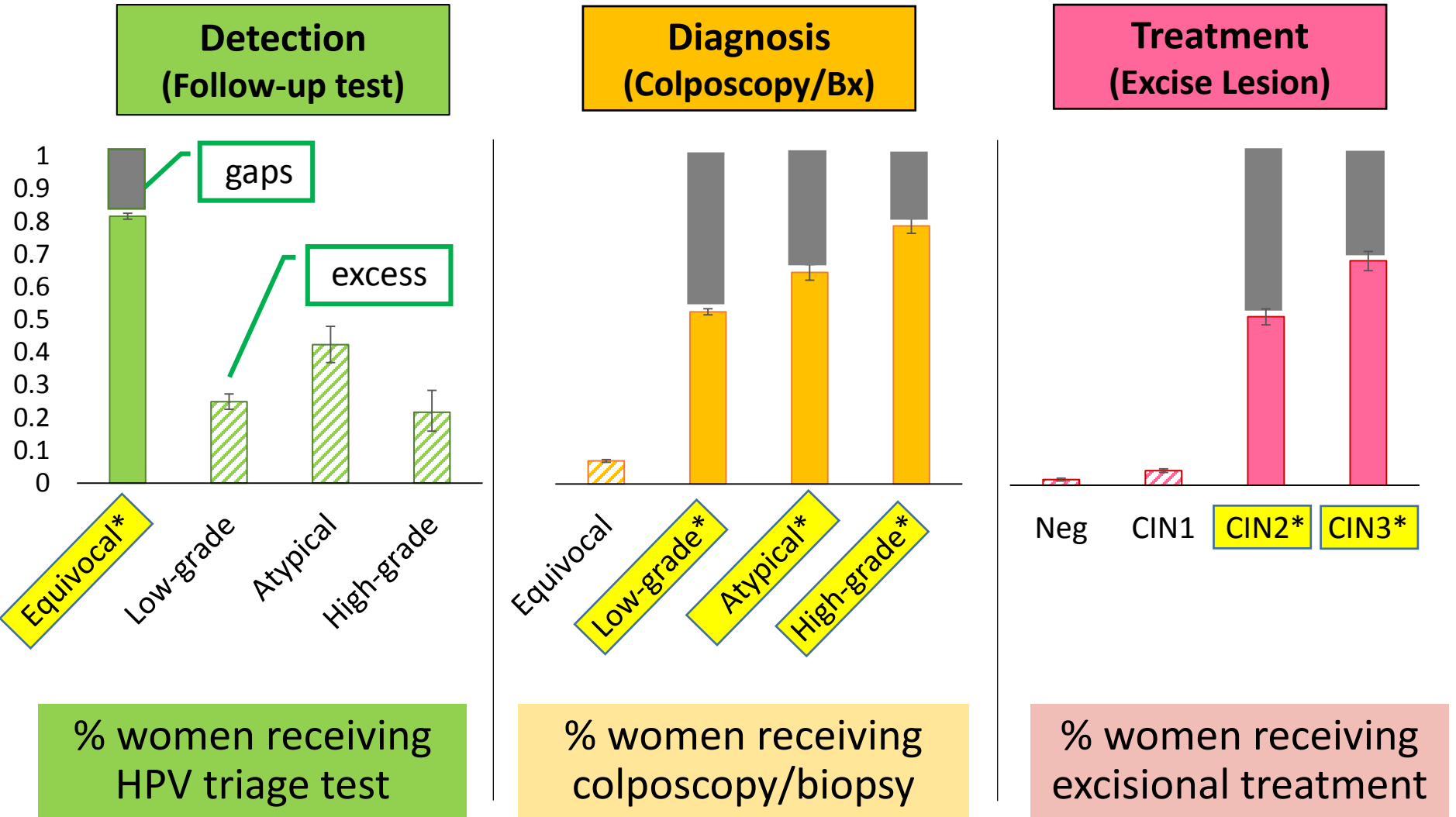
# Adherence to Clinical Management

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# Adherence to Clinical Management



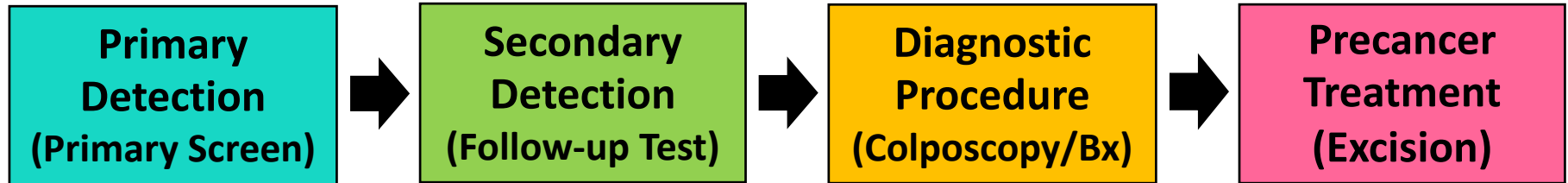
\* should receive procedure, according to guidelines

Nearly 60% are  
not screened  
enough

20% do not  
get HPV triage  
testing

20-50% do not  
get colposcopy  
and biopsy

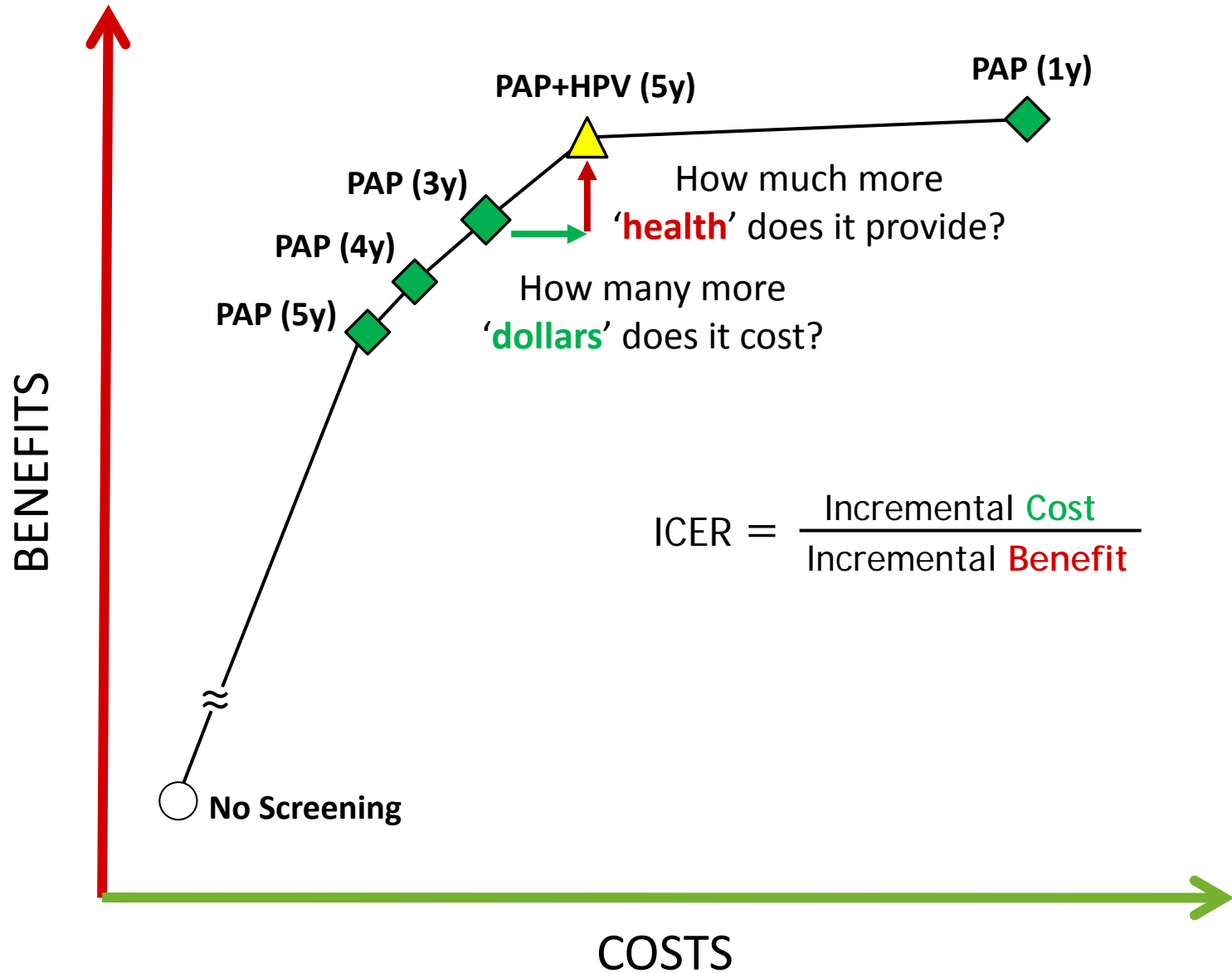
30-50% do not  
get excisional  
treatment



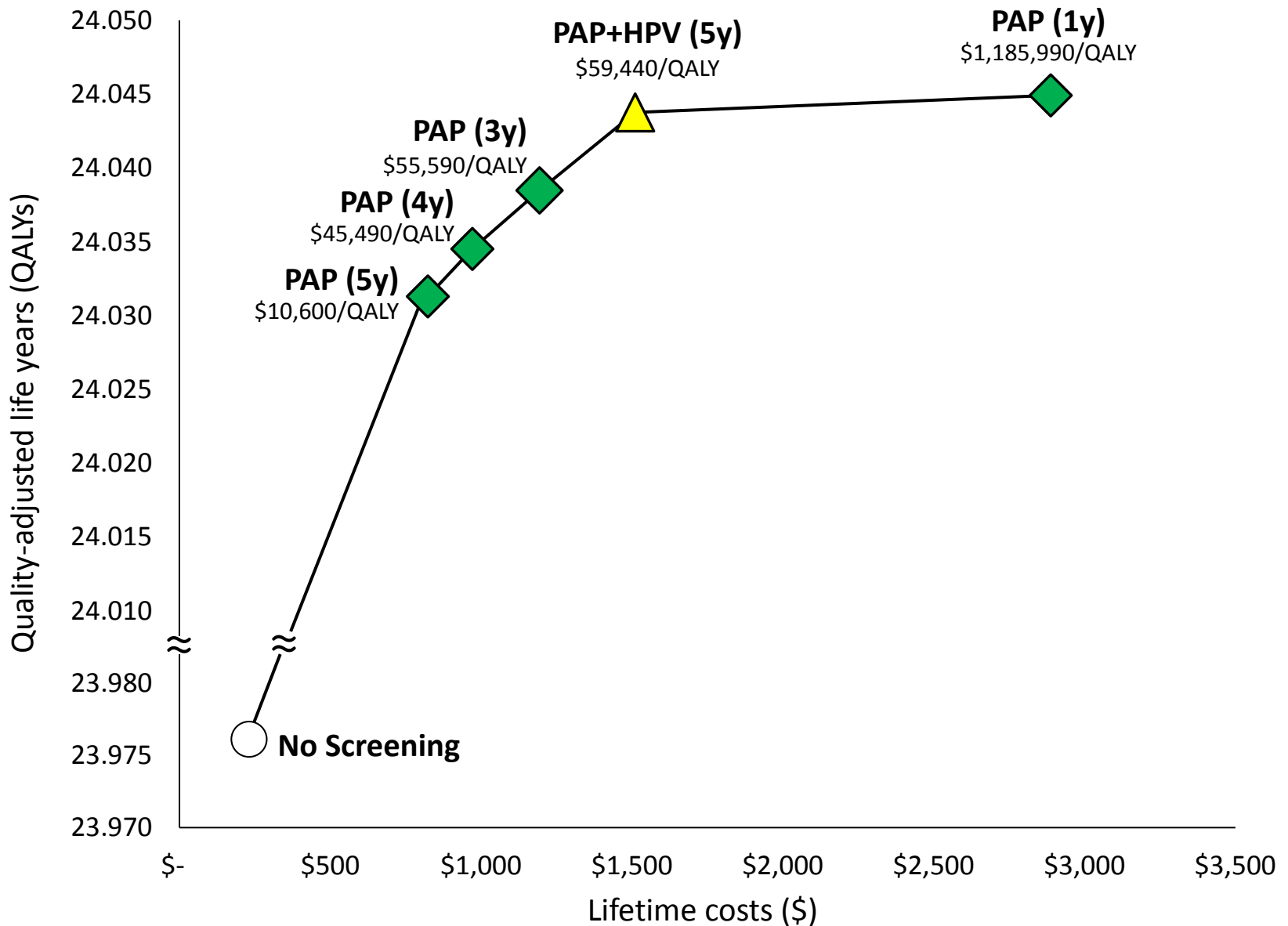
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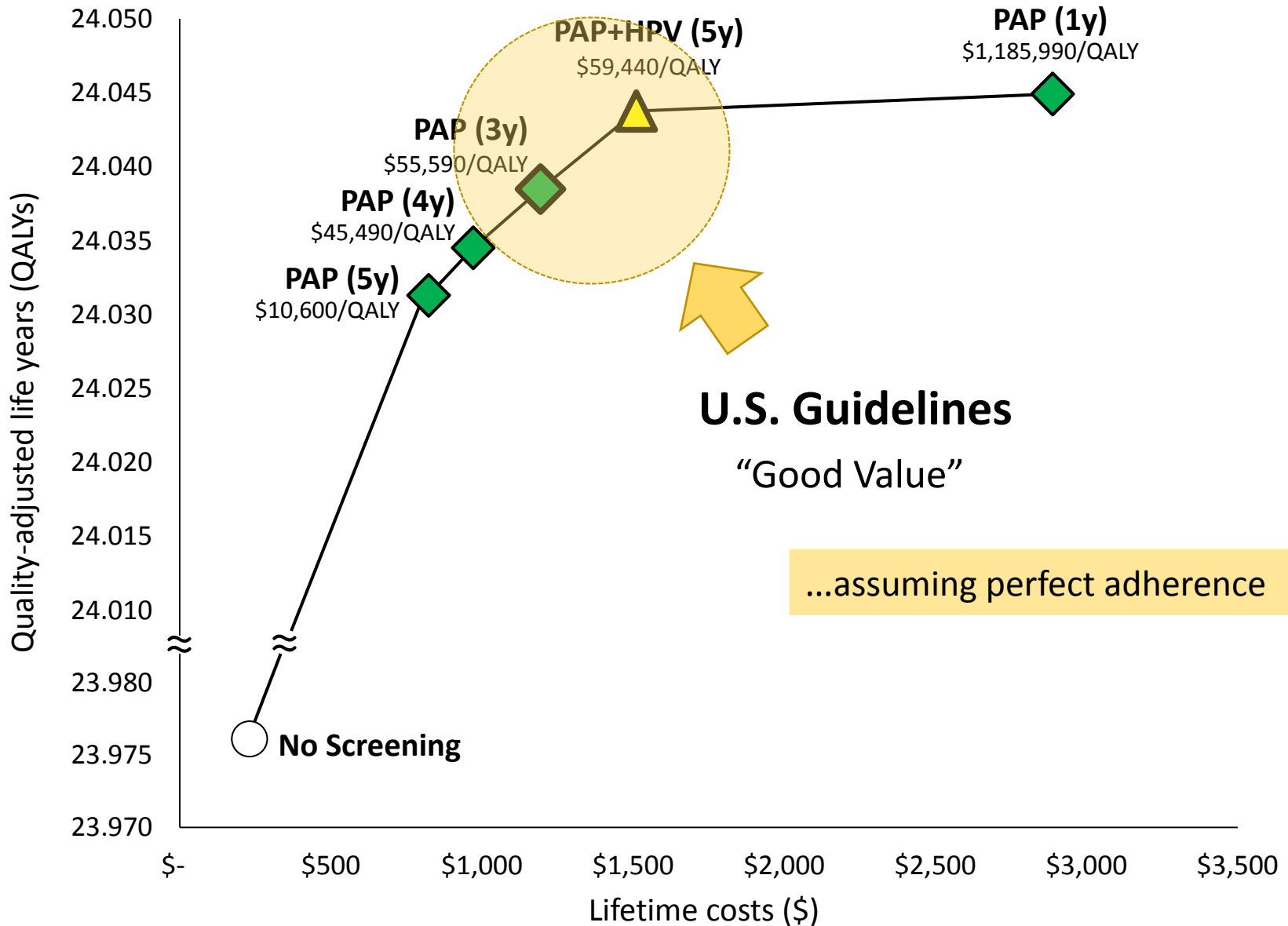
# US Cervical Cancer Screening



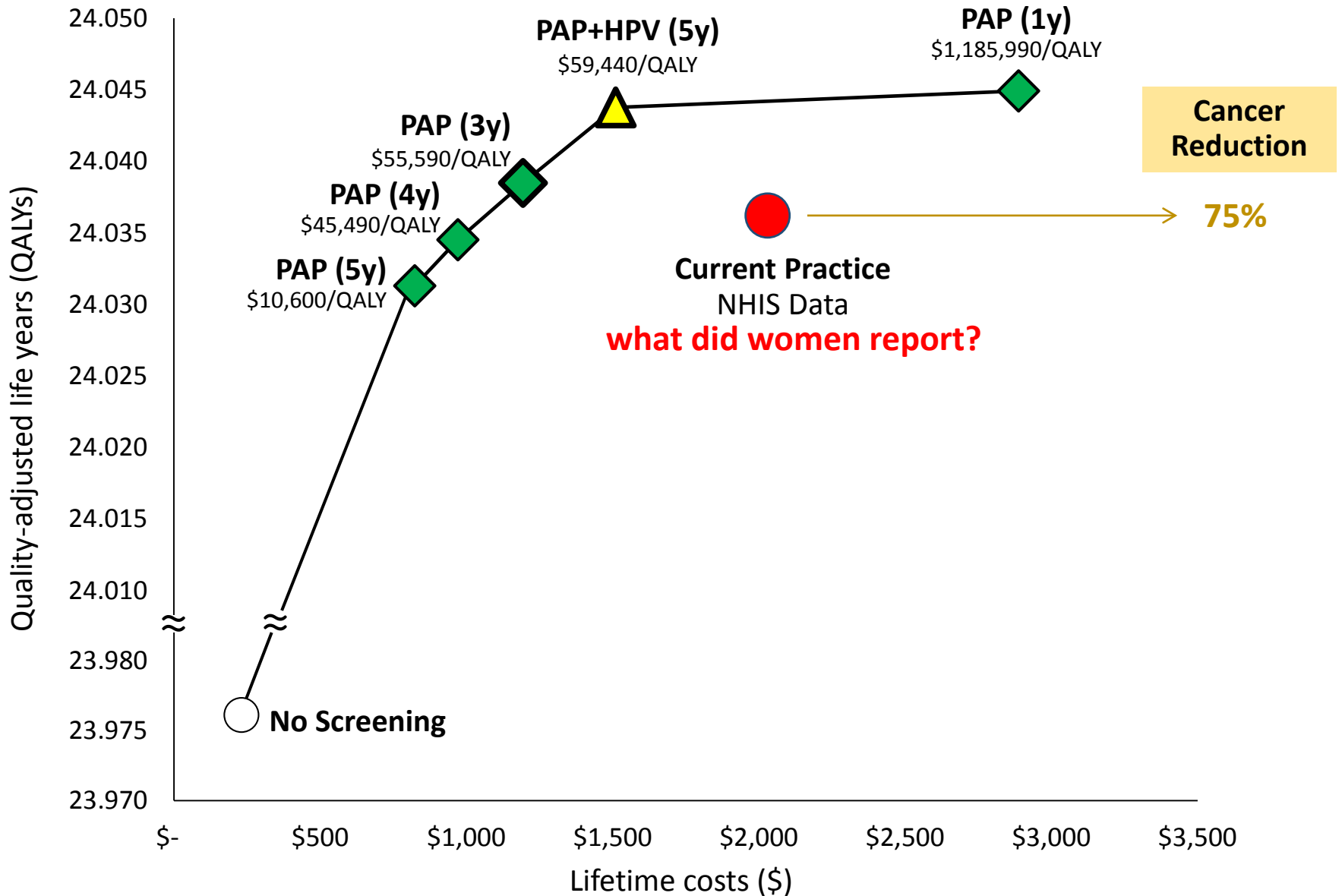
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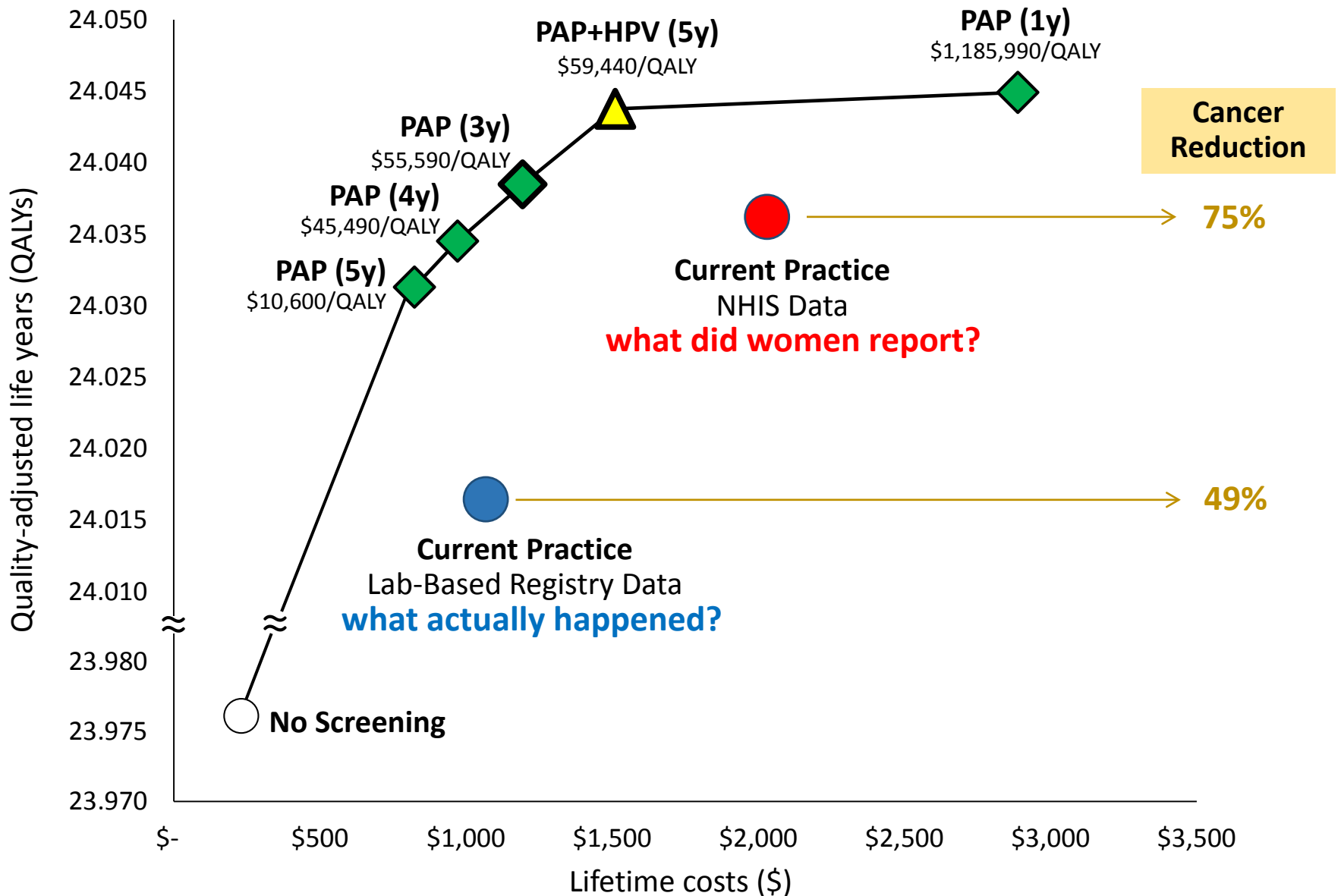
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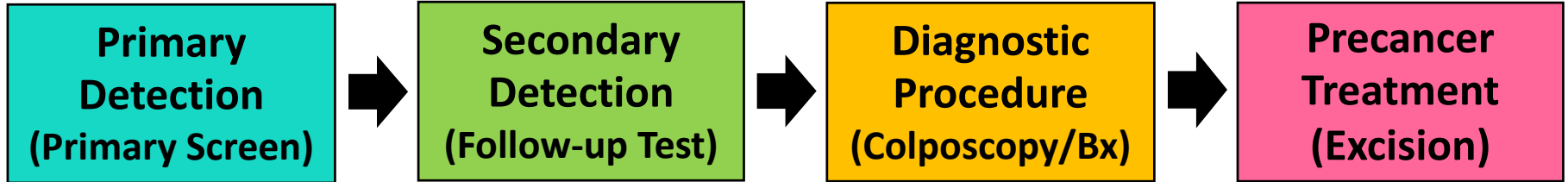


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## Objectives:

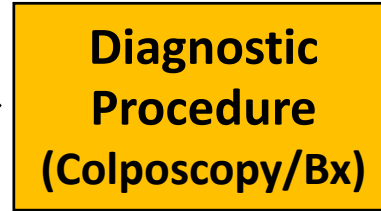
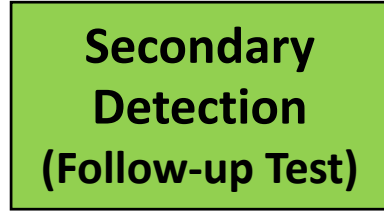
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treatment



**Improve  
Screening**

Ensure all women  
get Pap screen  
every 3 years

**Improve  
Detection**

Ensure all women  
with equivocal  
result get HPV triage

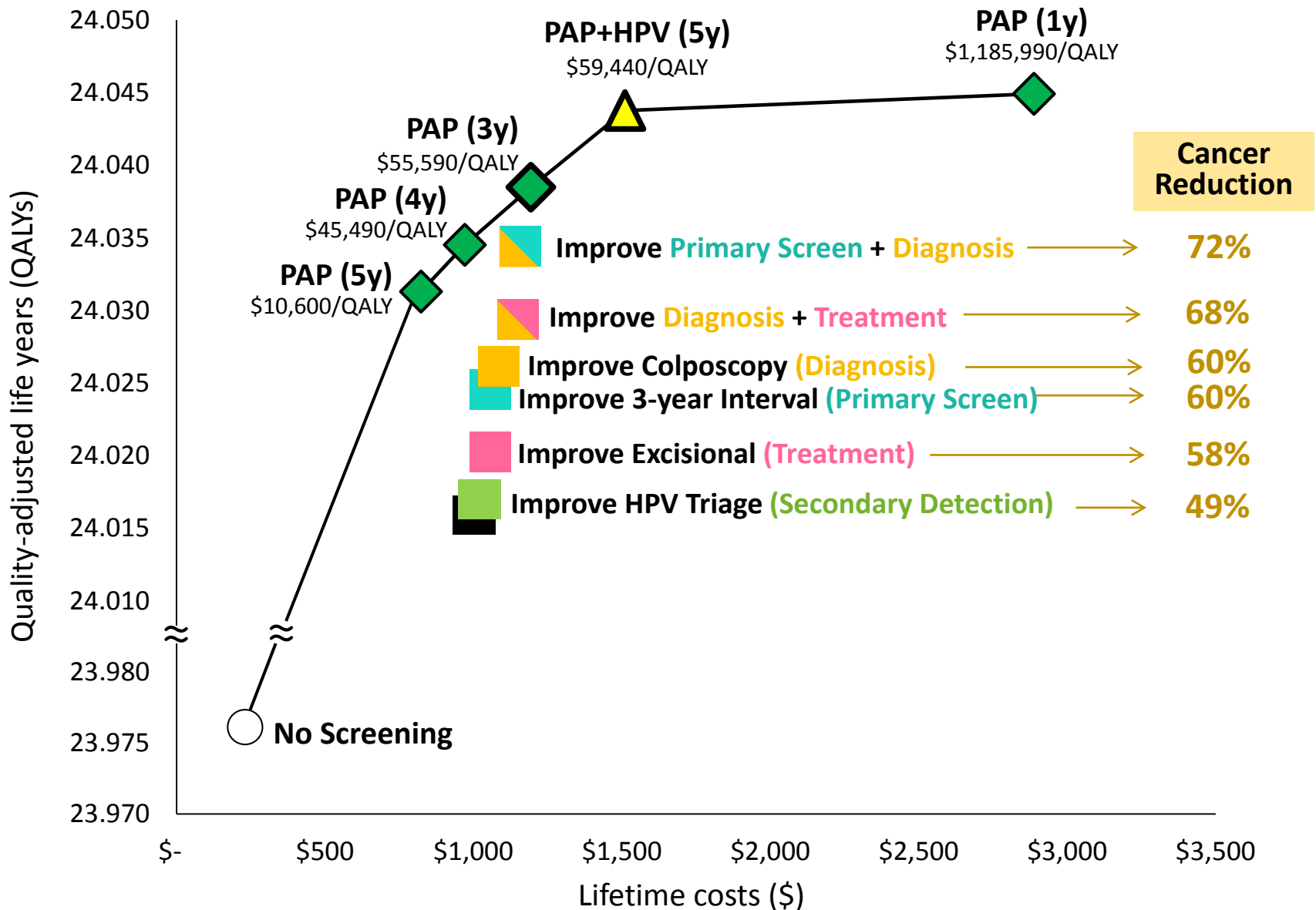
**Improve  
Diagnosis**

Ensure follow-up  
with colposcopy/  
biopsy referral

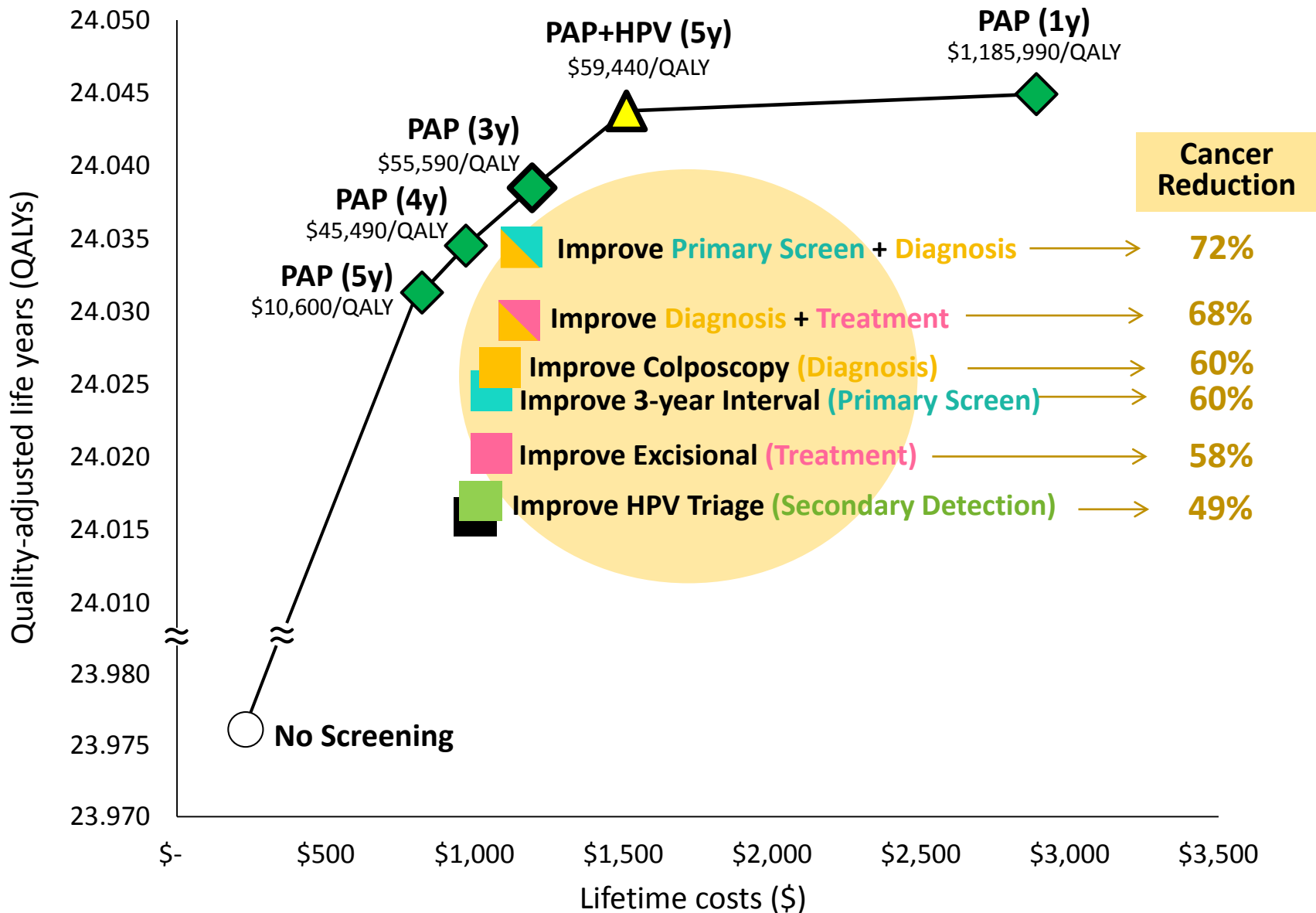
**Improve  
Treatment**

Ensure follow-up  
with excisional  
treatment referral

# US Cervical Cancer Screening



# US Cervical Cancer Screening



What **could** it cost to accomplish these improvements?

# ICER

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- Incremental cost-effectiveness ratio (ICER)

$$\mathbf{ICER} = \frac{\text{Incremental Cost}}{\text{Incremental Benefit}} = \frac{\Delta\text{Cost}}{\Delta\text{Benefit}}$$

# ICER and INMB

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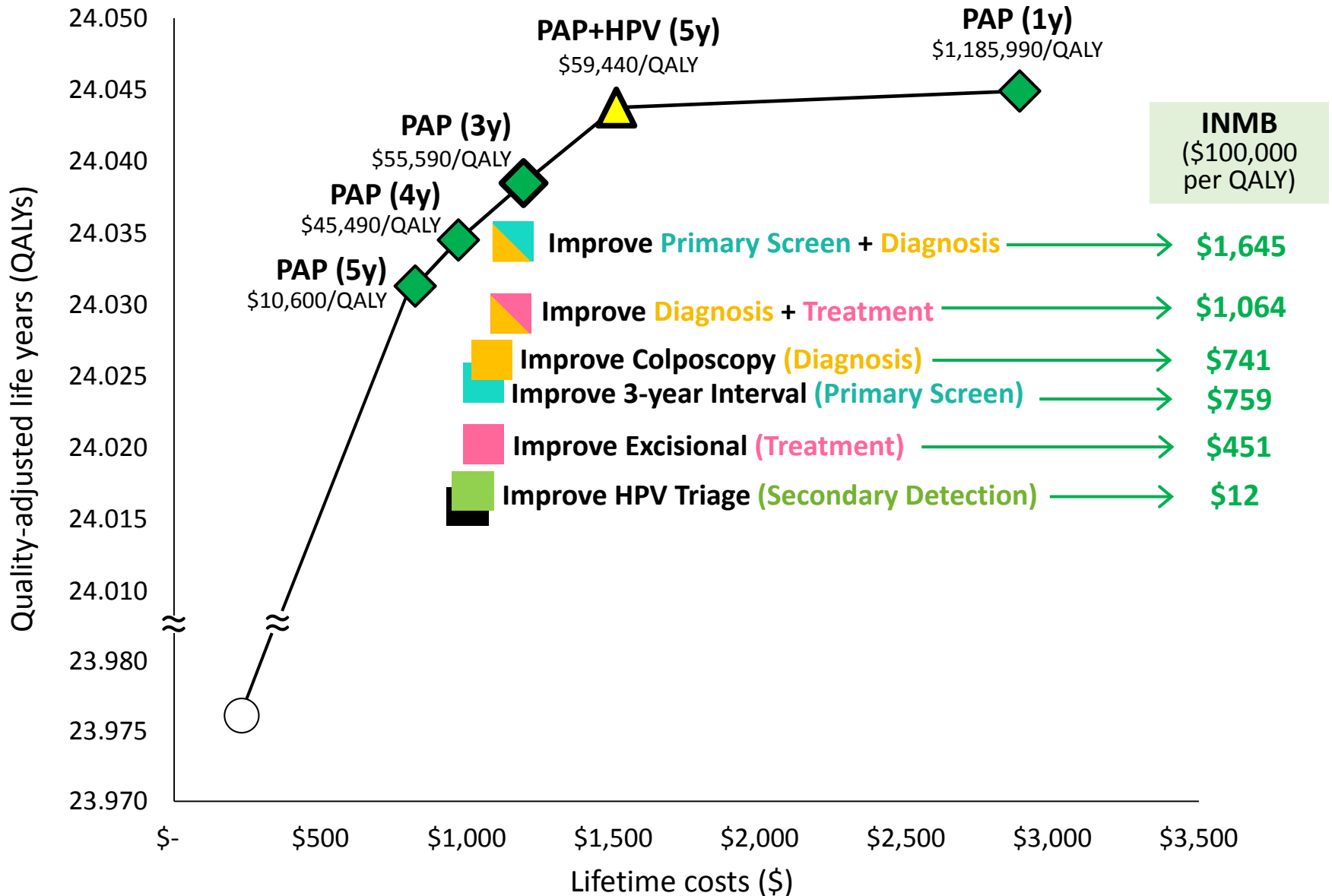
- Incremental cost-effectiveness ratio (ICER)

$$\mathbf{ICER} = \frac{\text{Incremental Cost}}{\text{Incremental Benefit}} = \frac{\Delta\text{Cost}}{\Delta\text{Benefit}}$$

- Incremental net monetary benefit (INMB)

$$\mathbf{INMB} = \underbrace{\Delta\text{Benefit} \times \text{WTP}}_{\text{“expected cost”}} - \underbrace{\Delta\text{Cost}}_{\text{“actual cost”}}$$

# US Cervical Cancer Screening

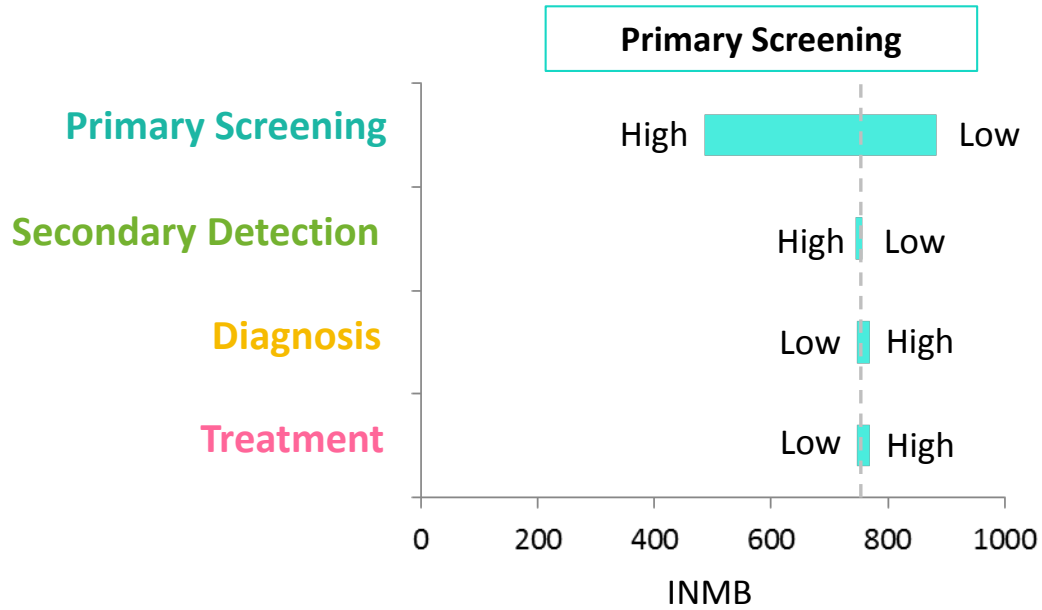




# Sensitivity Analyses

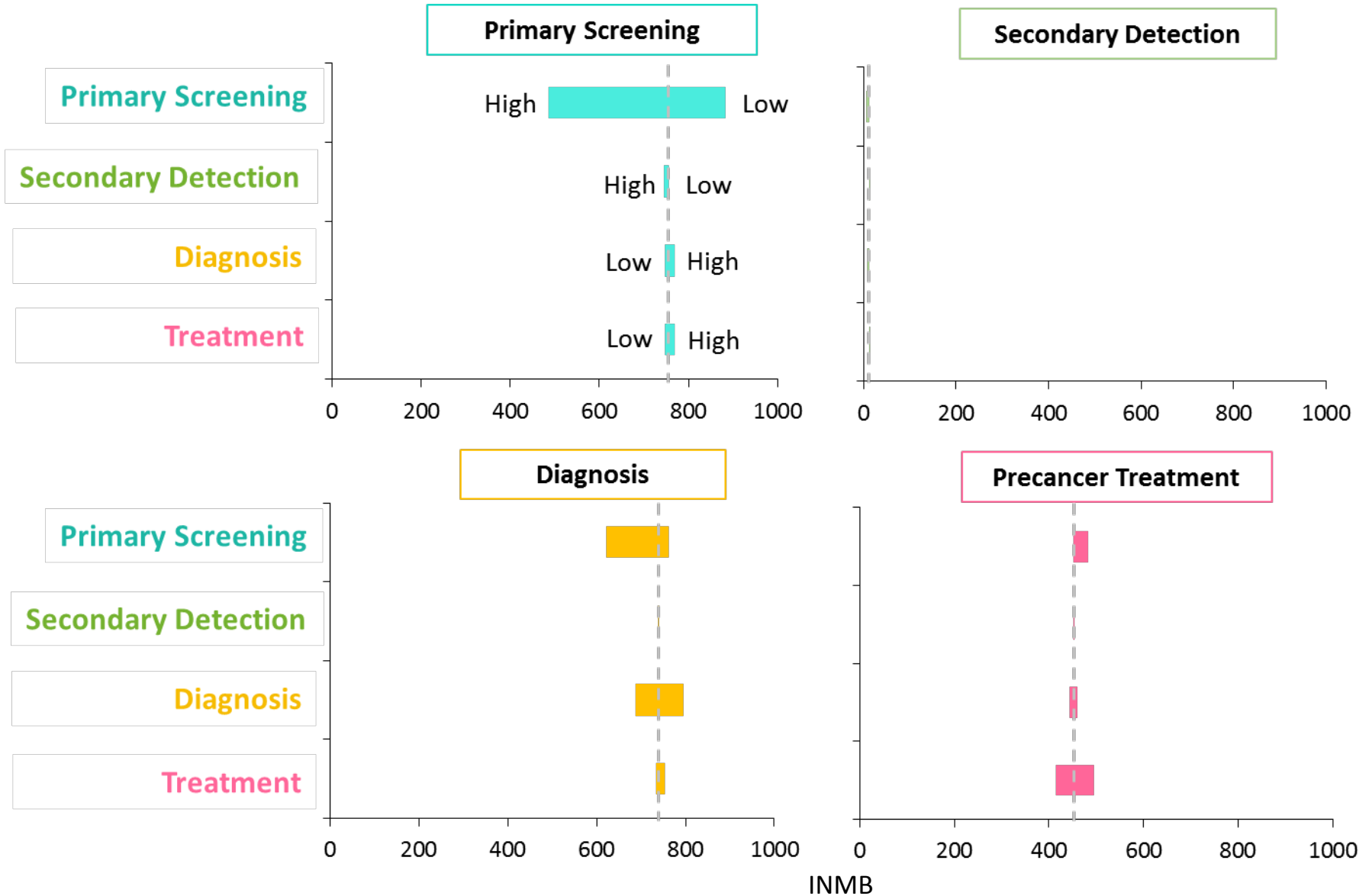
Impact of Uncertainty on INMB (WTP, \$100,000 per QALY)

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# Sensitivity Analyses

Impact of Uncertainty on INMB (WTP, \$100,000 per QALY)



# Insights and Impact

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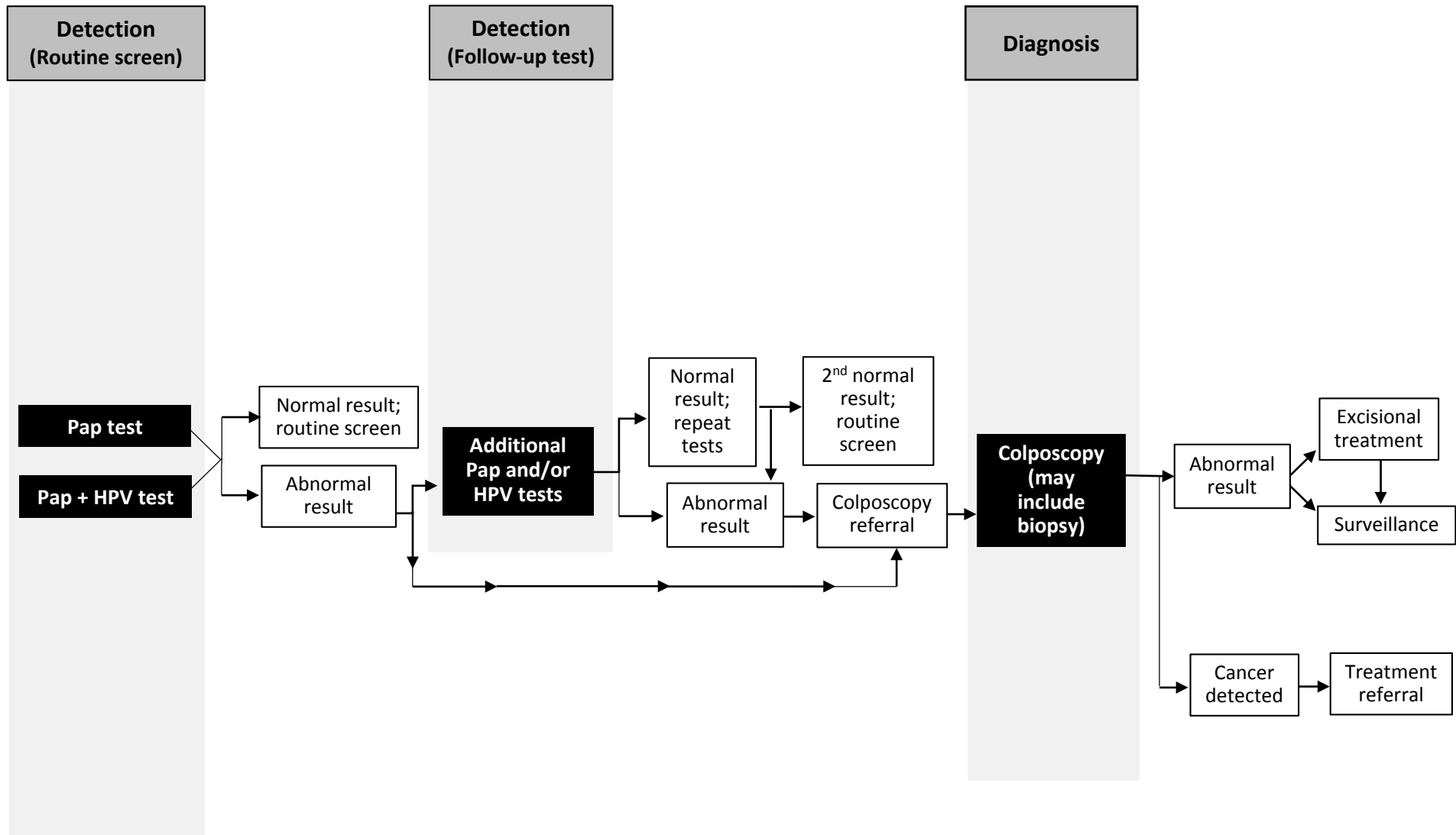
- **Insights**

- Inefficiency and opportunities for improvement
- Investment towards improvement can be high

- **Impact**

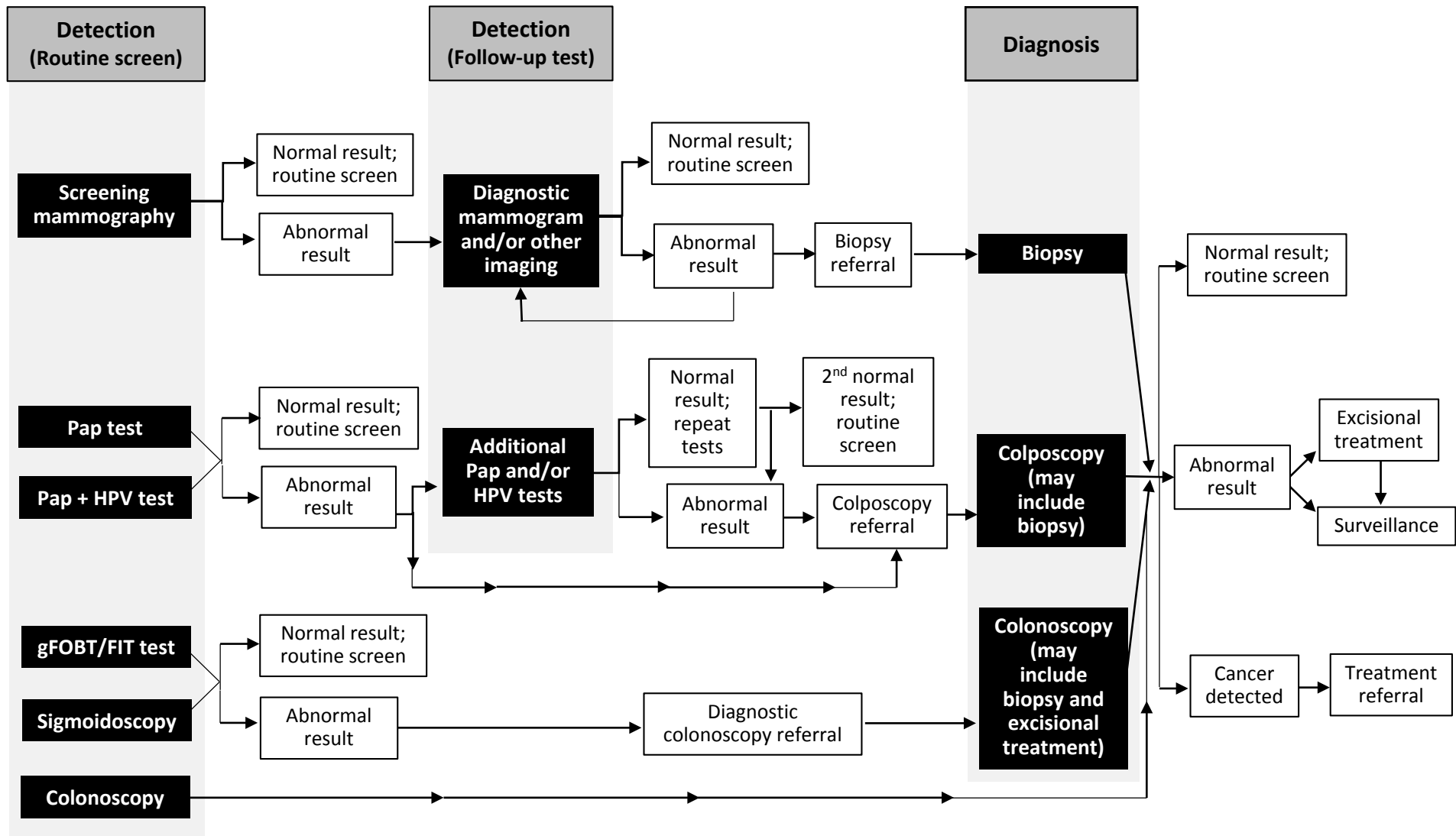
- Emphasis on health care delivery
- New data collection efforts
- New model-based analyses for other cancers

# Cervical Screening Process Model\*



\* Beaber et al (JNCI 2015)

# Broad Screening Process Model



\* Beaber et al (JNCI 2015)

# Related Work

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- US
  - Cancer Intervention and Surveillance Modeling Network (CISNET) Cervical working group
  - US Preventive Services Task Force (USPSTF) cervical cancer screening guidelines
- Global
  - Investment in new technologies and scale-up in LMIC (Bill and Melinda Gates Foundation)
  - National adoption and scale-up of see-and-treat screening (Ministries of Health)
  - 1-dose HPV vaccine trial (National Cancer Institute)

# Acknowledgments

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- Research team

- Emily Burger, Nicole Campos, Jamie Cohen, Fangli Geng, Cassie Regan, Steven Sweet, Stephen Sy

- Funding sources

- National Cancer Institute (R01, U54, U01)