

Model-informed precision dosing for tamoxifen therapy in breast cancer patients: Comparison of different target attainment metrics

A. Mueller-Schoell (1,2), L. Klopp-Schulze (1), R. Michelet (1), W. Huisinga (3), M. Joerger (4), C. Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany,

(2) and Graduate Research Training program PharMetriX, Germany,

(3) Institute of Mathematics, Universitaet Potsdam, Germany,

(4) Medical Oncology and Clinical Pharmacology, Dept. of Internal Medicine, Cantonal Hospital St. Gallen, Switzerland



Background and Objectives

- The breast cancer (BC) drug tamoxifen (TAM) is transformed to its most active metabolite endoxifen (ENDX) via two metabolic pathways. An efficacy threshold for ENDX minimal concentrations at steady state ($C_{SS,min}^{ENDX}$) has been determined to be 5.97 ng/mL [1].
- An alternative target attainment (TA) metric is the **antiestrogenic activity score (AAS)** which considers the concentrations of TAM, its three major metabolites (including ENDX) and their respective antiestrogenic potencies [2]. Based on the same data used for determining the ENDX threshold, an efficacy threshold of $AAS > 1798$ has been established.
- Current therapeutic drug monitoring (TDM) approaches use the ENDX threshold as target attainment (TA) metric [3]. We aimed to investigate the impact of using the **AAS vs. the ENDX threshold as TA metric** on dose selection in model-informed precision dosing (MIPD) and to assess whether ENDX or AAS-guided dosing would be more suitable for TA.

Methods

Step 1:

- Generation of 10.000 virtual BC patients
- Initial CYP2D6-guided TAM dosing (gNM: 20 mg, gIM: 40mg, gPM: 60 mg)
- Virtual TDM sampling after 2,4 and 6 weeks)

Step 2:

- Prediction of $C_{SS,min}^{ENDX}$ and AAS at 6 months** for each virtual patient for the full dose range (5-120 mg q.d.) by Bayesian Forecasting (BF), using virtually measured concentrations (s. step 1) of:
 - TAM and ENDX in the **ENDX-guided dosing group**
 - TAM and its three major metabolites in the **AAS-guided dosing group**
- Selection of lowest respective doses needed for ENDX and AAS TA

Step 3:

- Assessment of predictive performance of BF by calculating "true" TA at 6 months according to both (1) and (2), using the respective doses selected in step 2 and PK parameters chosen in step 1

- MIPD was simulated (s. steps 1-3; left) for 10.000 virtual BC patients using a previously developed nonlinear mixed-effects physiologically-based pharmacokinetic (NLME-PBPK) model of TAM and its three major metabolites [4]. Simulations were performed in NONMEM (v. 7.4.).
- Relevant covariates (age and CYP2D6 activity score (AS)) in the virtual patient population of CYP2D6 genotype-predicted normal, intermediate and poor metabolisers (gNM, gIM, gPM) were generated to represent the respective frequencies observed in a pooled database of 6 clinical studies [5] (gNM/gIM/gPM: 60.2%/34%/5.8%).
- Genotype-predicted phenotypes were classified based on patients' CYP2D6 activity scores (AS; gNM: $AS \geq 1.5$, gIM: $AS = 0.5-1.0$, gPM: $AS = 0$), according to the Clinical Pharmacogenetics Implementation Consortium guidelines (CPIC) [6].
- Individual TAM doses in step 2 could range between 5 and 120 mg (all once-daily (q.d.)), considering available tablet formulations and maximum reported doses in TAM dose escalation trials [7].
- Differences in dose selection for TA were investigated for the population as whole and for gNM, gIM and gPM separately.

Results

- In 76% of patients, the same doses were selected irrespective of the TA metric used, while in 24% of patients, different doses were selected.
- Different doses were selected for 23.2% of gNM, 19.1% of gIM and 61.7% of gPM.
- For 21.9% of all gNM, a higher dose in AAS- vs. ENDX-guided dosing was selected. For 9.94% of all gIM, a higher dose, and for 9.21% of all gIM, a lower dose. For 61.5% of all PM, a lower dose in AAS- vs. ENDX-guided dosing was selected.**

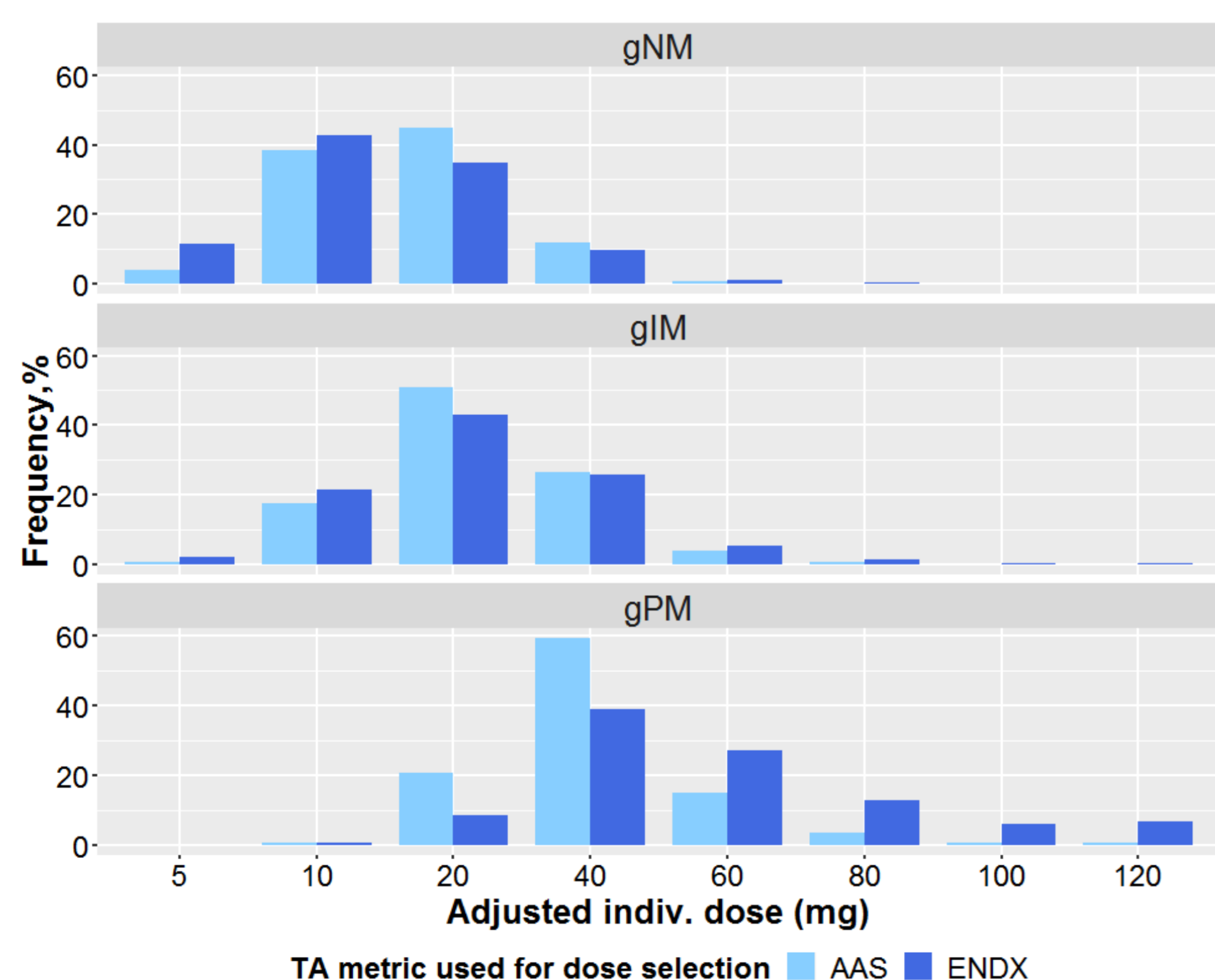


Figure 1: Frequency of selected doses in AAS- and ENDX-guided dosing for CYP2D6 gNM, gIM and gPM, respectively. Light blue bars: AAS-guided dosing, dark blue bars: ENDX-guided dosing. Abbreviations: AAS: antiestrogenic activity score, ENDX: endoxifen gNM: CYP2D6 genotype-predicted phenotype; NM: normal metaboliser, IM: intermediate metaboliser, PM: poor metaboliser.

- Median selected doses for gNM, gIM and gPM in the AAS and ENDX-guided dosing group were 20 mg, 20 mg and 40 mg and 10 mg, 20 mg and 60 mg, respectively.

- Frequencies of selected doses for gNM, gIM and gPM in each dosing group are shown in Figure 1.

Results (cont.)

Among virtual patients with different TAM dose selections:

- 77.2% of gNM, 85.3% of gIM and 100% of gPM reached at least one target (ENDX or AAS) in the ENDX-guided dosing group (Figure 2 a)**
- 98.9% of gNM, 92.2% of gIM and 88.3% of gPM reached at least one target (ENDX or AAS) in the AAS-guided dosing group (Figure 2 b)**

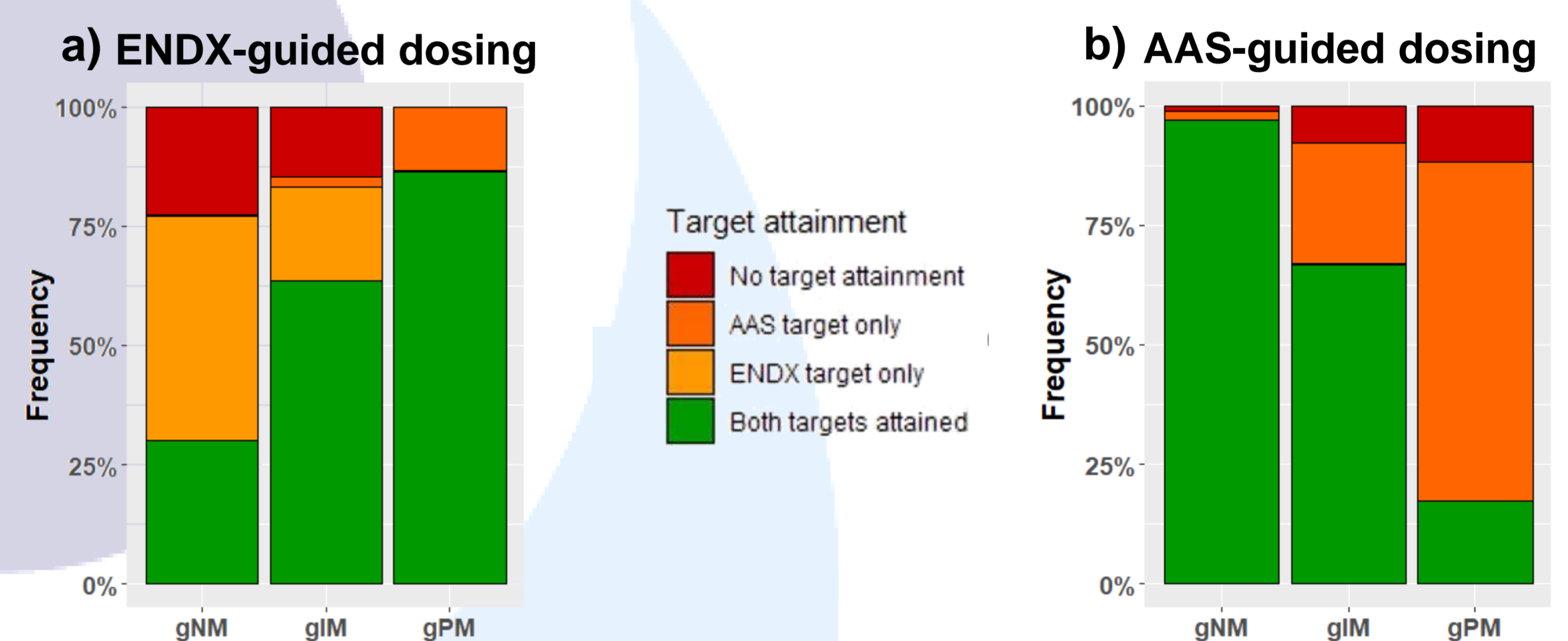


Figure 2: Frequencies of target attainment among patients with different dose selections in a) ENDX-guided dosing and b) AAS-guided dosing. Abbreviations: gXM: CYP2D6 genotype-predicted phenotype, NM: normal metaboliser, IM: intermediate metaboliser, PM: poor metaboliser; AAS: antiestrogenic activity score, ENDX: endoxifen

Virtual gNM with **high apparent formation and clearance of the ENDX precursor metabolite N-desmethyltamoxifen (NDMT)** were **at highest risk for too low dose selections in the ENDX-guided dosing group**. Differences in NDMT formation and clearance for gNM attaining/not attaining both targets are shown in Figure 3.

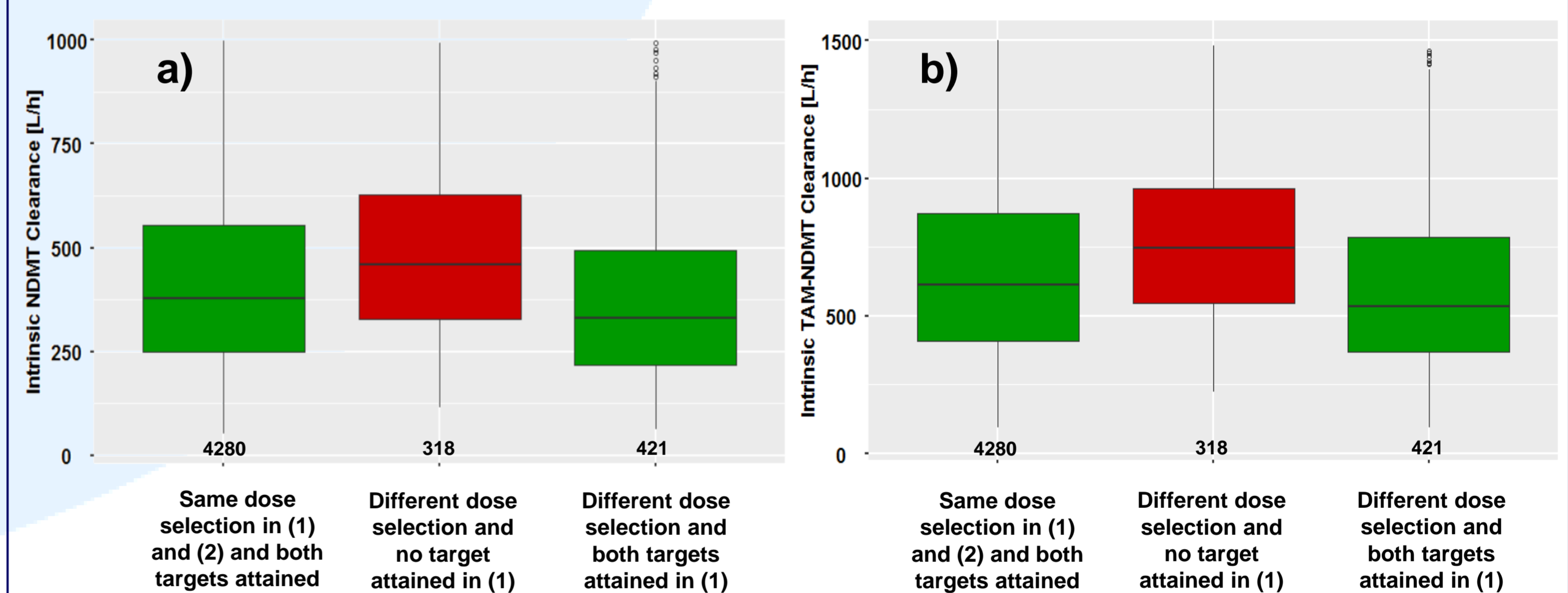


Figure 3: Intrinsic plasma clearances of a) tamoxifen (TAM) to N-desmethyltamoxifen (NDMT) and b) of NDMT (right panel) for three subgroups of gNM. Left boxplots: Clearance values of patients for whom the same dose was selected in ENDX (1) and AAS-guided dosing (2) and who reached both targets; Middle boxplots: Clearance values of patients for whom different doses were selected in (1) and (2) and who attained no target in (1); Right boxplots: Clearance values of patients for whom different doses were selected in (1) and (2) and who attained both targets in (1). Boxes: Interquartile range (IQR) including median; whiskers: range from hinge to lowest/highest value within 1.5 IQR; points: data outside whisker. Numbers below boxes show the number of patients in the respective group.

Discussion and Conclusions

- In this simulation study, comparing different TA metrics for model-informed precision dosing, more than **3 out of 4 patients received the same dose**, regardless of TA metric used.
- In patients with different dose selections, **AAS-guided dosing seemed preferable for gNM and gIM**, while **ENDX-guided dosing was preferable for gPM**.
- A possibly vulnerable **subpopulation of gNM with high apparent NDMT formation and clearance** was discovered and the clinical relevance of this finding should be further investigated.

References:

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For additional information, please contact
Anna Mueller-Schoell,
anna.mueller-schoell@fu-berlin.de

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