



# Incorporating Calibrated Model Parameters Into Sensitivity Analyses: Deterministic And Probabilistic Approaches

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# Acknowledgments

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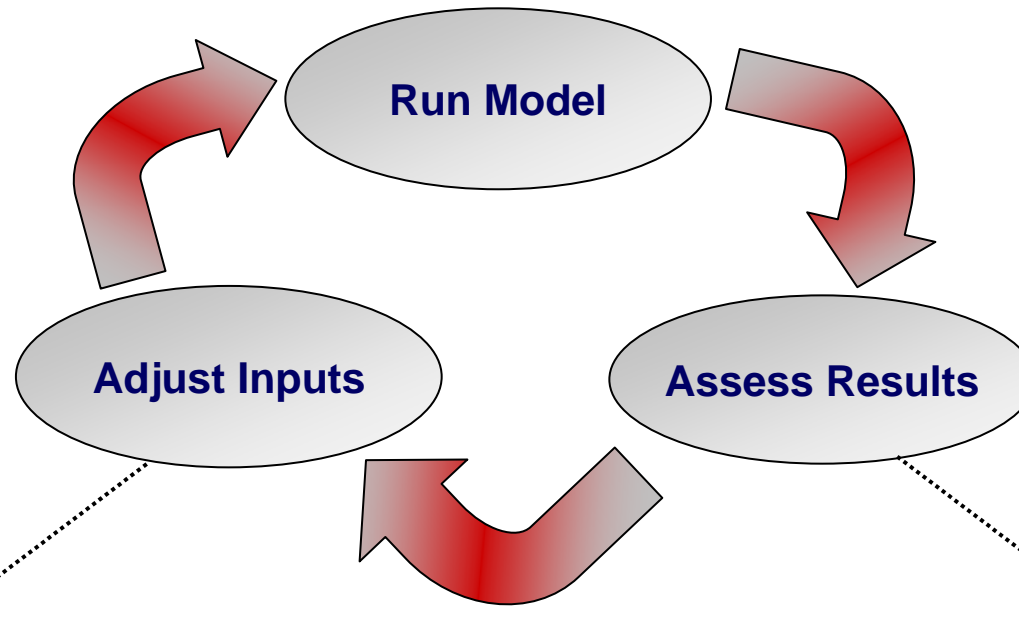
- GlaxoSmithKline provided funding for this research

# Introduction to Model Calibration

# What is Calibration?

- Process of empirically deriving model parameters such that the model outputs match target epidemiological data
- Usually performed when there are no data available to inform the model

# Calibration Cycle



## Model Calibration Approaches

Manual

Random

Nelder-Mead

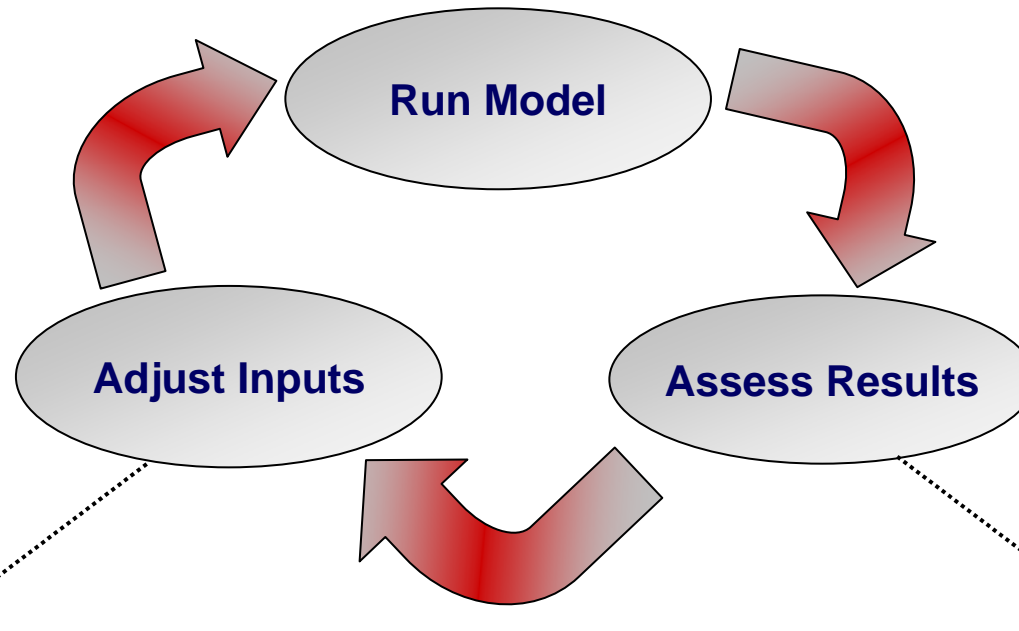
## Objective Function

Windows

Log Likelihood

Mean Percentage Deviation

# Calibration Cycle



## Model Calibration Approaches

Manual

Random

**Nelder-Mead**

## Objective Function

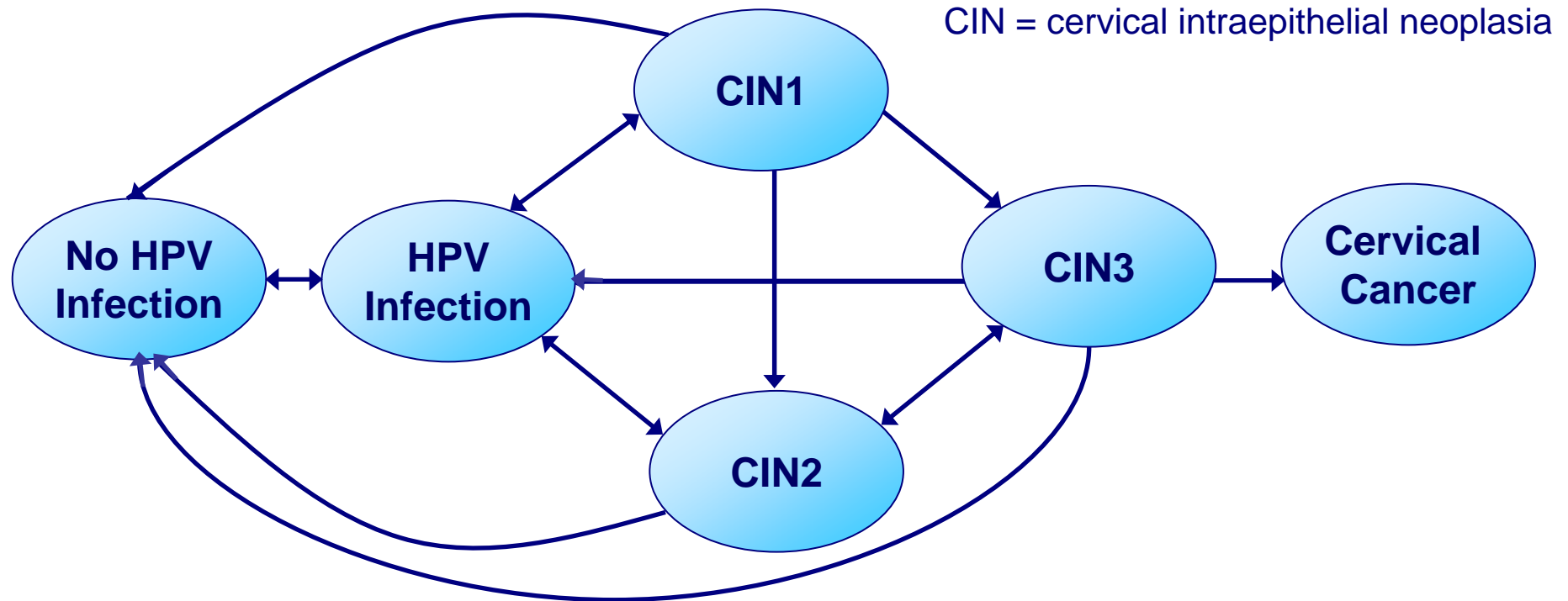
Windows

Log Likelihood

**Mean Percentage Deviation**

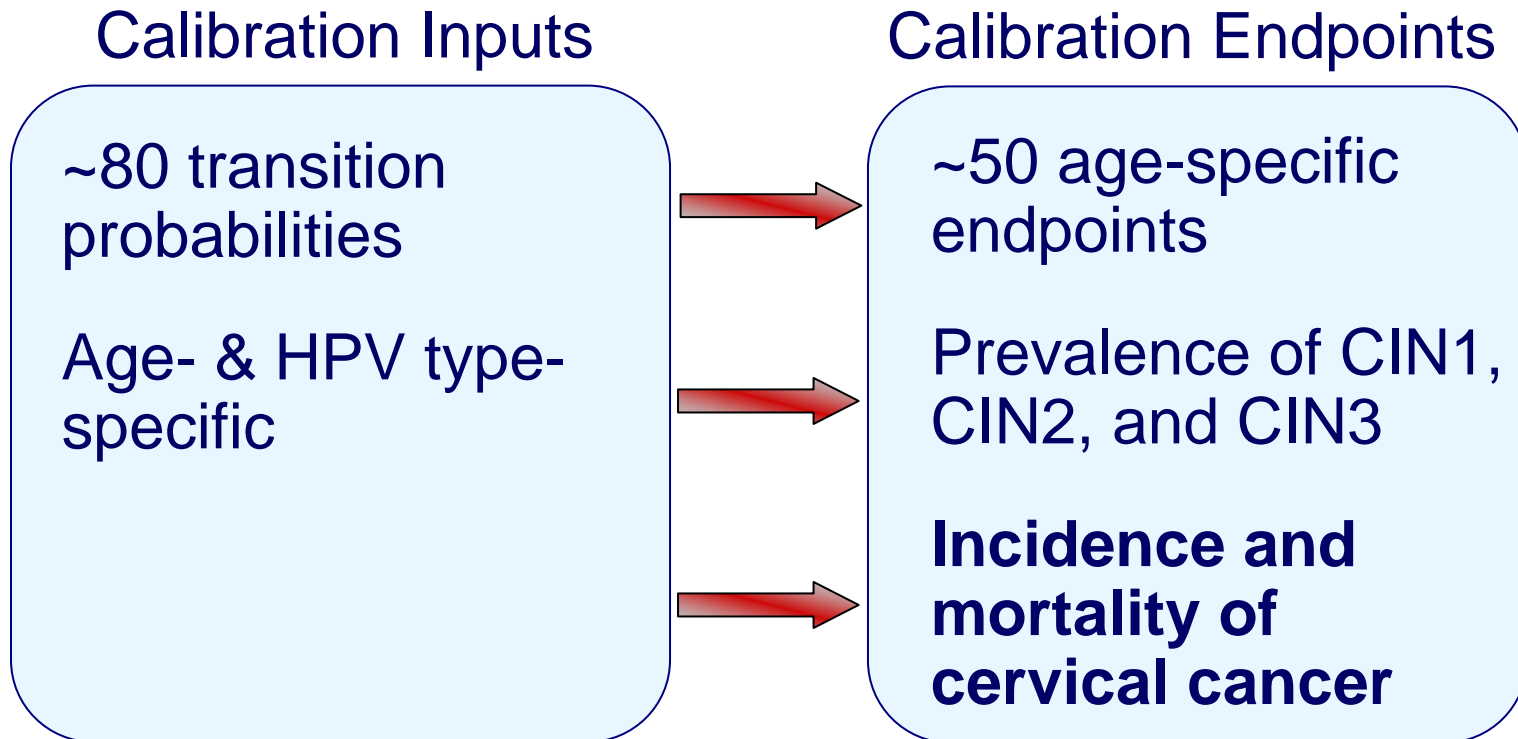
# Calibration of a Model of a Cervical Cancer Vaccine

# Model Structure



- Lifetime Markov model: simulates transitions between health states
- Health states are stratified by HPV type
- Transition probabilities are dependent on age and HPV type
- Mortality can occur throughout the model

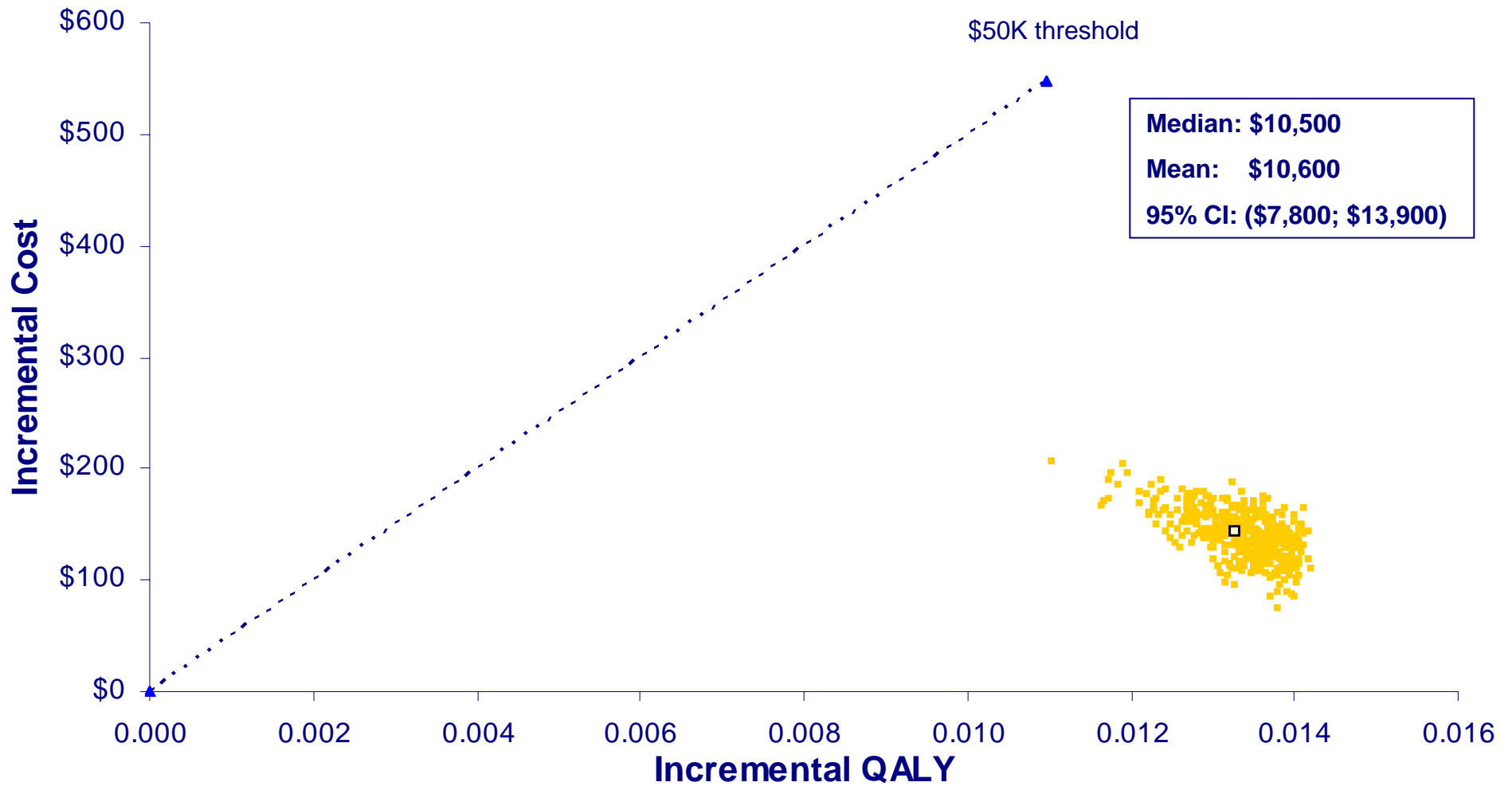
# Calibration Overview



- Calibration was performed using observed endpoints in a population without vaccination

# Calibration Sensitivity Analyses (CSA)

# Why CSA Was Needed



# Why CSA Was Needed

- Sources of uncertainty
  - Algorithm
    - Person in a manual calibration
    - Starting seed/search space in a random calibration
    - Starting simplex in Nelder-Mead calibration
  - Objective function
    - Is really quite subjective
    - Choices include:
      - Calibration targets
      - Weighting scheme
  - Stopping point

- Evaluated algorithm uncertainty by choosing 5 different starting simplexes
- Evaluated objective function uncertainty by choosing 5 different objective functions
  - Percentage deviations weighted 1,3,3 and 1,6,3 for CIN & CC incidence and mortality, respectively
  - Squared percentage deviations with above weights
  - Maximum likelihood
- Combined simplexes and weights for a total of 25 different calibrations

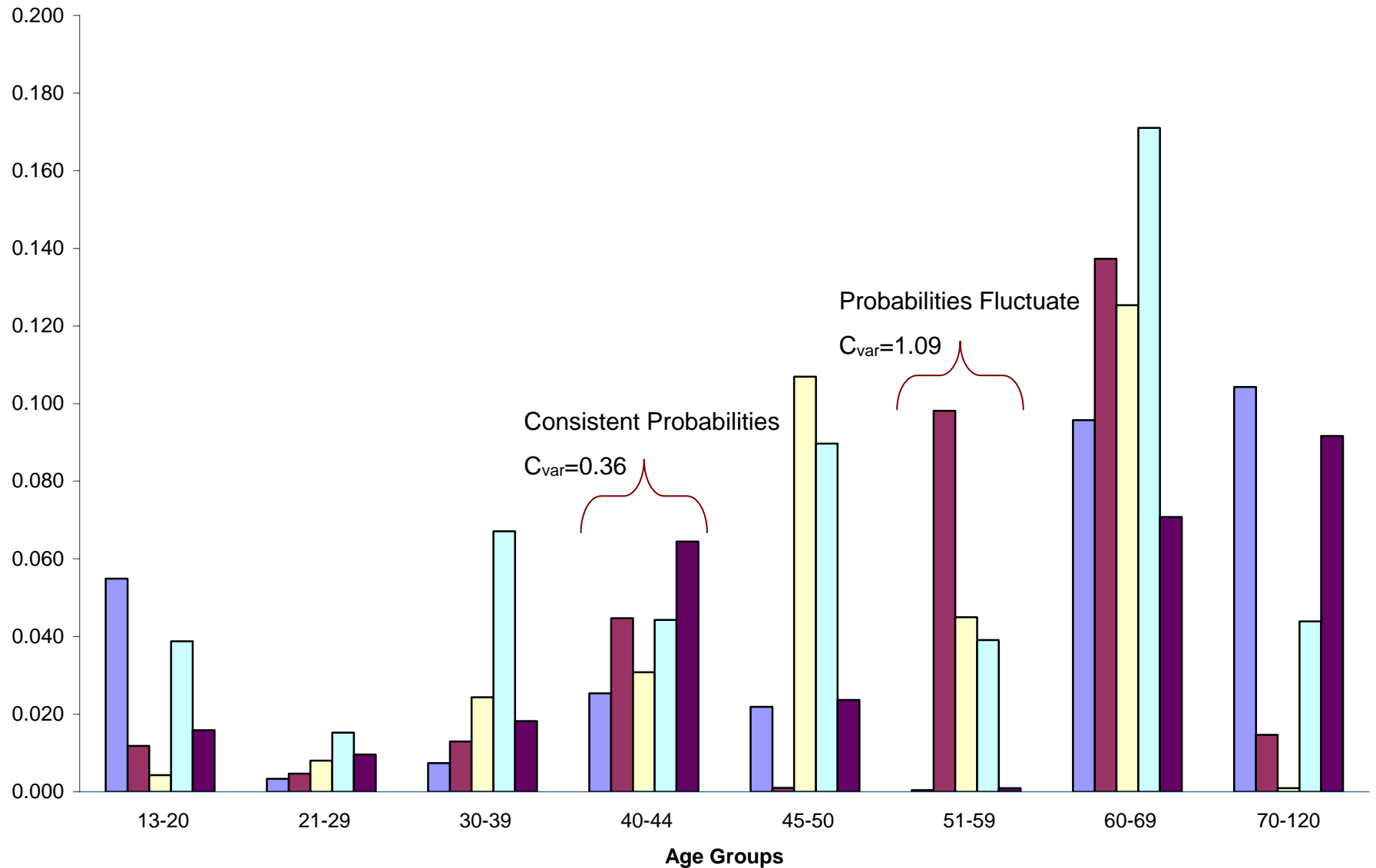
## CSA Methods (continued)

- Deterministic sensitivity analysis was performed by examining cost-effectiveness results for each calibration while holding all other parameters constant
- Probabilistic sensitivity analysis was performed by bootstrapping (with equal probability) the 25 calibrations within a 2<sup>nd</sup> order Monte Carlo simulation for other model parameters

# CSA Results



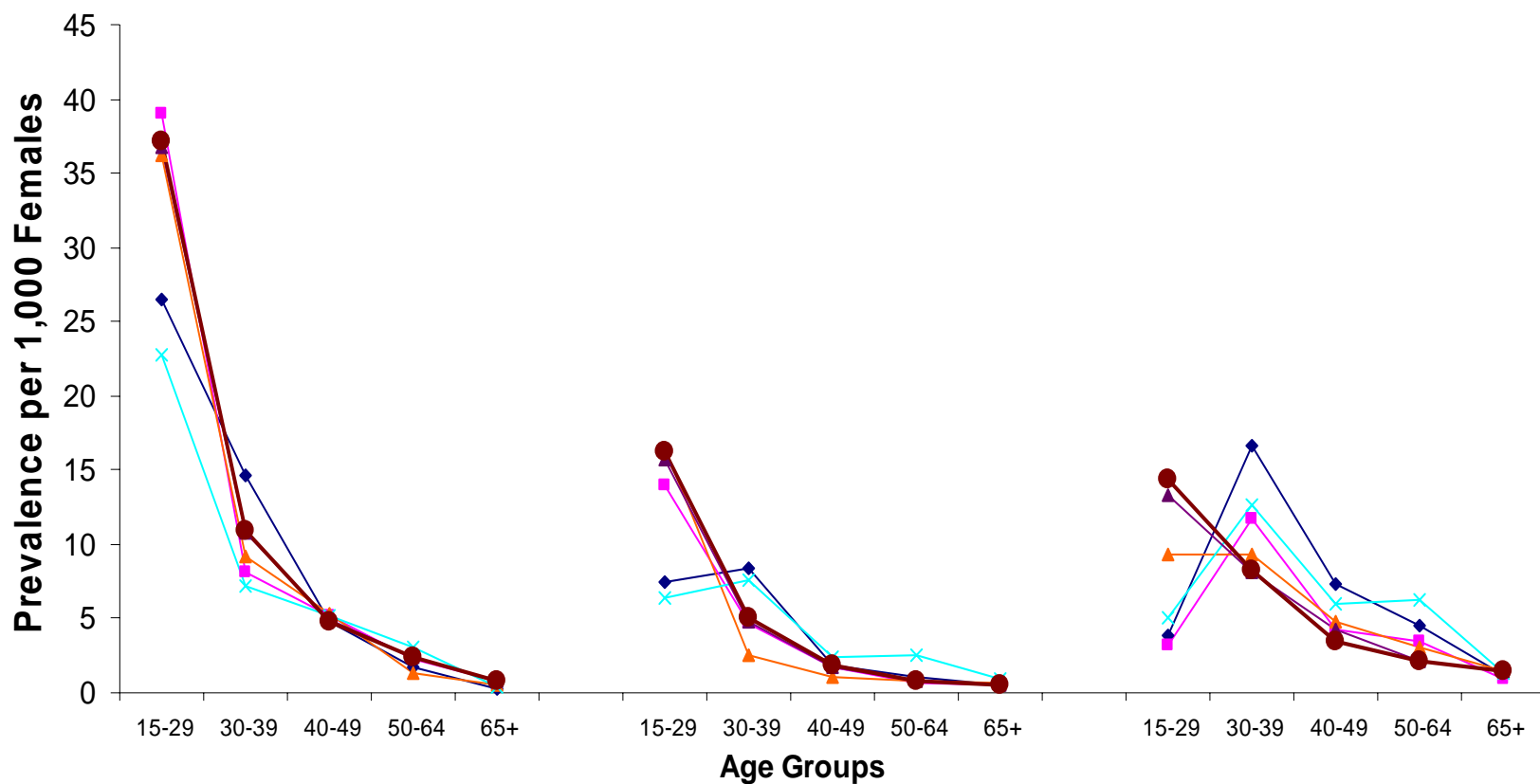
# Comparison of Transition Probabilities\* Weighting scheme 163



\*For CIN3 to CANCER

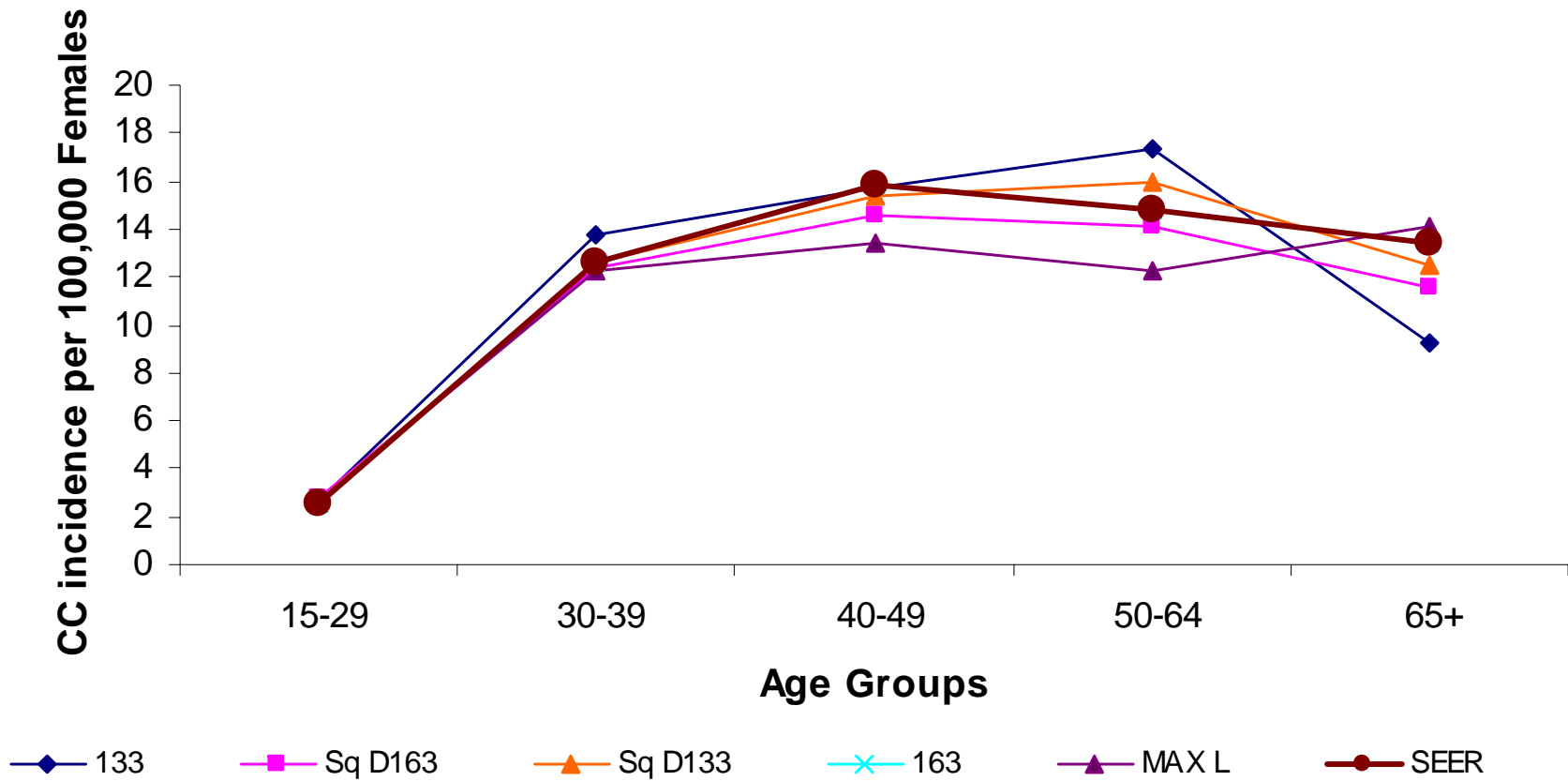
■ Simplex 1 ■ Simplex 2 ■ Simplex 3 ■ Simplex 4 ■ Simplex 5

# Calibration Fit: Prevalence of CIN1, 2, & 3 by Age Simplex 1

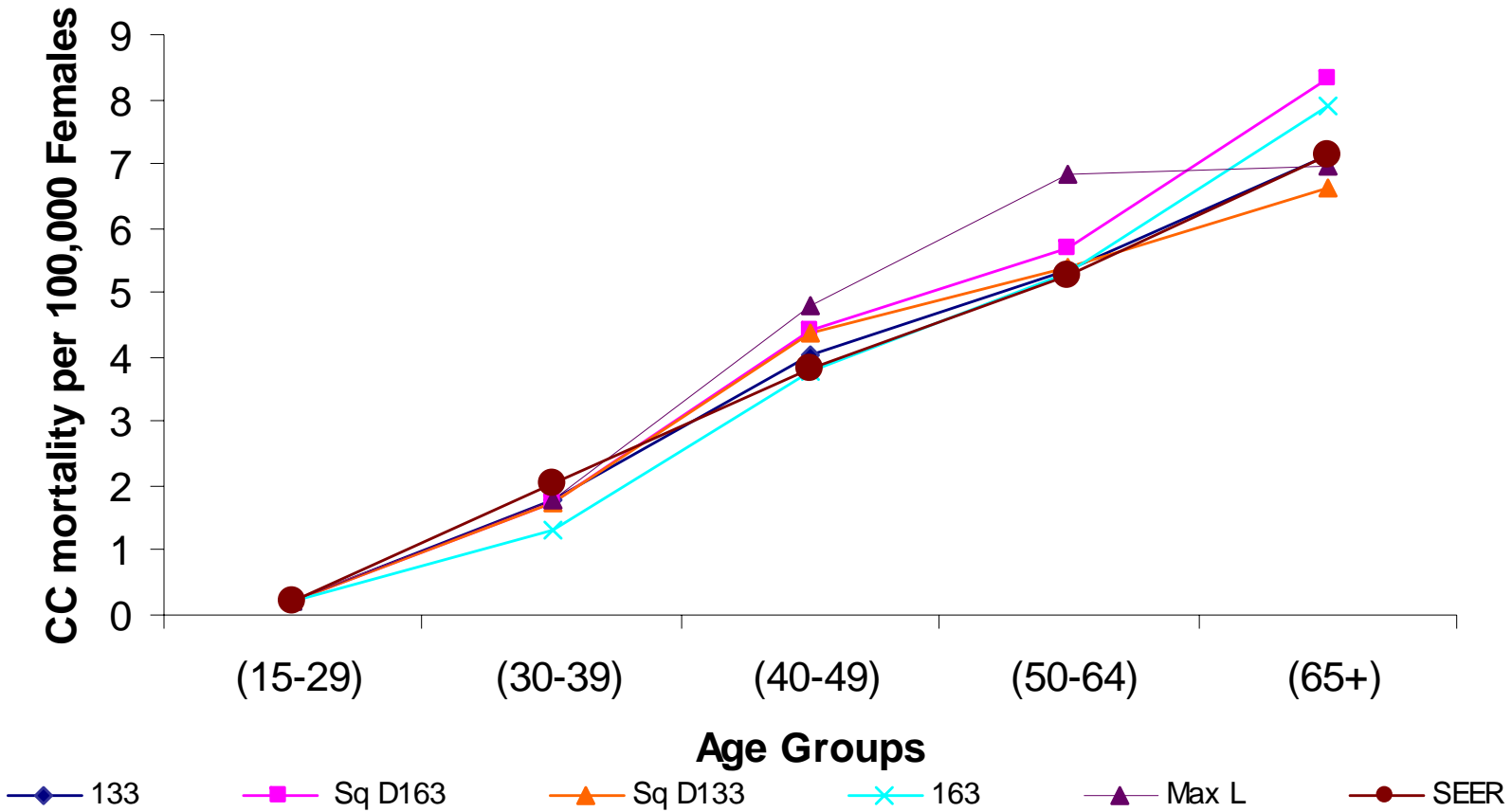


◆ 133    ■ sq D163    ▲ sq D133    × 163    ▲ MaxL    ● Target

# Calibration Fit: Cervical Cancer Incidence by Age Simplex 1



# Calibration fit: Cervical Cancer Mortality by Age Simplex 1



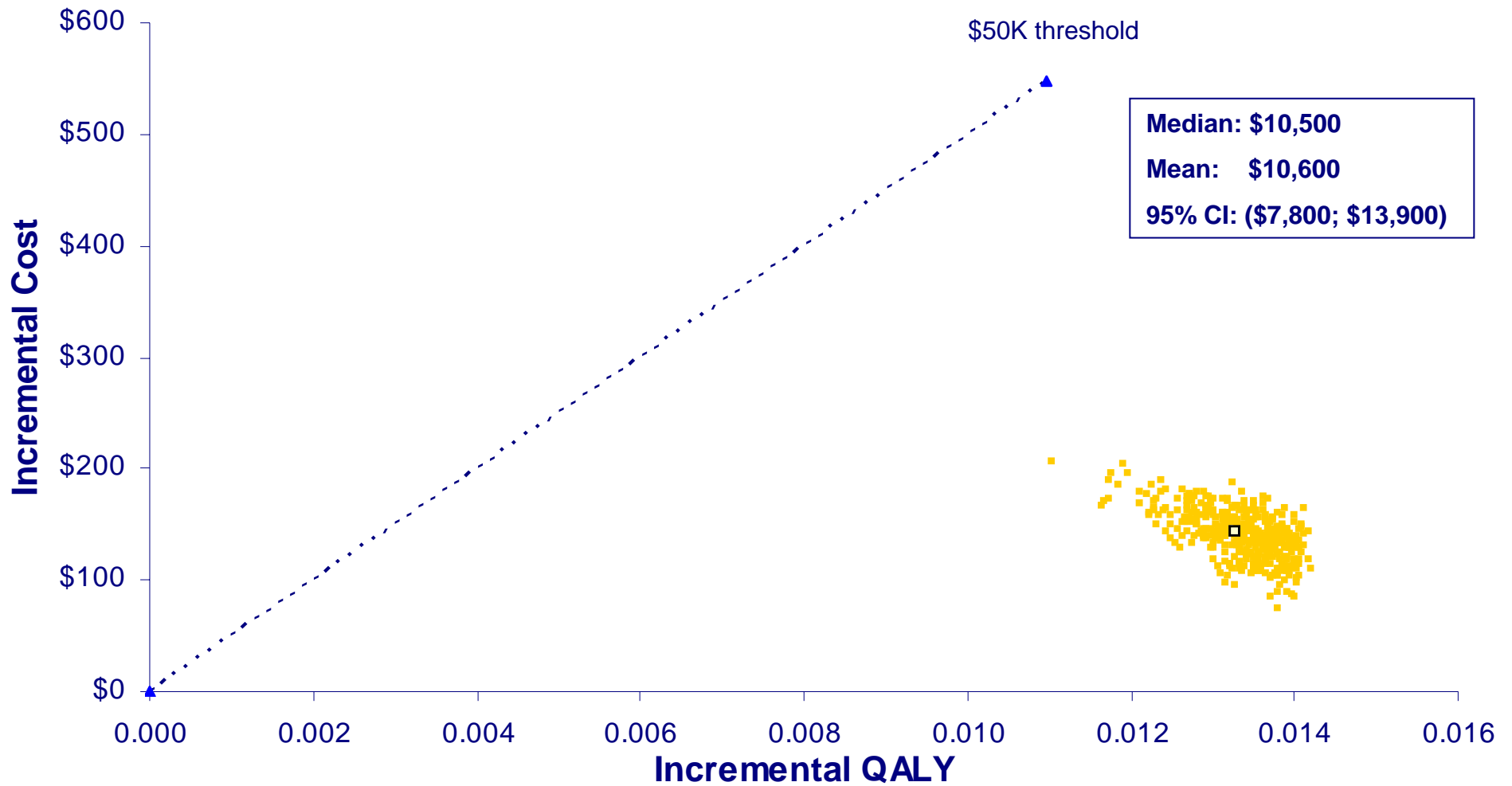
# CSA Deterministic Results

- ICER\* by simplex and weighting scheme

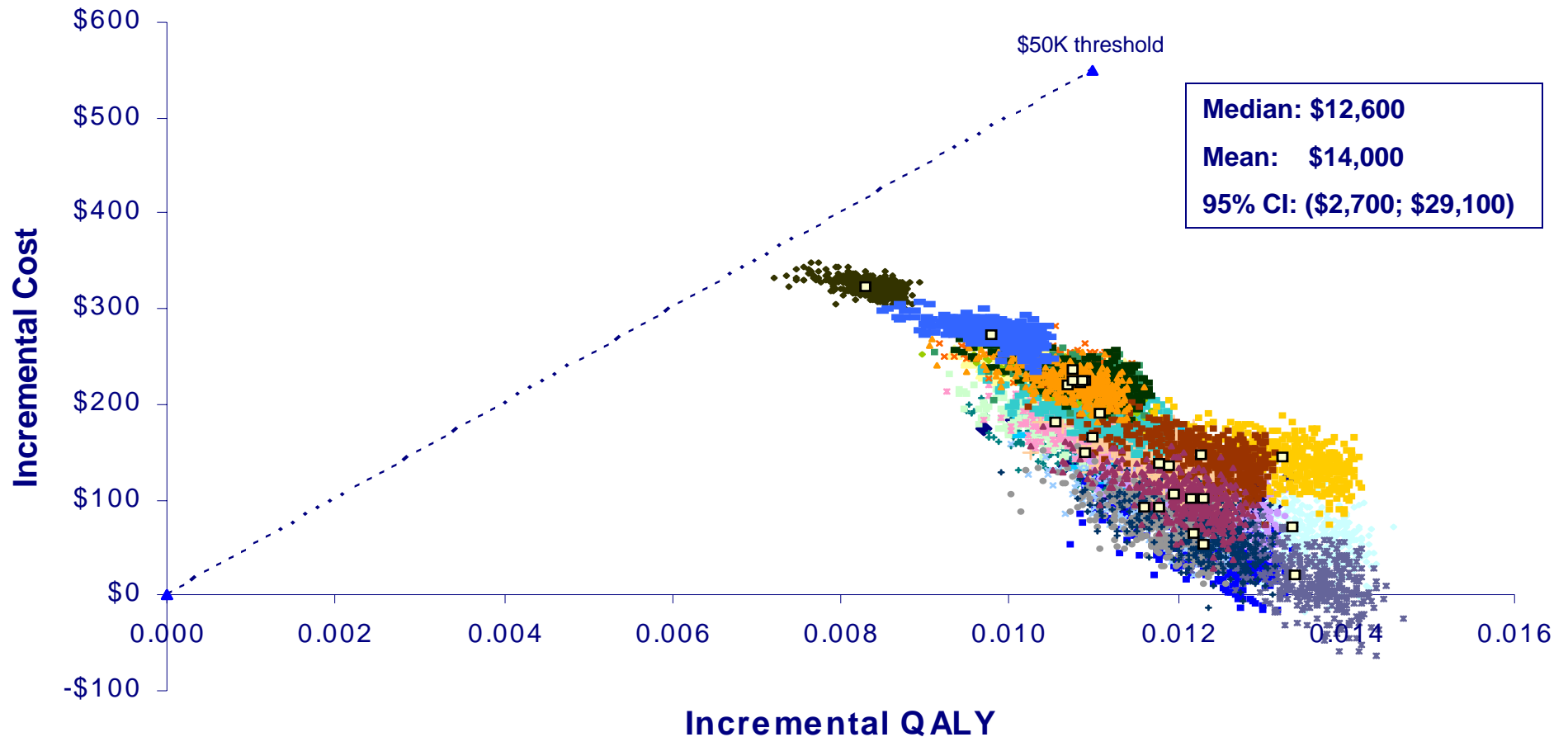
	133	163	Max L	SqD 133	SqD 163
Simplex 1	\$8,400	\$13,800	\$4,400	\$11,600	\$5,300
Simplex 2	\$17,100	\$20,800	\$7,800	\$15,100	\$8,100
Simplex 3	\$20,500	\$11,500	\$27,800	\$17,300	\$10,900
Simplex 4	\$20,700	\$22,000	\$1,500	\$8,000	\$5,400
Simplex 5	\$20,700	\$21,000	\$39,100	\$12,100	\$8,900

- Median ICER: \$12,600
- Mean ICER: \$14,000
- Range: \$1,500 - \$39,000

# PSA for a Single Calibration



# CSA Probabilistic SA Results



Vaccination of age cohorts are compared with no vaccination among same age cohorts.  
Each square represents a calibration and each color represents the PSA around those calibrations.

- Number of calibration iterations was limited due to the length of time it took to run the model
- With more time, the Nelder-Mead runs with the different starting simplexes may converge and therefore lead to less variability in the results
- Continuing investigation suggests existence of locally optimal solutions

- Time is always a limiting factor – with more time a “better” solution can almost always be found
- Calibration can affect the interpretation of cost-effectiveness results
- In order to characterize the uncertainty in a calibrated model:
  - Results should be reported as a range from different calibrations
  - Calibration should be included in probabilistic sensitivity analyses



**Questions?**

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