UNIVERSITY OF TWENTE.

# METAMODELING TO EVALUATE (ALL) SCREENING STRATEGIES

*An illustration in colorectal cancer screening*

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# Conflict of interest statement

No conflicts of interest to declare.

This study was not funded.

# BACKGROUND

## HEALTH ECONOMIC MODELS FOR EVALUATING TEST/SCREENING STRATEGIES

- Models to estimate impact of testing become more complex
  - Reflect increasingly complex (clinical) pathways
  - Reflect a wide range of testing aspects and (indirect) consequences[1]
- Optimization of testing strategies is of increasing interest
  - For tests: timing, threshold values, combinations,…
  - For screening: start/stop age, interval, subgroup-specific thresholds

1. **Kip MMA et al**. *Towards alignment in the reporting of economic evaluations of diagnostic tests and biomarkers: The AGREEDT checklist*. MDM. 2018 38(7) 778-788.

# BACKGROUND

## HEALTH ECONOMIC MODELS FOR EVALUATING TEST/SCREENING STRATEGIES

- Evaluating 100s, 1000s or more testing strategies to identify the best one is not always computationally feasible

*Metamodeling is* one *way to reduce the computational burden of simulation based analyses in healthcare*

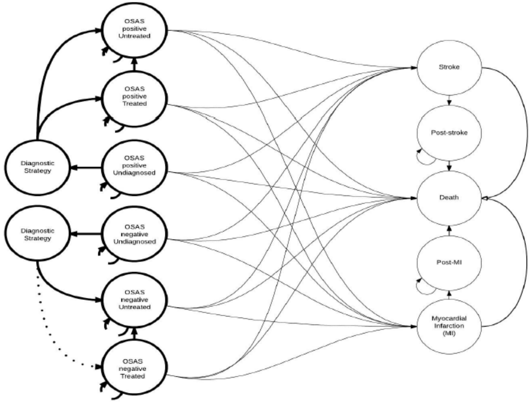
# WHAT IS METAMODELING

*A MODEL OF A MODEL*

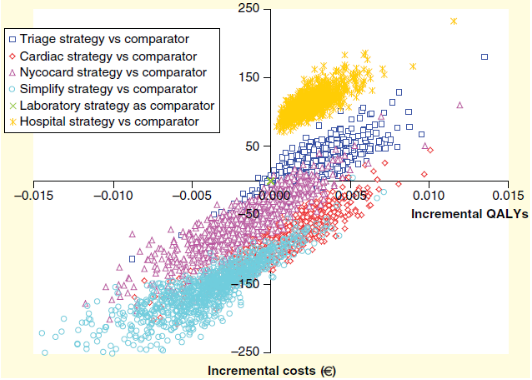
## Input parameters (X)

| *Parameters* | *Base Case Value* | *Standard Deviation* | *Distribution* | *Source* |
|---|---|---|---|---|
| *Cohort characteristics* | | | | |
| *Sex* | Male | | | |
| *Age* | 50 | | | |
| *OSAS prevalence (AHI≥15)* | 43% | 0.06 | Beta distribution | DiagnOSAS pilot* |
| *Test characteristics* | | | | |
| *Sensitivity PSG* | 1 | Fixed | | Gold Standard |
| *Specificity PSG* | 1 | Fixed | | Gold Standard |
| *Sensitivity DiagnOSAS* | 0.97 | 0.03 | Beta distribution | DiagnOSAS pilot* |
| *Specificity DiagnOSAS* | 0.47 | 0.07 | Beta distribution | DiagnOSAS pilot* |
| *Average time to diagnosis* | 5.35 (yr) | Fixed | | [6] |
| *Scenario time to diagnosis* | 2.68 (yr) | Fixed** | | [6] |
| *Probabilities* | | | | |
| *Car accident* | 0.0461 | 0.00006 | Beta distribution | [19,20] |
| *Probability car accident is fatal* | 0.00035 | 0.00003 | Beta distribution | [19,28] |
| *Stroke (per 1000 person-yrs)* | 1.30 | 0.08 | Normal distribution | [21] |
| *MI (per 1000 person-yrs)* | 2.66 | 0.02 | Normal distribution | [22] |
| *Adjusted all-cause mortality (age- & gender-specific)* | 0.000574 | Fixed | | [15-18] |
| *CPAP non-adherence (annual)* | 0.023 | 0.003 | Normal Distribution | [27] |
| *OSAS related Risks* | | | | |
| Untreated OSAS | *Compared to healthy individuals* | | | |
| *Car accident (Relative Risk)* | 2.43 | 0.36 | Log.Norm Distribution | [14] |
| *Stroke (Hazard Ratio)* | 3.48 | 0.03 | Log.Norm Distribution | [23] |
| *MI (Hazard Ratio)* | 3.06 | 0.08 | Log.Norm Distribution | [23] |
| CPAP-treated OSAS | *Compared to healthy individuals* | | | |
| *Car accident (Risk Ratio)* | 1.29 | 0.43 | Log.Norm Distribution | [26] |
| | *Compared to untreated OSAS* | | | |
| *MI (Relative Risk)* | 0.54 | 0.17 | Log.Norm Distribution | [24] |
| *Stroke (Relative Risk)* | 0.27 | 0.10 | Log.Norm Distribution | [25] |
| Stroke | | | | |
| *1-year case fatality (Probability)* | 0.21 | 0.04 | Normal Distribution | [30] |
| *All-cause mortality (Hazard ratio)* | 3.9 | 0.10 | Log.Norm Distribution | [31] |
| MI | | | | |
| *1-year case fatality (Probability)* | 0.07 | 0.005 | Normal Distribution | [29] |
| *All-cause mortality (Hazard ratio)* | 1.47 | 0.16 | Log.Norm Distribution | [32] |

## Decision analytic model (simulator)



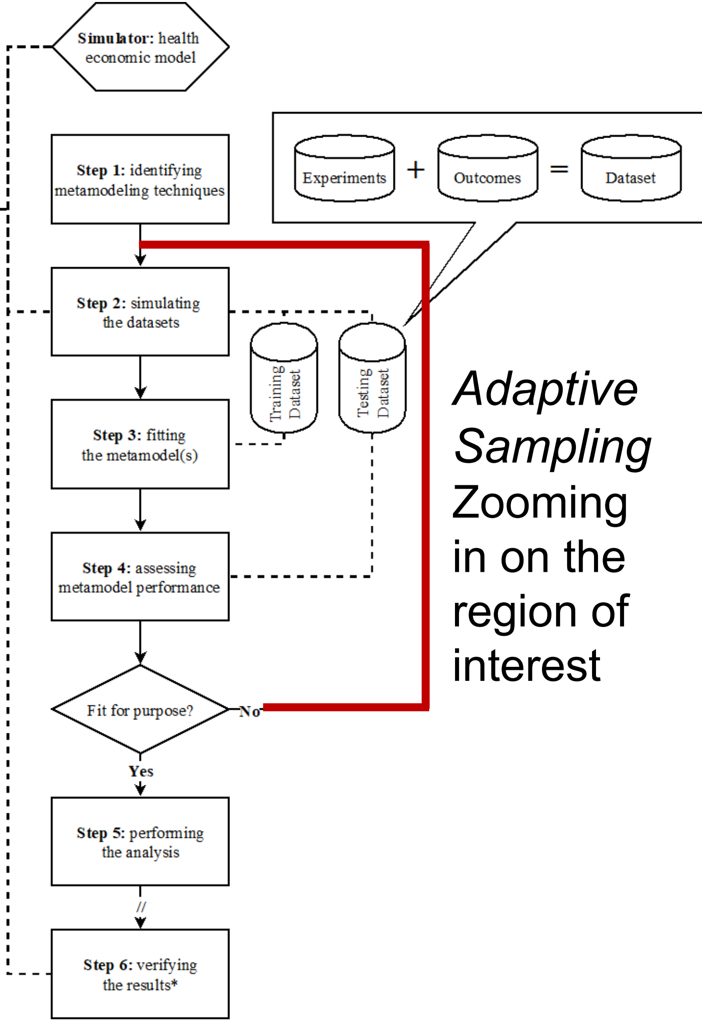

## Output estimates (Y)




**Metamodel**
***F*(X) = Y**

# METAMODELING PROCESS[1]

- Starting point: validated model
- Metamodeling techniques[2]
- Training and testing datasets
- Fitting metamodels
- Metamodel validation
- Update technique/data/specification
- Use the metamodel
- Verify the results




*Adaptive Sampling*
Zooming in on the region of interest

* Optional, depending on the analysis performed in Step 5.

1. **Degeling et al**. (2020) Introduction to Metamodeling for Reducing Computational Burden of Advanced Analyses with Health Economic Models: A Structured Overview of Metamodeling Methods in a 6-Step Application Process. Med Decis Making.
2. **Carvalho et al**. (2021) Choosing a Metamodel of a Simulation Model for Uncertainty Quantification. Med Decis Making.

# QUESTION FOR YOU…

## ON METAMODELING PERFORMANCE

**Why can we expect prediction accuracy to be better for metamodels than for regression models fitted on real-world data?**

**Type your suggestion in the chat**

*Prediction based on simulated outcomes:*

- Has no missing input or outcomes, or censored data
- Has no measurement error
- Can make use of large sample sizes
- Has independent X's (may be correlated) and independent Y's, with a causal relationship between X and Y induced by the simulator

# APPLICATION OF METAMODELING

## OPTIMIZING SCREENING FOR COLORECTAL CANCER (CRC)

- Primary screening program for CRC in the Netherlands
- Referral based on fecal immunochemical test (FIT)
- Currently *available capacity* for colonoscopies after referral is ~550 colonoscopies per 1,000 individuals *lifelong*
- The validated ASCCA model[1] was developed to evaluate screening strategies in terms of life years gained (LYG) and costs, compared to no screening
  - Model programmed in C++, runtime still approx. 15 min/strategy due to internal calibration to Dutch observational data, *without PA*...

1. **Greuter MJ et al**. Modeling the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA). Risk Anal. 2014 May;34(5):889-910.

# APPLICATION OF METAMODELING

## SCREENING STRATEGIES

- Basic relevant screening characteristics (parameters)
  - Starting age (years, 30-90)
  - Screening interval (years, 1-60)
  - Number of screening rounds (1-30)
  - FIT cutoff (ng/mL) (discrete: 50, 75, 100, 150)
- Number of strategies > 450,000
  - Max screening age = 90 yrs leads to **40,864** *plausible strategies*
  - Evaluation of all plausible strategies with ASCCA model unfeasible

# APPLICATION OF METAMODELING

## COMPARISON OF TWO APPROACHES

### Approach 1

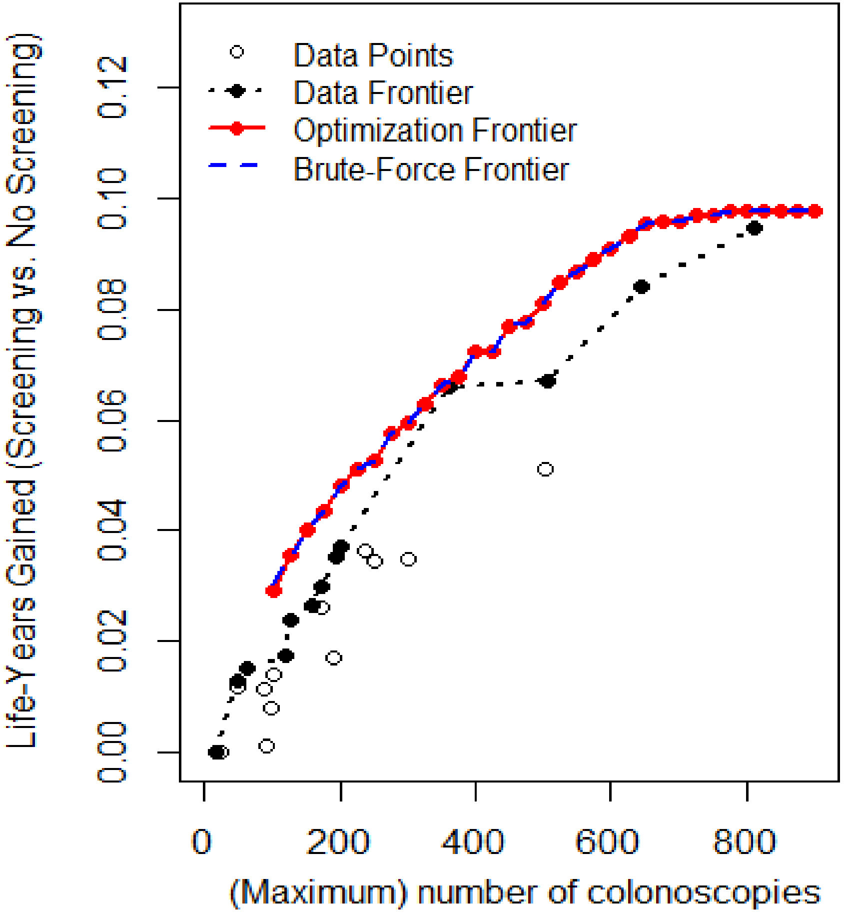
- Run the original ASCCA model for a *fixed number of strategies* and pick the best strategy (in terms of LYG)
- While varying the number of strategies (25-150)

### Approach 2

- Use these ***exact same*** strategies to fit a *Gaussian Process* metamodel (3 separate models: for #colonoscopies, LYG, costs)
- Use the metamodel to identify the best strategy (using optimization or brute force analysis)

# RESULTS: OPTIMIZATION FRONTIER FOR *LYG*

## BASED ON 25 STRATEGIES



# RESULTS: BEST STRATEGIES IDENTIFIED

## BRUTE FORCE ANALYSIS

Table 3. Top 10 screening strategies in terms of LYG for a colonoscopy capacity of 550. [1]

| Screening strategy identified as optimal | | | | Predicted strategy outcomes* | | |
|---|---|---|---|---|---|---|
| Start age screening (years) | Screening interval (years) | Number of screening rounds | FIT cutoff‡ for referral (ng/mL) | Number of colonoscopies† | LYG | Incremental costs (€) |
| 33 | 2 | 21 | 150 | 546 | 0.0920 | -361 |
| 34 | 2 | 20 | 150 | 545 | 0.0919 | -348 |
| 36 | 2 | 19 | 150 | 548 | 0.0917 | -348 |
| 35 | 2 | 19 | 150 | 541 | 0.0916 | -361 |
| 33 | 2 | 20 | 150 | 537 | 0.0914 | -359 |
| 32 | 2 | 21 | 150 | 538 | 0.0912 | -343 |
| 34 | 2 | 19 | 150 | 533 | 0.0911 | -343 |
| 37 | 2 | 18 | 150 | 543 | 0.0911 | -361 |
| 36 | 2 | 18 | 150 | 536 | 0.0910 | -343 |
| 38 | 2 | 18 | 150 | 549 | 0.0909 | -347 |

## Current Dutch screening guideline

- Start age: 55, interval: 2 years, screening rounds: 11, FIT cutoff: 75 ng/ml

1. **Koffijberg et al**. (2021) Using Metamodeling to Identify the Optimal Strategy for Colorectal Cancer Screening. Value Health.

# INTERPRETATION AND CONCLUSION

- Metamodels can generate outcomes for parameter values that may be beyond the support of the original model (!)
- Optimizing colorectal cancer screening with a metamodel may improve health outcomes without requiring additional colonoscopy capacity

# TAKE HOME MESSAGES

- Metamodeling allows evaluation of all screening strategies
  - Iterative by nature, requires comprehensive validation of outcomes
  - Required for further tailoring (age/sex specific FIT cutoff values)
  - Feasible, widely applicable, but introduces additional complexity
- A metamodel inherits the original model's validity, limitations and plausibility
  - Start with a *validated model you understand*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# THANK YOU


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