Model-Informed Precision Dosing of Busulfan in HSCT:
A critical evaluation of current PK models and dose recommendations

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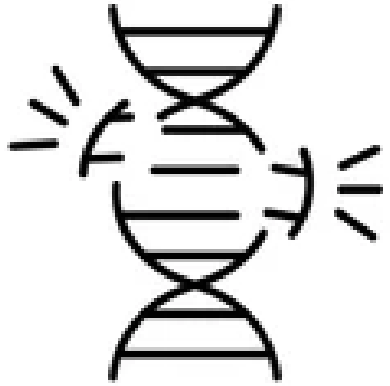
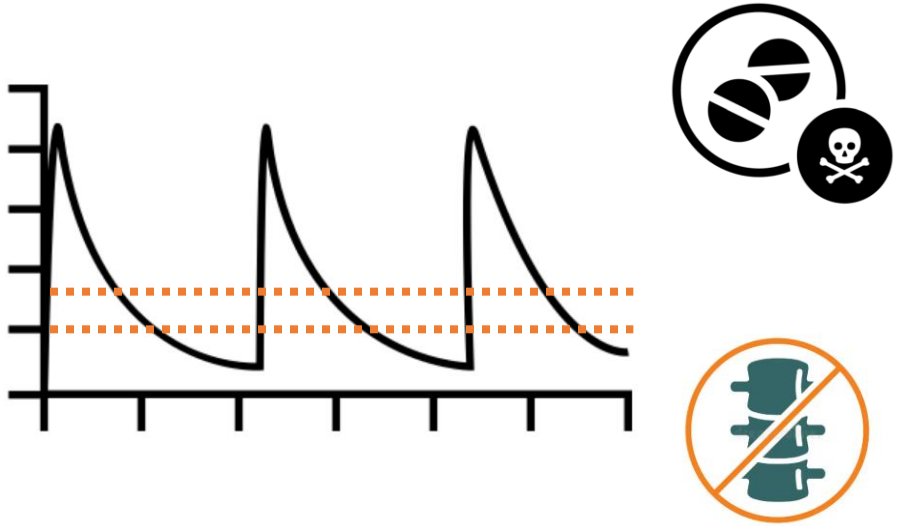
Busulfan: A little background



Alkylating agent



Narrow
therapeutic window

4-day cumulative AUC
of 90 mg*hour/L

Precision dosing:
efficacy vs. toxicity

Bartelink, I.H. et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. Lancet Haematol. 3, e526-e536 (2016).

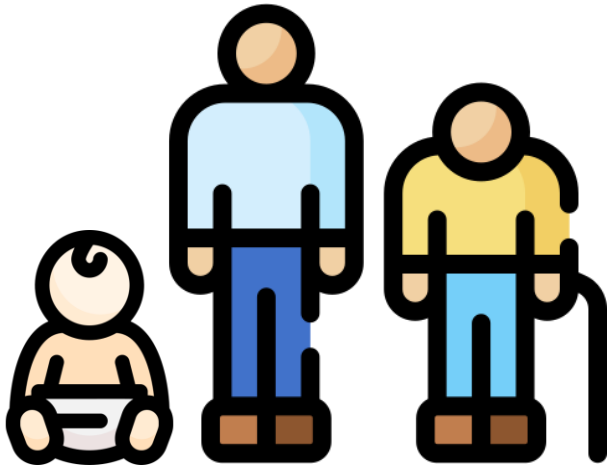
Busulfan: Challenges in real-world practice

- **Model-informed precision dosing (MIPD):**
  Optimizes individual drug exposure by integrating tailored doses, patient-specific factors, and plasma drug concentration measurements using population PK models.

- **Takahashi et al.:**
  Identified 46 PK models for IV busulfan.

Takahashi, T., Jaber, M.M., Brown, S.J. & Al-Kofahi, M. Population pharmacokinetic model of intravenous busulfan in hematopoietic cell transplantation: systematic review and comparative simulations. Clin. Pharmacokinet. 62, 955-968 (2023).

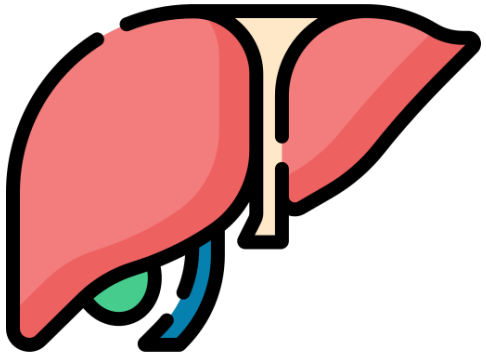
Busulfan: High inter- and intra-patient PK variability



Maturation of age

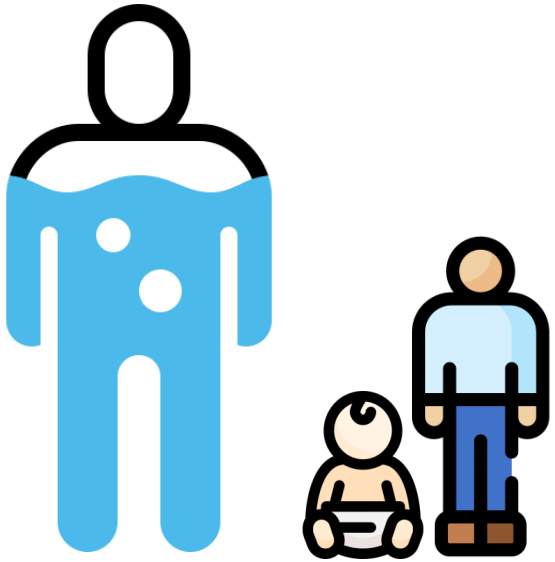
Maturation of weight

Maturation of fat-free mass

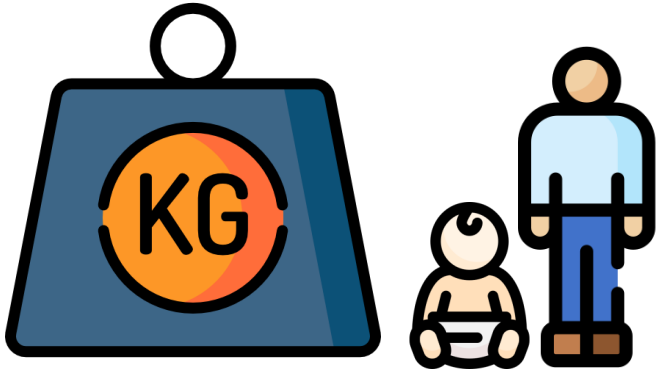


Time-dependent Gluthathion (GSH) depletion

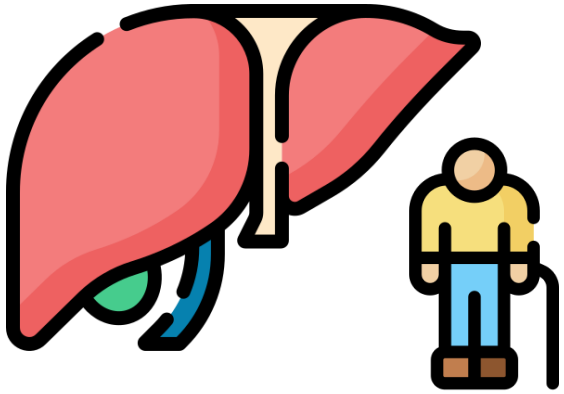
The PK models: Bognàr, Langenhorst & McCune



McCune



Bognàr



Langenhorst

Bognàr, T. et al.. Transplant. Cell. Ther. 28, 196-202 (2022). | Langenhorst, J.B. et al.. Br. J. Clin. Pharmacol. 86, 1499-1509 (2020). | McCune, J.S., Clin. Cancer Res. 20, 754-763 (2014).

Study Hypothesis & Objectives

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  PK models capturing maturation & GSH depletion predict clearance better.

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- **Secondary objective:**
  To determine if *a priori* model-based dosing alone can replace TDM in achieving target exposure.

TDM Evaluation

- **Evaluated:**
  - SmPC dosing: 4 times daily according, 2 hours per infusion (**QID SmPC dosing**);
  - **The most predictive of the 3 selected PK models**, comparing the model's clearance on days 1-4 to a target AUC of 90 mg*h/L across all patient body weights and ages (**QD MIPD**).

- Exposure **with/without TDM**.

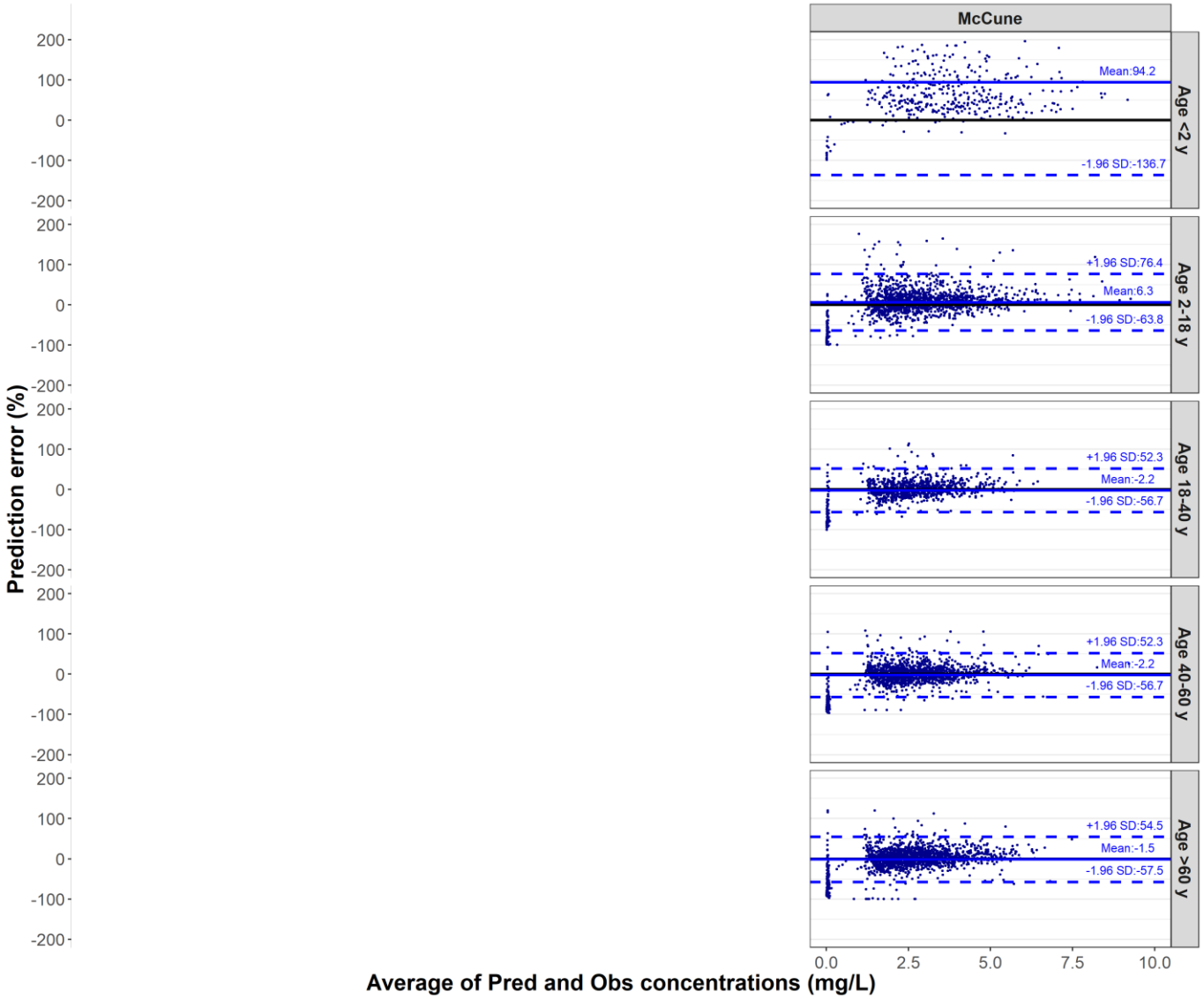
Study Design & Data

- **Retrospective cohort analysis:**
  - 2 large tertiary hospitals in the Netherlands:
    - Amsterdam UMC & UMC Utrecht
  - **535** pediatric and adult HSCT **patients**.
  - July 31, **2014** and November 12, **2021**:
    - All received TDM-guided, IV busulfan precision dosing prior to HSCT and;
    - at least 2 PK samples available, analyzed by liquid chromatography–tandem mass spectrometry (LC-MS/MS).

Patient characteristics

		UMCU (N=455)		Amsterdam UMC (N=80)	
Patient demographics		%	n	%	n
Gender	Male	44.6	203	43.8	35
	Female	55.4	252	56.3	45
Age (years)	Median (range)	44.1 (0.18-73.6)		61.0 (25.0-72.0)	
	<2	7.2	39	0	0
	2-18	24.8	133	0	0
	18-40	14.7	67	11.3	9
	40-60	21.8	99	35.0	28
	>60	25.9	118	53.8	43
Weight (kg)	<10	4.8	22	0	0
	10-40	23.7	108	0	0
	40-60	11.6	53	11.2	9
	>60	59.8	272	88.8	71
BMI (kg/m2)	0-18.5	25.7	117	3.74	3
	18.5-25	41.1	187	40	40
	25-30	24.4	111	31.2	25
	>30	8.8	40	15	12
Hematopoietic cell transplantation-related characteristics					
Conditioning regimen	Busulfan/fludarabine	60.2	274	100	80
	Busulfan/cyclophosphamide/melphalan	0.2	1	0	0
	Busulfan/fludarabine/clofarabine	39.6	180	0	0
Serotherapy	None	2.0	9	9	7
	ATG*	67.0	305	0	0
	Alemtuzumab	0.2	1	0	0
	Cyclophosphamide post SCT	0	0	91	73
	Missing/other	30.8	140	0	0

Predictive performance of the PK models



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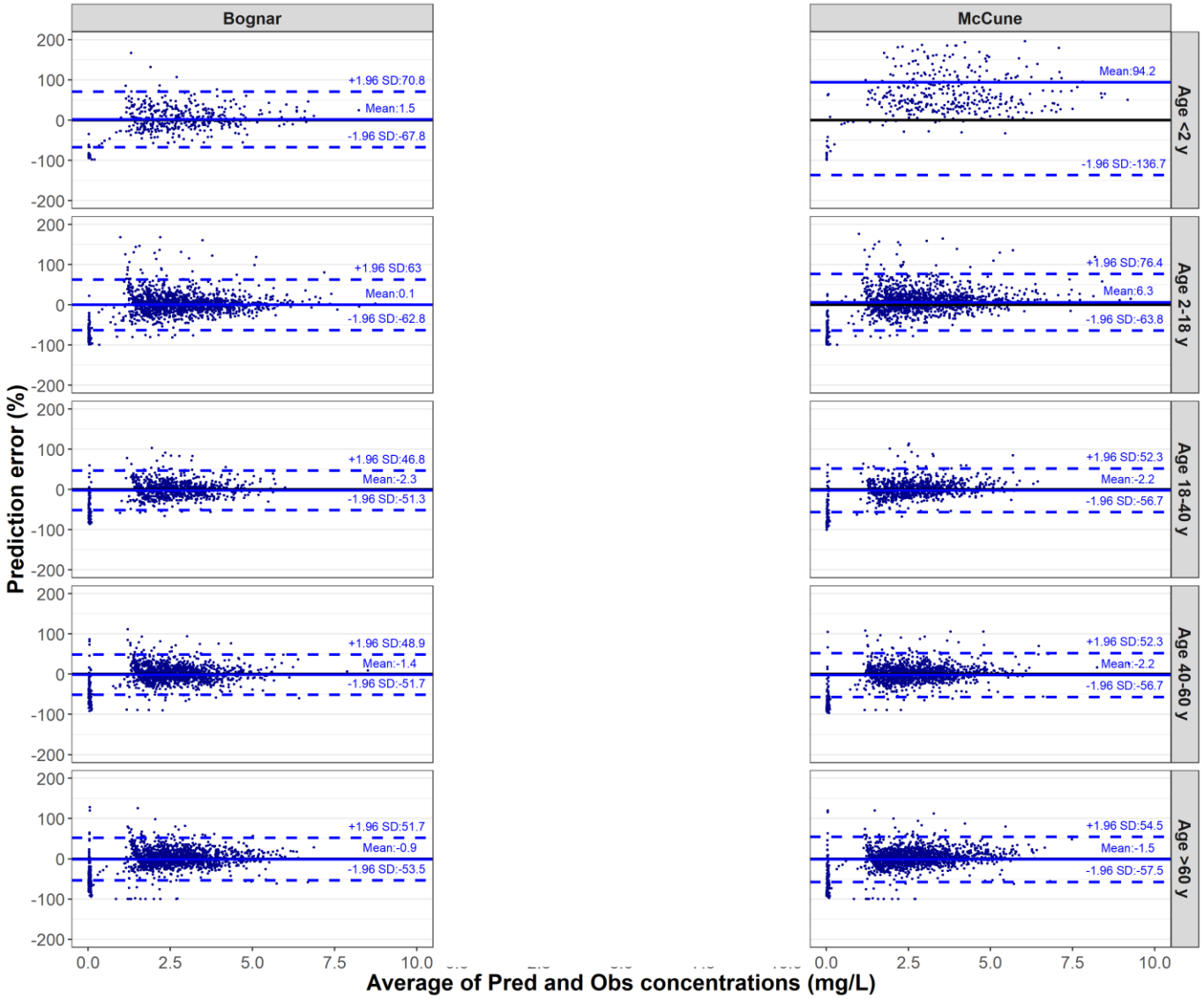
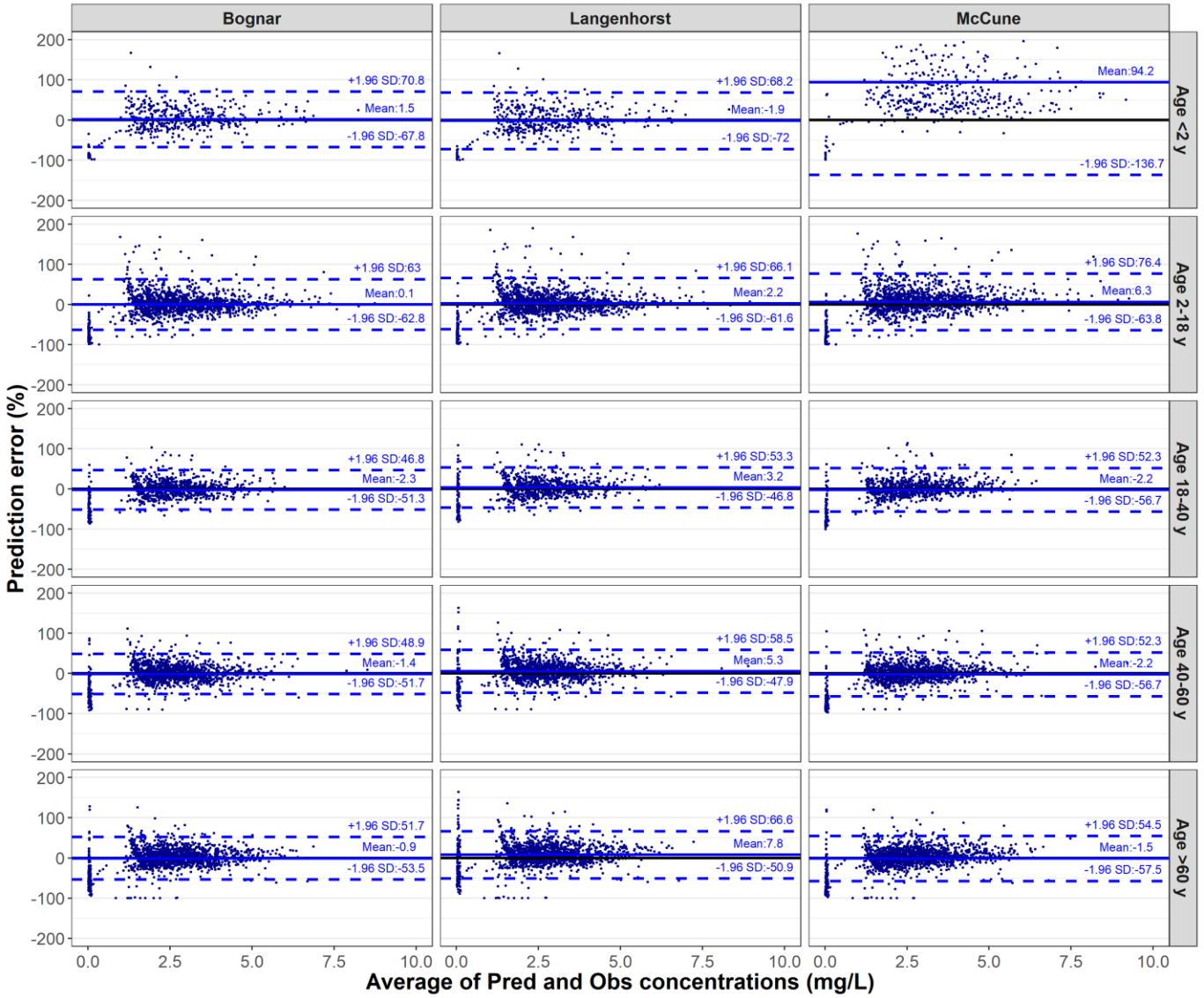


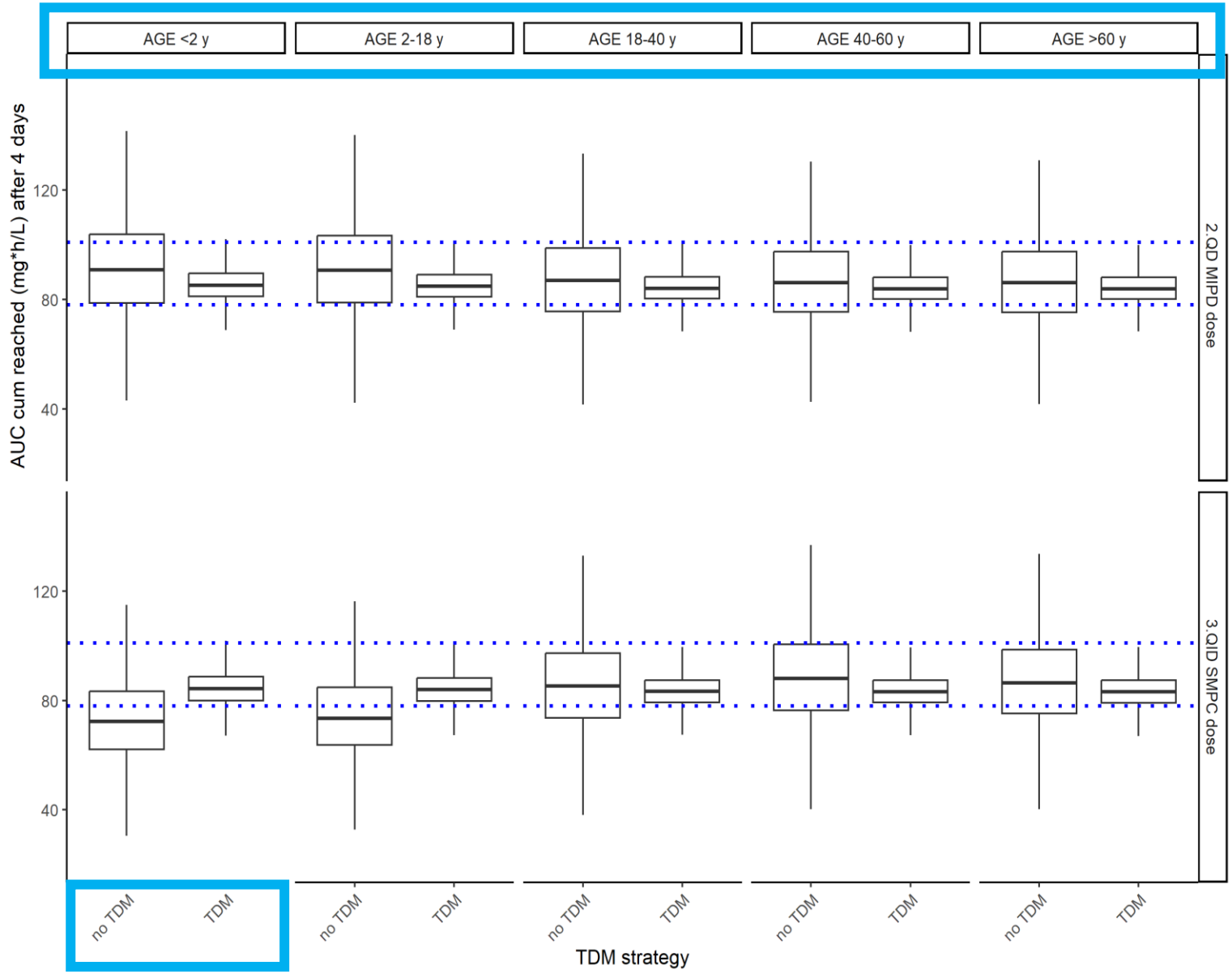
Predictive performance of the PK models

- McCune did not perform better in pediatrics patients (but worse!).
- Langenhorst (GSH) did not perform better in elderly patients.
- The simple body weight approachof Bognar did best in all patients, with no additional adjustment for age required in children or the elderly.



Impact on target attainment

- MIPD did not improve target attainment over SmPC-based dosing.
- TDM-based MIPD with a single TDM on days 2–4 significantly improved target attainment (49% vs. 87%).



Implications for real-world practice: Take to work messages

- **Simply the best:**
  - The Bognar, two-compartment model using body weight, accurately described busulfan PK in all age groups.
  - Simpler PK models may be preferable in clinical MIPD applications.

- **To TDM or not to TDM?**
  - The routine use of TDM for busulfan dosing, regardless of patient age, is warranted:
    - MIPD without TDM fails to reliably hit target AUC.

Strengths and Limitations

- First real-world external validation of 3 widely used MIPD models.
- No new model created – focus on clinical relevance of existing ones.
- The use of simpler models (e.g. Bognar) may suffice.

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- The use of simpler models (e.g. Bognar) may suffice.
- Single-country cohort – 2 Dutch tertiary centers.
- Overlap with Bognar (21%) and Langenhorst (25%) model datasets.
- Retrospective design – not optimized for sampling strategy analysis.

Thank you, on behalf of…

Tim Bognàr	UMC Utrecht, the Netherlands
Kaj E. van Schie	Amsterdam UMC location VUmc, the Netherlands
dr. Ilse T. Kuipers	Amsterdam UMC location VUmc, the Netherlands
Moniek A. de Witte	UMC Utrecht, the Netherlands
Prof. dr. Jurgen H.E. Kuball	UMC Utrecht, the Netherlands
dr Erfan Nur	Amsterdam UMC location VUmc, the Netherlands
Bram J. Wilhelm	Amsterdam UMC location VUmc, the Netherlands
dr. Marise R. Heerma van Voss	Amsterdam UMC location VUmc, the Netherlands
dr. Linda Franken	Amsterdam UMC location VUmc, the Netherlands
dr. Arief Lalmohamed	UMC Utrecht, the Netherlands
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dr. Dave C. de Leeuw	Amsterdam UMC location VUmc, the Netherlands
dr. Imke H. Bartelink	Amsterdam UMC location VUmc, the Netherlands

Full text paper

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Donor-related characteristics					
Diagnosis	Malignant	64.0	291	100	80
	Non-malignant	12.5	57	0	0
	Missing	1.8	8	0	0
Donor	Family	5.1	23	25	31.5
	Unrelated	26.4	120	Haplo 15 MUD 40	18.8 50
	Missing	68.6	312	0	0
Matching status	Matched	54. 5	248	78.8	63
	Mismatch	23.7	108	21.2	17
	Missing	21.8	99	0	0
Donor source	Bone marrow	11.9	54	?	?
	Peripheral blood	44.0	200	?	?
	Cord blood	22.4	102	0	0
	Missing	21.8	99		
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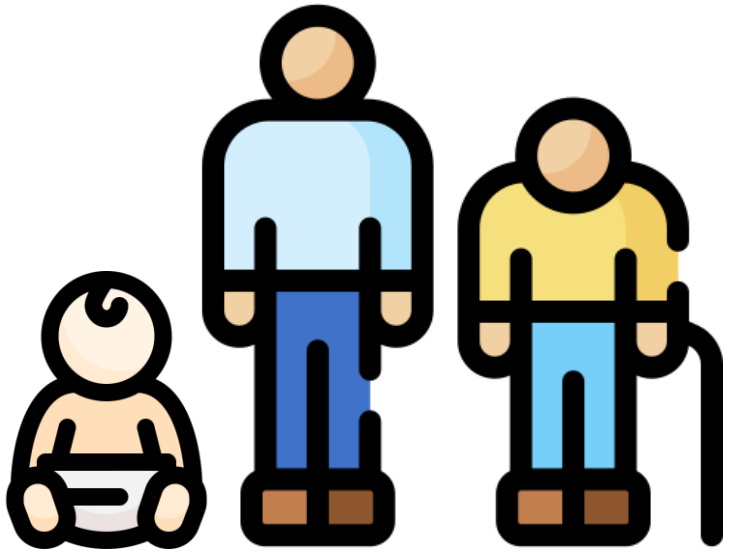
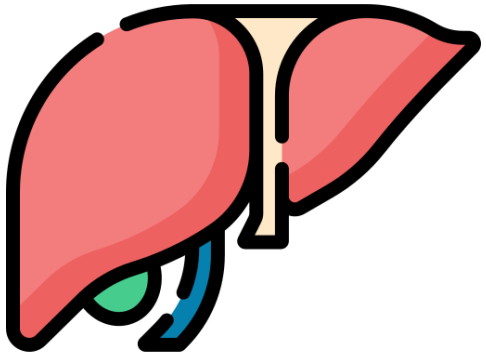


Bognàr



Langenhorst

McCune