Dose Selection by Covariate Assessment on the Optimal Dose for Efficacy

Application of Machine Learning in the Context of PKPD

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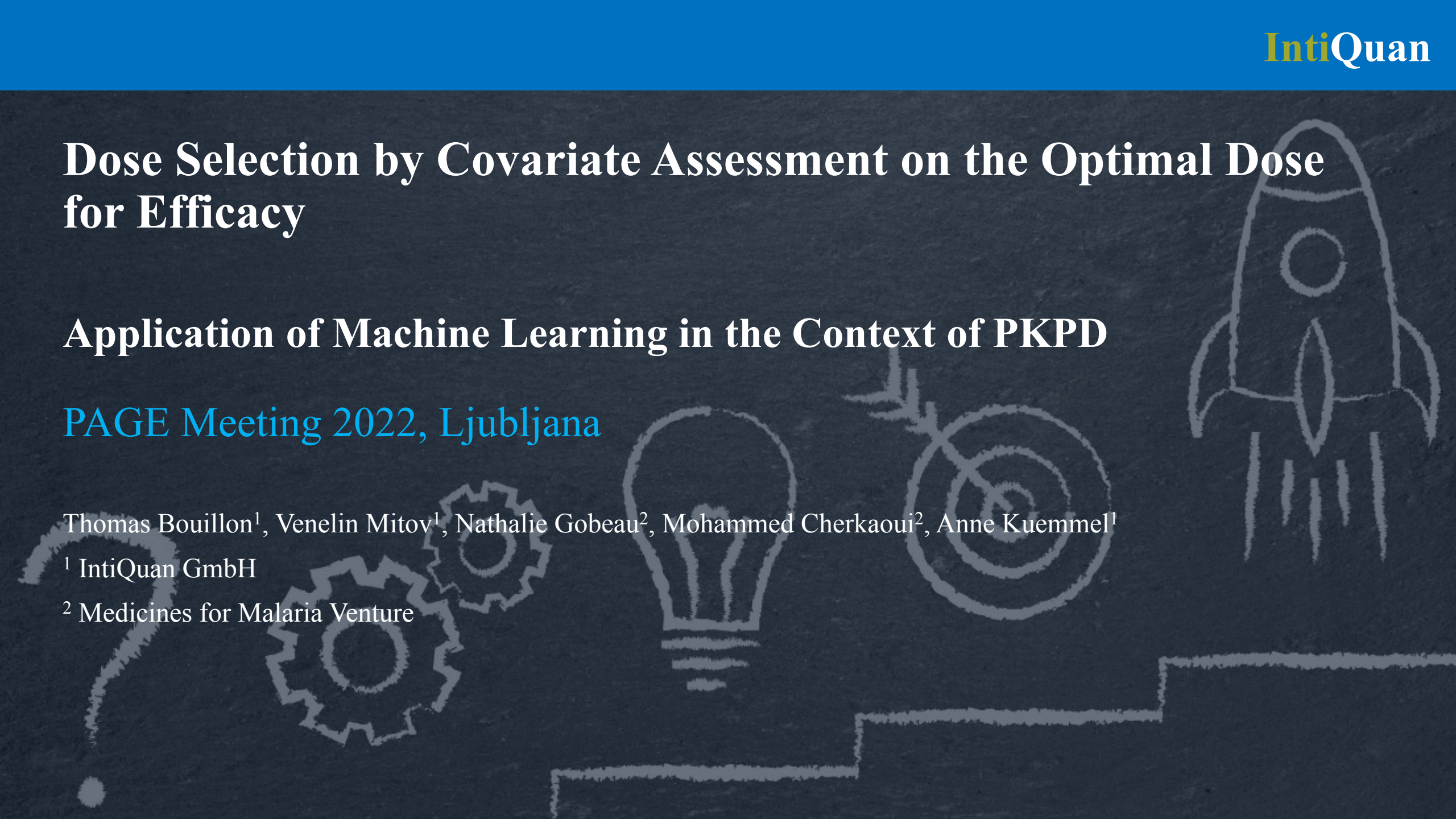

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The opinions expressed are those of the authors. They do not purport to reflect the opinions or views of other members of IntiQuan or MMV.

The demonstration is based on a virtual drug/substance. Any resemblance to a real drug is purely coincidental, likewise the resemblance to substances under development or substances for which development was suspended or terminated.

Introduction

Problem:

- Dose and covariate selection is complex and time-consuming

- Complexity: Multidimensionality, potentially correlated covariates, different functional relationships (e.g., linear, log linear, exponential, power)

Solution:

- Reduce dimensionality targeting the optimal efficacious dose during covariate search

- Increase efficiency (less NLME runs, (semi)automatic detection of covariates and functional relationships, output is easily translatable to label).

Objectives

Based on a virtual example, we will demonstrate that the approach is able to:

- Predict a safe and effective optimal dosing regimen (robustness increases proportional to the amount of clinical information)
- Identify the relevant covariates on and their functional relationship to the optimal dose of the preferred regimen
- Predict a realistic covariate adjusted dosing regimen
- Assess its performance with regard to safety and efficacy

Predicting a safe and effective optimal dosing regimen using the best information available

What is the safe and effective optimal dosing regimen using the best information available?

- Structural PKPD model
- Individual PKPD parameters
- Individual covariates

PK/PD
- Efficacy criterion + targeted value
- Safety criterion + targeted value

Dose range and regimen

Optimization of individual doses on meeting criteria

Step 1

For a given dose range and regimen:
- Fraction of optimally dosed individuals
- Individual doses

Simulation

Apply Machine Learning to identify relevant covariates and the functional relationship on the individual optimal doses (MARS used).

Step 2

Covariate adjusted doses

Simulation

Check target attainment and safety

« Is the safety limit respected for all dosed individuals?»
« How big is the difference between optimal and covariate adjusted efficacy?»

MARS: multivariate adaptive regression splines

Application of Machine Learning

Requirement:

- (Semi)automatic selection of covariate and functional relationship
- Explicit human readable set of rules

Chosen Method:

- MARS: Multivariate Adaptive Regression Splines

Additional advantage of MARS:

- Applicable to both regression and classification problems

Example: Finding a dosing regimen for a virtual population of malaria patients

What is the safe and effective optimal dosing regimen using the best information available?

- Structural PKPD model
- Individual PKPD parameters
- Potential individual covariates

PK/PD
- Efficacy criterion + targeted value
- Safety criterion + targeted value

Dose range and regimen

Optimization of individual doses on meeting criteria

For a given dose range and regimen:
- Fraction of optimally dosed individuals
- Individual doses

Apply Machine Learning to identify relevant covariates and the functional relationship on the individual optimal doses.

Step 2

Covariate adjusted doses

What is the safe and effective optimal dosing regimen using the best information available?

- Efficacy criterion: „Cure“ expressed as 1/(min(Parasite))
- Targeted value: >=1 [1/n] (in approx. 95% of the population)
- Safety criterion: AUC_{inf} based on NOAEL
- Targeted value: 100 [mg/L*h]
- **Regimens to evaluate: Single dose, 3x QD, 5x QD**

QD: daily dosing

- **Regimen to be carried forward + frct. «dosable» patients**
- Optimal and covariate adjusted doses
- Scaled doses to meet fraction cured in «dosable» population
- Assessment of safety and efficacy

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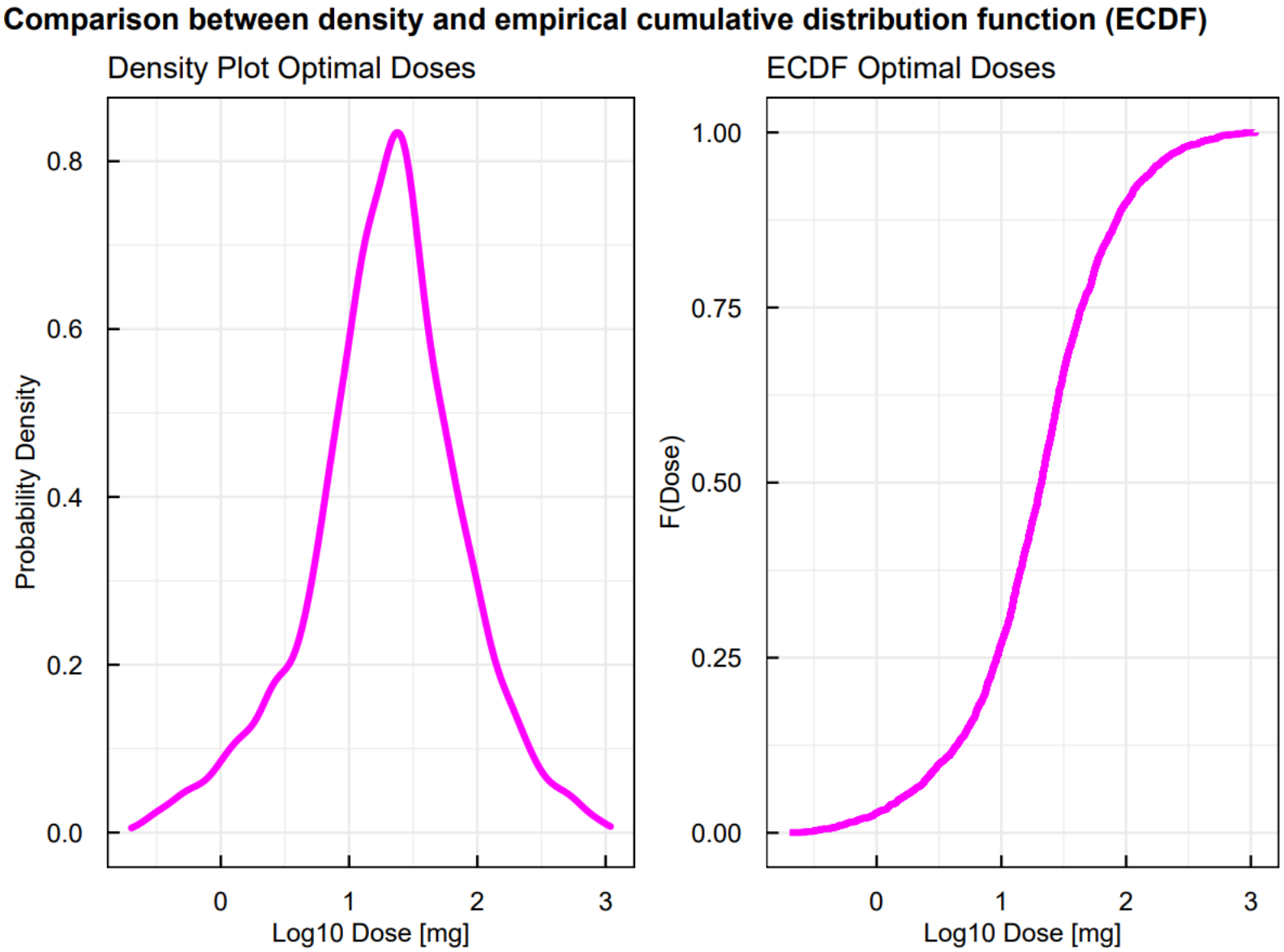
Display of results: Density or Empirical Cumulative Distribution Function? Shown: Optimal Doses 5 x QD reg.



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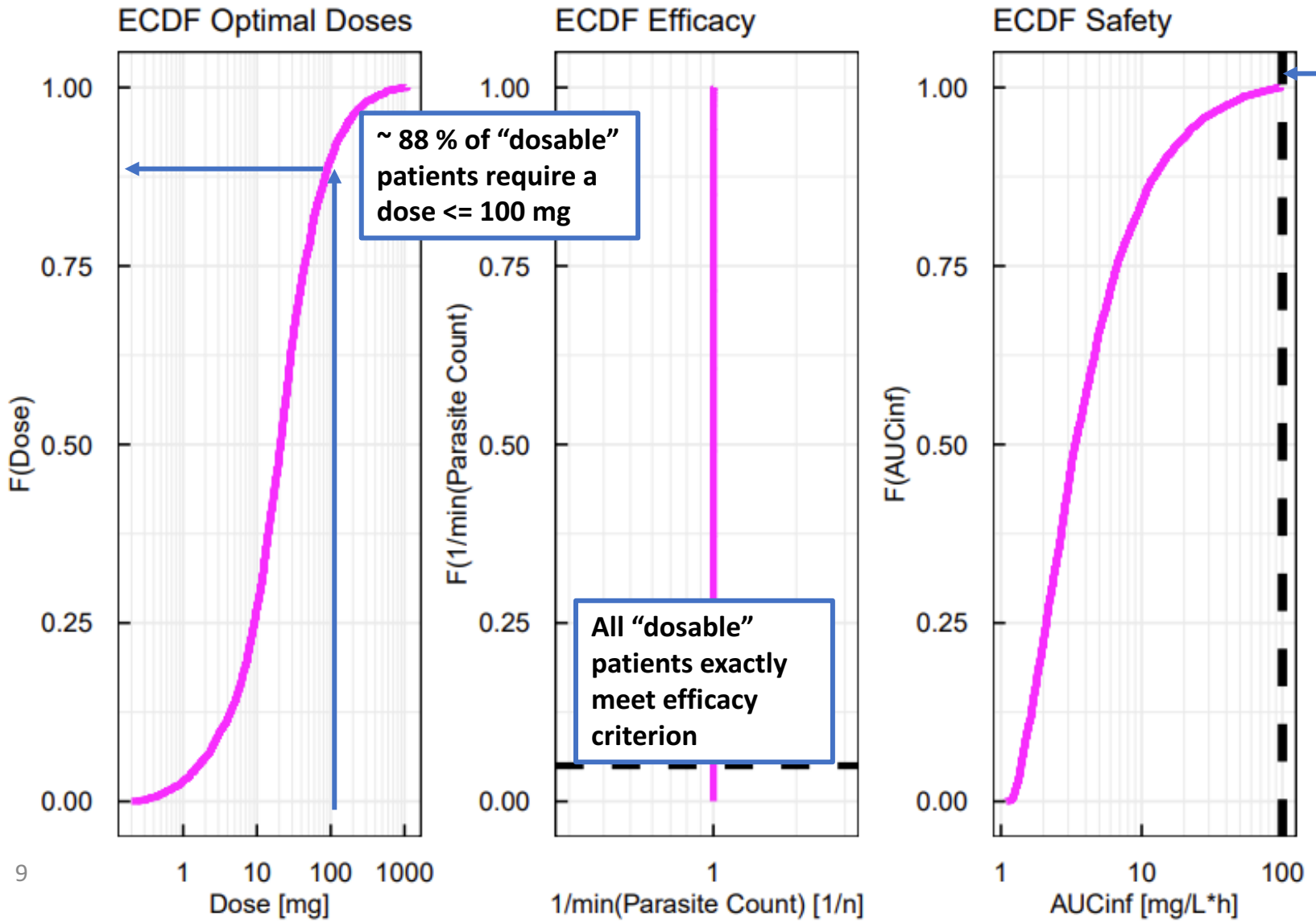
Step 1: Optimal individual Doses for target criteria

Synopsis: Dosing, Efficacy, Safety (Optimal Dose)



ECDF: empirical cumulative distribution function

Based on the individual parameters,
An **optimal dose** could be determined that fulfills the efficacy and safety criterion in **98% of virtual patients for the 5x QD regimen.**

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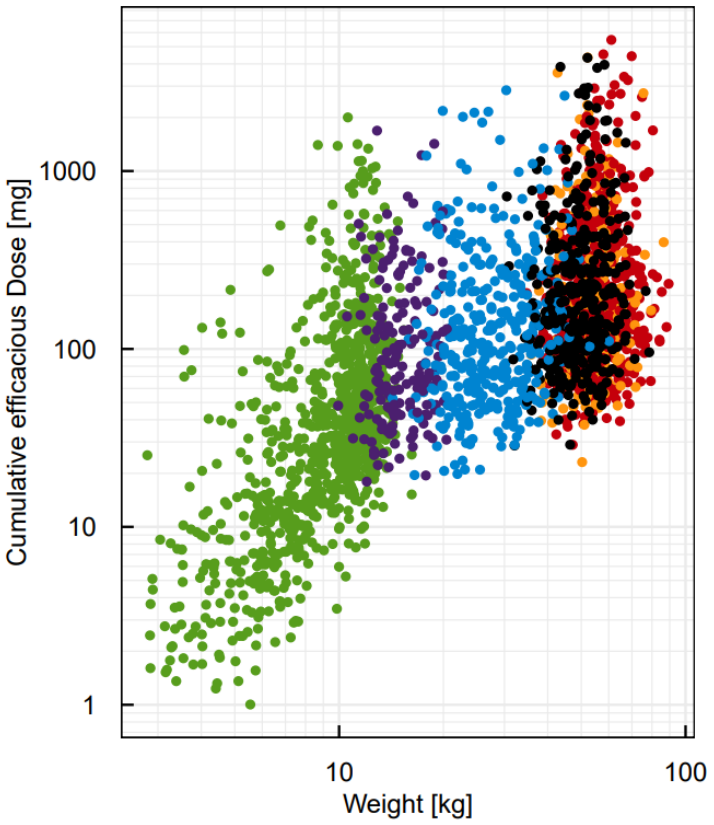
Input Step 2: Optimal Doses + potential Covariates

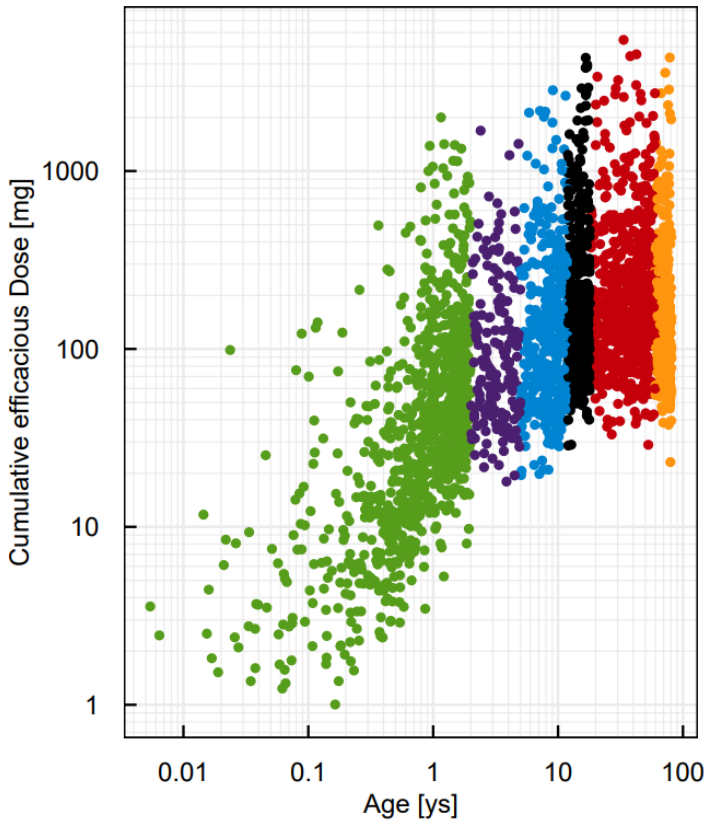
Weight as Predictor of optimal Dose

Weight influences PK parameters and determines total parasite load



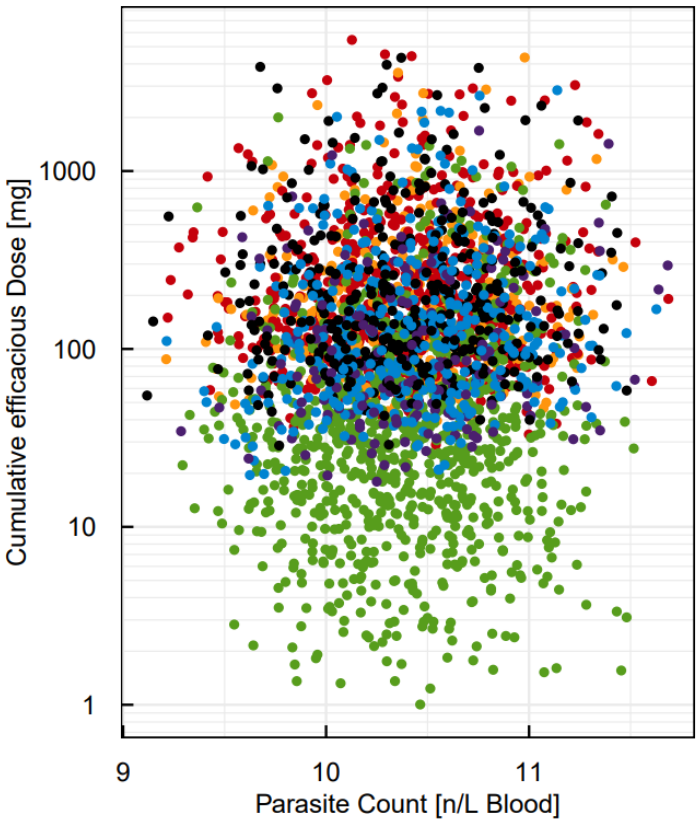
Age as Predictor of optimal Dose

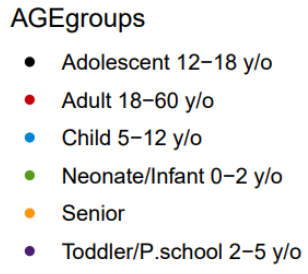
Age determines maturation, CAVE correlation with Weight



Initial Parasite Count as Predictor of optimal Dose

Minimal effect of initial Parasite Count on optimal Dose





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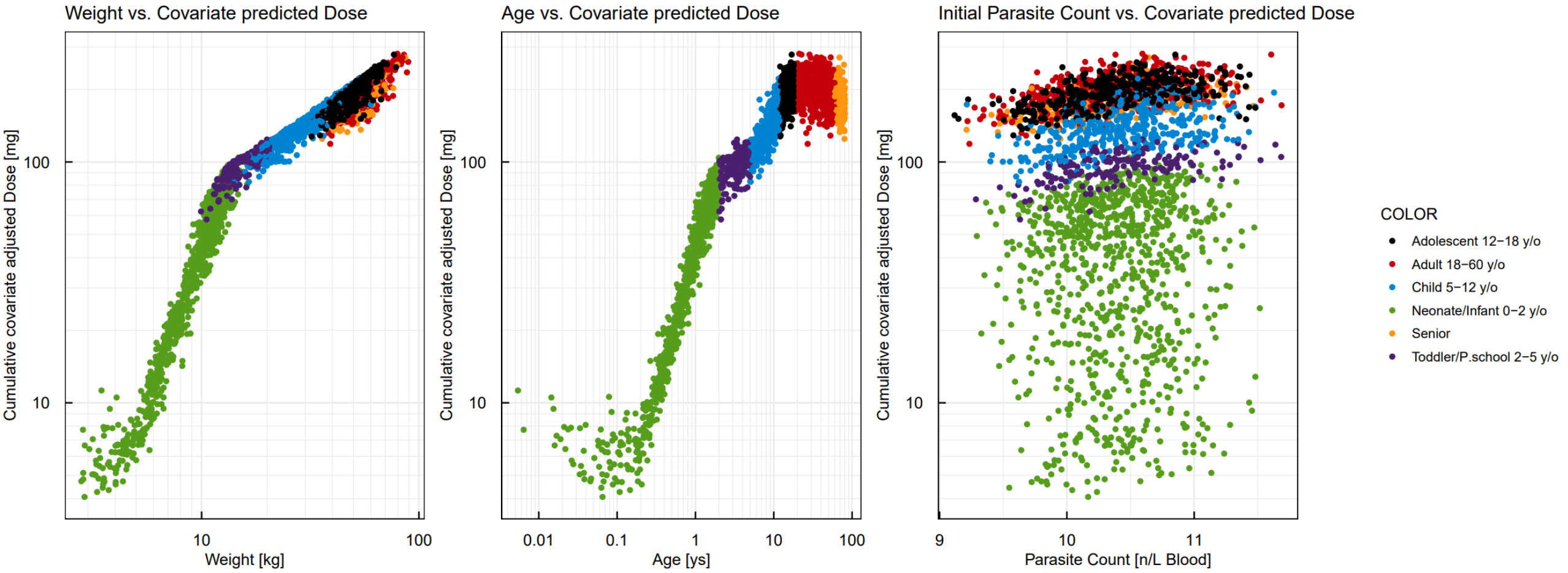
Output Step 2: Covariate adjusted Doses (by MARS)



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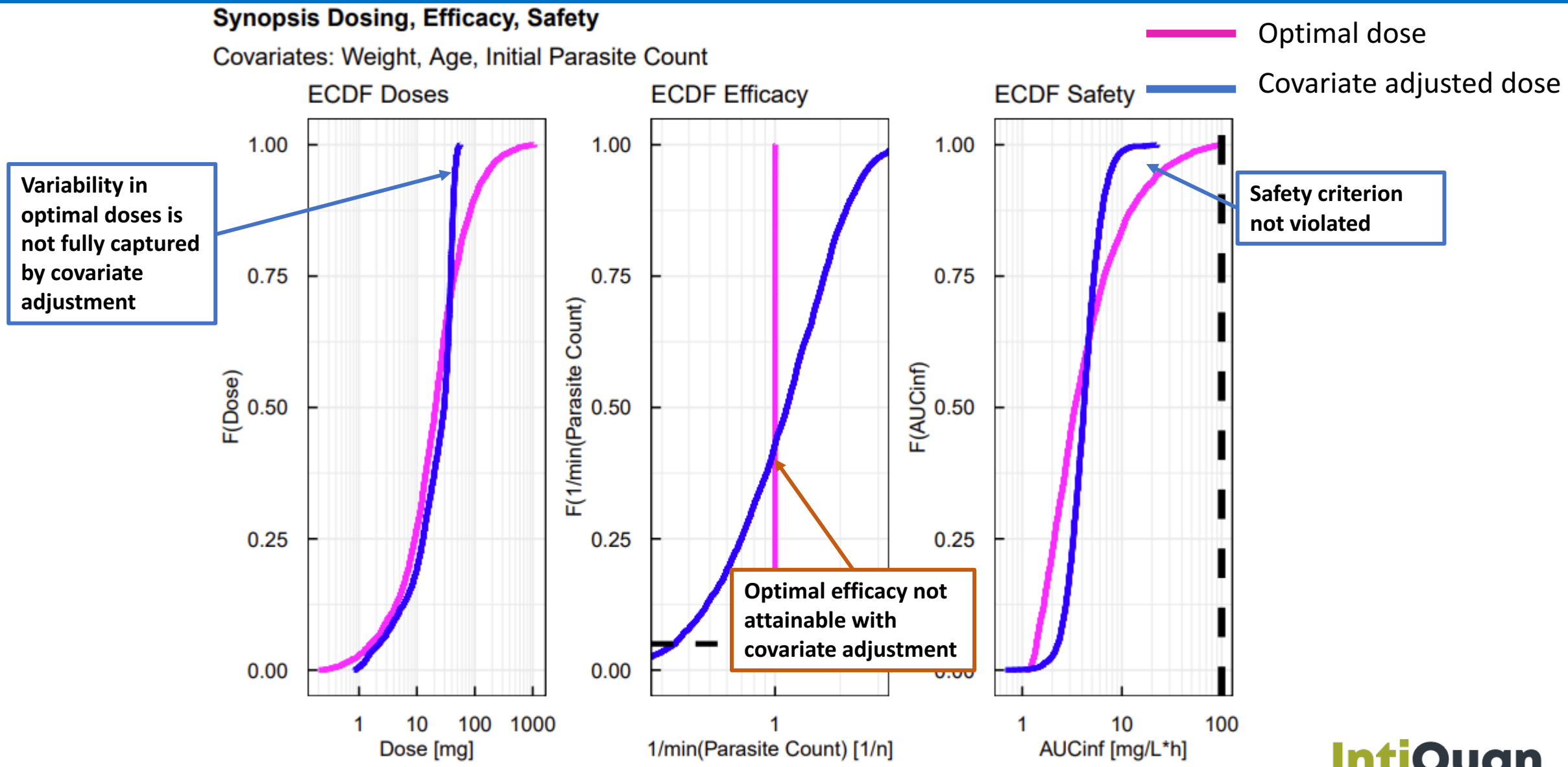
Step 2: Assessment of target attainment



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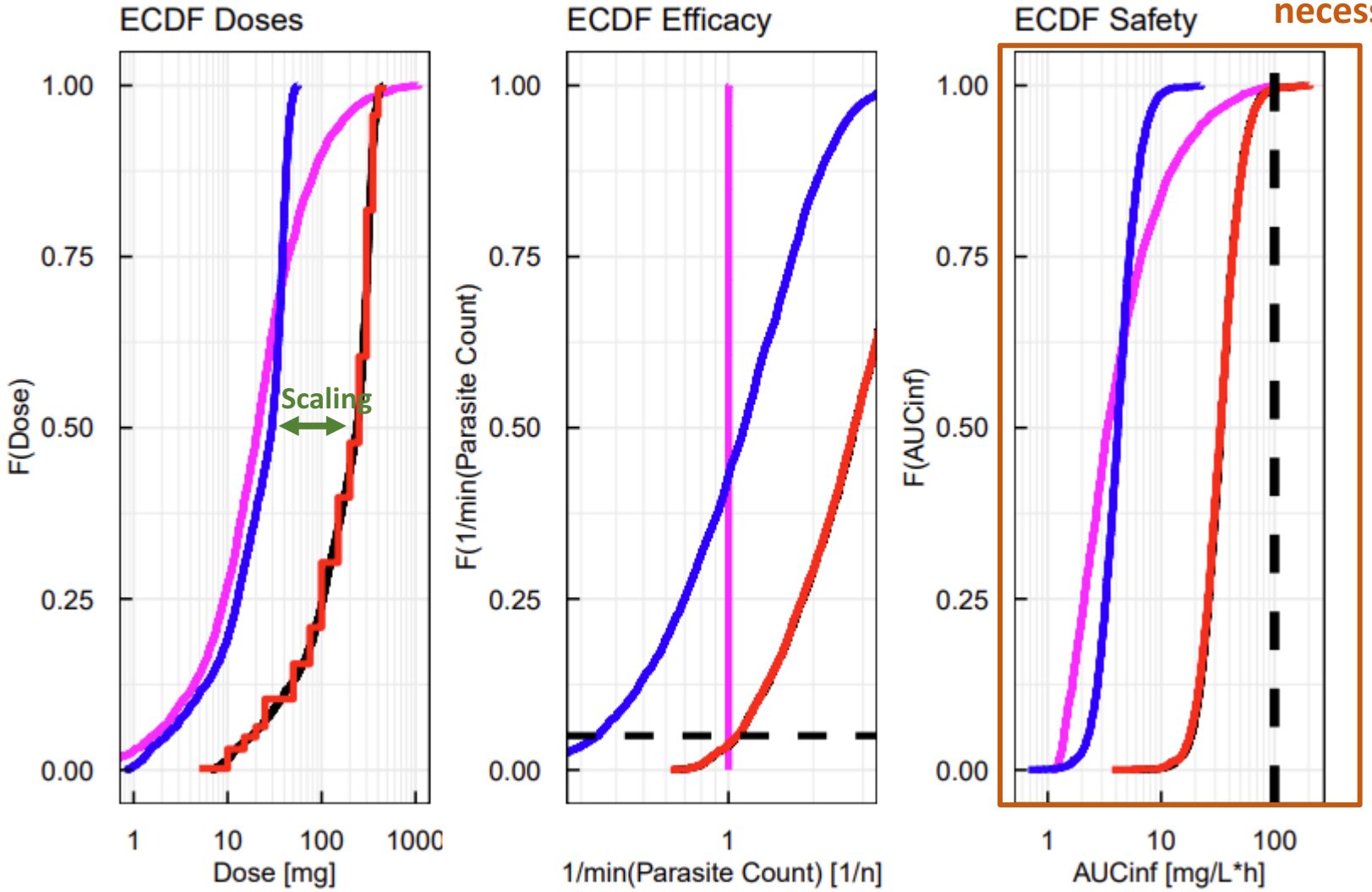
Additional correction: Adjustment to target attainment in the population and dose discretization

Synopsis Dosing, Efficacy, Safety

Covariates: Weight, Age, Initial Parasite Count. Discrete Dose Sizes: 5, 25, 50 mg



Scaling for efficacy in the population necessitates re-assessment of safety

The covariate adjusted doses were scaled up to meet the efficacy target criterium in approx. 95% of the <u>overall</u> population (0.98 frct. dosable*0.96 frct. "cured" in dosable population = 0.94, 94% overall.

- Optimal dose
- Covariate adjusted dose
- Cont. scaled doses
- Discretized scaled doses

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Conclusions + Outlook

- Safe and effective optimal dosing regimen determined
- Covariate adjusted doses for selected regimen were identified (semi)automatically by MARS
- Efficacy target in the population was attained by upscaling of the covariate adjusted doses
- Discretization of dosing allows for development of a usable oral regimen
- Efficacy and safety target attainment were checked for each dosing regimen

Outlook:

- Validation on real-world problems by comparison with standard approaches (retrospectively and prospectively)
- Potential GUI-based Expert System operable by physicians

BACKUP

Details wrt. Multivariate Adaptive Regression Splines (MARS), a.k.a. Enhanced Adaptive Regression Through Hinges (earth), R-package

- Supervised Learning Method (see Applied Predictive Modeling (Max Kuhn))
- Function call (no interaction): BestDose <-earth(log(Dose) ~ log(WTKG)+log(AGEY) + LPC + SEXF, data=Population, degree=1)

Advantages of MARS:

- Intuitively understandable output (depends on complexity of the covariate model)
- No transformation/scaling needed
- Provides both selection of covariate and functional relationship
- Handles both regression and classification problems
- Performs «satisfactorily» compared to other methods

Disadvantages of MARS:

- Forward inclusion
- Handling of highly correlated variables?
- Performs «suboptimally» in comparisons with other methods

MARS is not the uniformly best method but performs «well».