Insight RX

Steps Toward Model-Informed Precision Dosing of PEG-Asparaginase in Children and Young Adults

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Background

- Polyethylene glycol-conjugated asparaginase (PEG-ASNase) is integral in the treatment for acute lymphoblastic leukemia (ALL) in children and young adults and has been shown to improve the overall survival.

- Notable clinical realities of PEG-ASNase include:

  - Prevalent **treatment-limiting toxicities**: hypersensitivity, pancreatitis, thrombosis, and liver dysfunction.

  - Recent and ongoing work has shown older children experience toxicity to a higher degree and higher dosing intensity relates to higher rates of grade 3 and 4 toxicities. Neither PK/PD models of this relationship nor an upper limit PK marker have been established.[1]

  - Measurement of ASNase activity level (AAL) is already standard clinical practice and is primarily utilized for assessment inactivation of PEG-ASNase by anti-ASNase antibodies (at least in the US).

  - **High pharmacokinetic variability** with subtherapeutic AAL <0.1 IU/ML is associated with inferior disease-free survival.[1,2,3,4]

  - **Significant cost**: up to 20,000 - 30,000 USD per dose (in US).

- Published pediatric population pharmacokinetic (PopPK) models:

  - Würthwein et al. characterizes the notably high inter- and intrapatient variability present in the treatment population and includes a variety of covariate effects.[3]

  - Kloos et al. additionally proposes a traditional therapeutic drug monitoring (TDM) and dose adjustment framework.[4]

- Given standard of practice measurements of ASNase activity, prevalence of toxicity and inefficacy, high pharmacokinetic variability, and significant cost, a model-informed precision dosing (MIPD) approach to PEG-ASNase dosing may significantly improve target attainment and decrease cost.

Objectives

1. Prospectively validate and refit the PopPK model developed by Würthwein et al. in a novel pediatric PEG-ASNase dataset.
2. Conduct simulations to evaluate a model-informed precision dosing (MIPD) approach for PEG-ASNase.

Methods

- Patient data were collected as a part of an observational clinical research project led by Children's Hospital of Orange County (CHOC), USA.

- Model refitting was completed in NONMEM (v7.5) utilizing the FOCEI method and ignoring BLQ and individuals who met criteria for inactivation of PEG-ASNase by anti-ASNase antibodies.

- The PsN tool *proseval* was utilized to evaluate model prospective forecasting performance as quantified by mean percentage error (MPE) and normalized root-mean square error (nRMSE).

- Dosing strategy simulations with doses given every 14 days intravenously:
  - **FDA/COG:** Body surface area (BSA) based dosing as recommended by US Federal Drug Administration (FDA) and Children's Oncology Group guidelines (COG)
  - **FDA/COG + TDM:** FDA/COG starting dose with dose adjustments based on the TDM framework described by Kloos et al.[4]
  - **MIPD:** covariate informed *a priori* initial dose and *a posteriori* dose adjustment.

- For MIPD simulations, an InsightRX developed R package, *mipdtrial,* was used for individual PK curve simulation, MAP Bayesian estimation, and dose adjustment based on model estimates and variability.[5]
  - **Initial dose:** Target AAL of 0.3 IU/mL based on the population model and patient covariates.
  - **Dose Adjustments:** If measured AAL was outside of the acceptable range (0.1 – 0.5 IU/mL), MAP Bayesian estimates of pharmacokinetic parameters for each patient were used to re-adjust the dose to attain the target of 0.3 IU/mL.

Results

Model Performance & Refit

Table 1. Patient Demographics

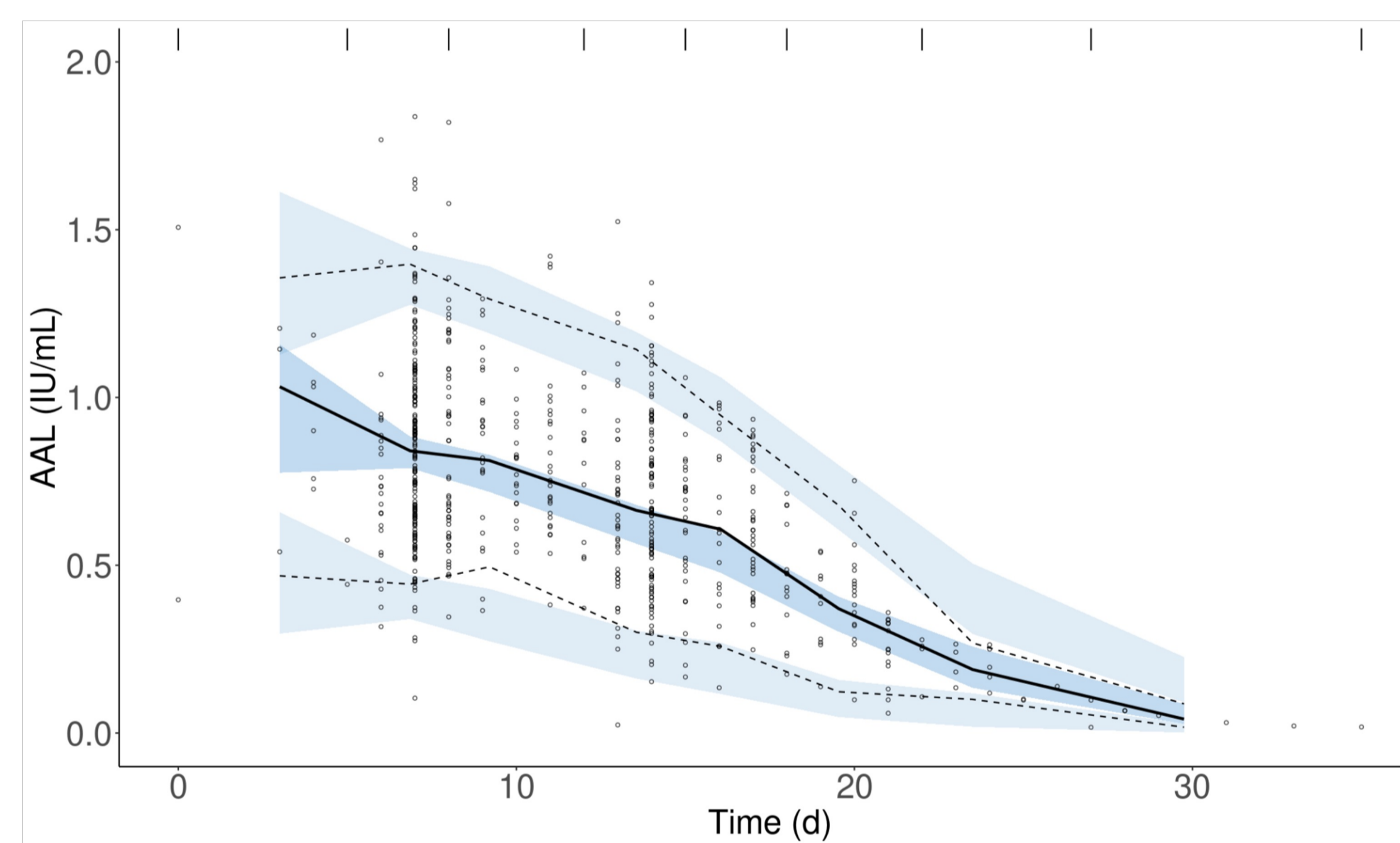| Characteristic	Value
Patients - n	143
Sex	
M - n (%)	88 (62)
F - n (%)	55 (38)
Wt (kg) - median (range)	23.6 (10.6 - 144)
Ht (cm) - median (range)	126.2 (57.1 - 187.0)
BSA (m^2) - median (range)	1.14 (0.49 - 2.71)
BMI (kg/m^2) - median (range)	17.4 (12.1 - 43.2)
Age (yr) - median (range)	7.5 (1.1 - 23.9)
Dose (IU/m^2) – median (IQR)	2200 (1209 – 3421)
ASNase Activity Levels (AAL)	
AAL (IU/mL) - median (range)	0.69 (0.02 - 2.59)
n	667
BLQ - n (%)	25 (3.7%)
Patients w/ Inactivation - n (%)	10 (7.0)

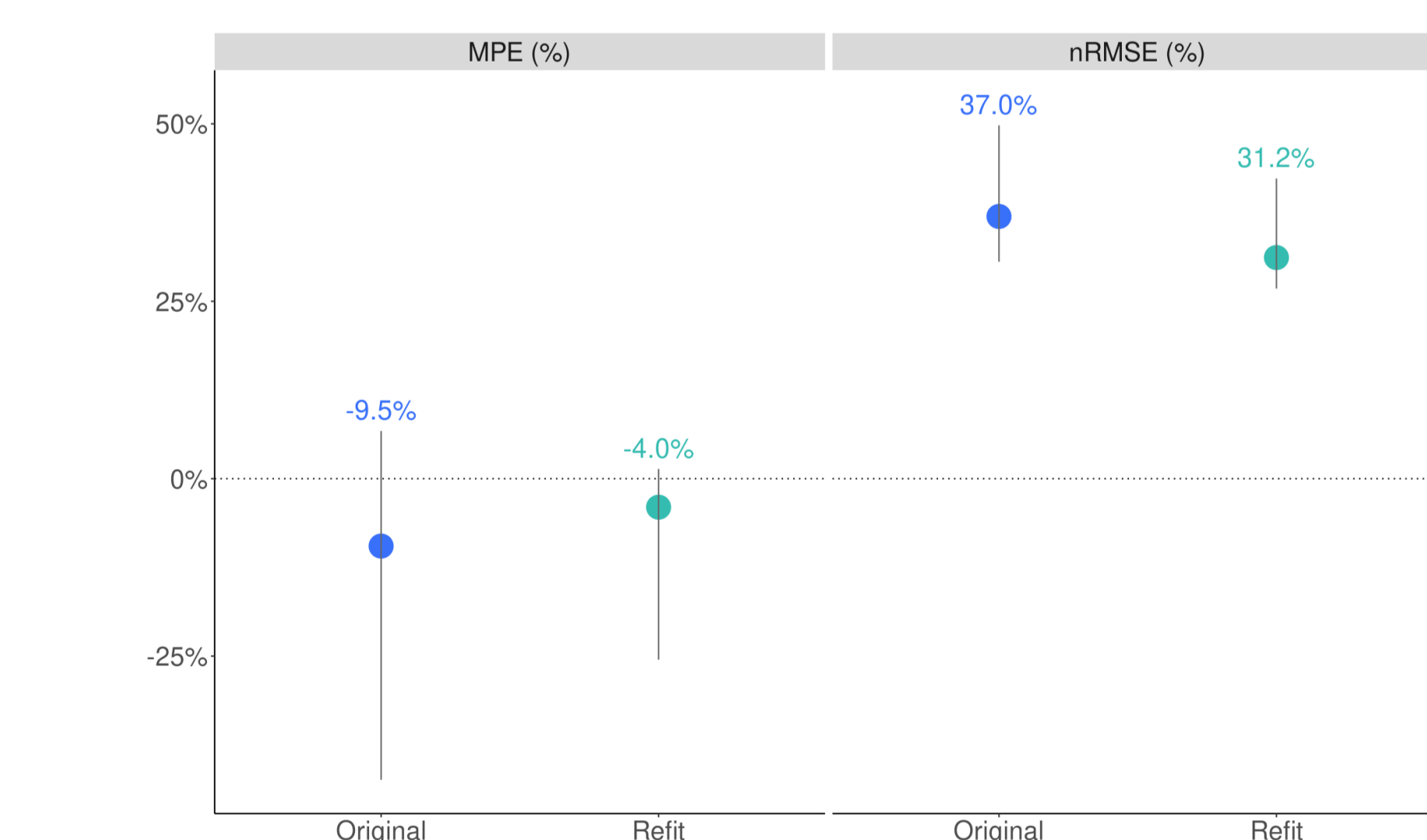**Figure 1.** Visual Predictive Check of Würthwein refit model on the CHOC pediatric dataset.

Figure 2. Prospective forecasting model performance quantified as MPE and nRMSE for both the original and refit models.

Table 2. Key Refit Model Parameter Estimates

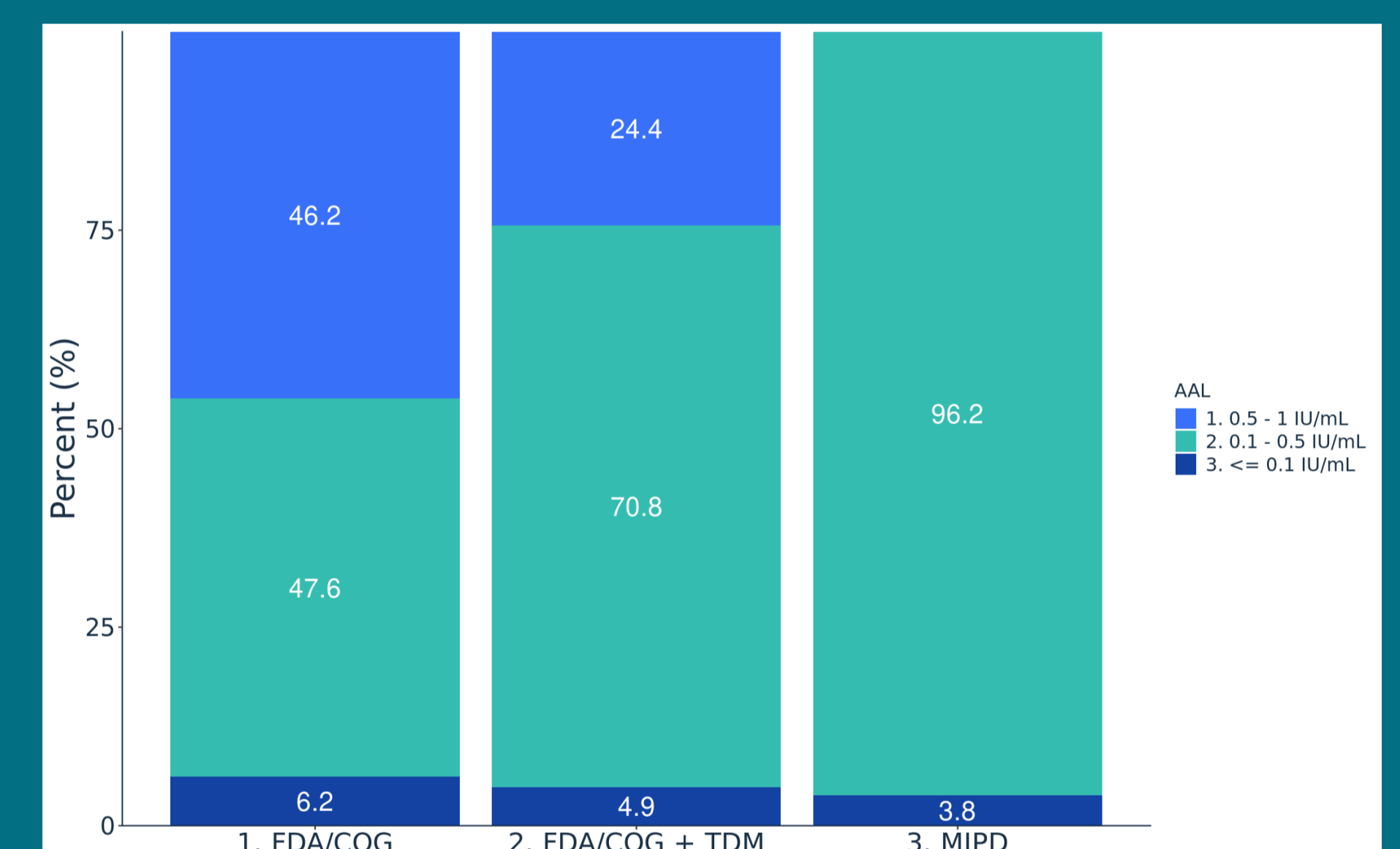| Parameter	Refit Estimates	RSE (%)
Vd (L/m^2)	1.672	3.8
CL ($L/day/m^2$)	0.054	8.9
Q ($L/day/m^2$)	1.042	5.3
IIV CL (%CV)	64.1	11.1
Prop. Error (%)	25.1	6.1
Add. Error (IU/mL)	0.0102	12.2

MIPD Simulations

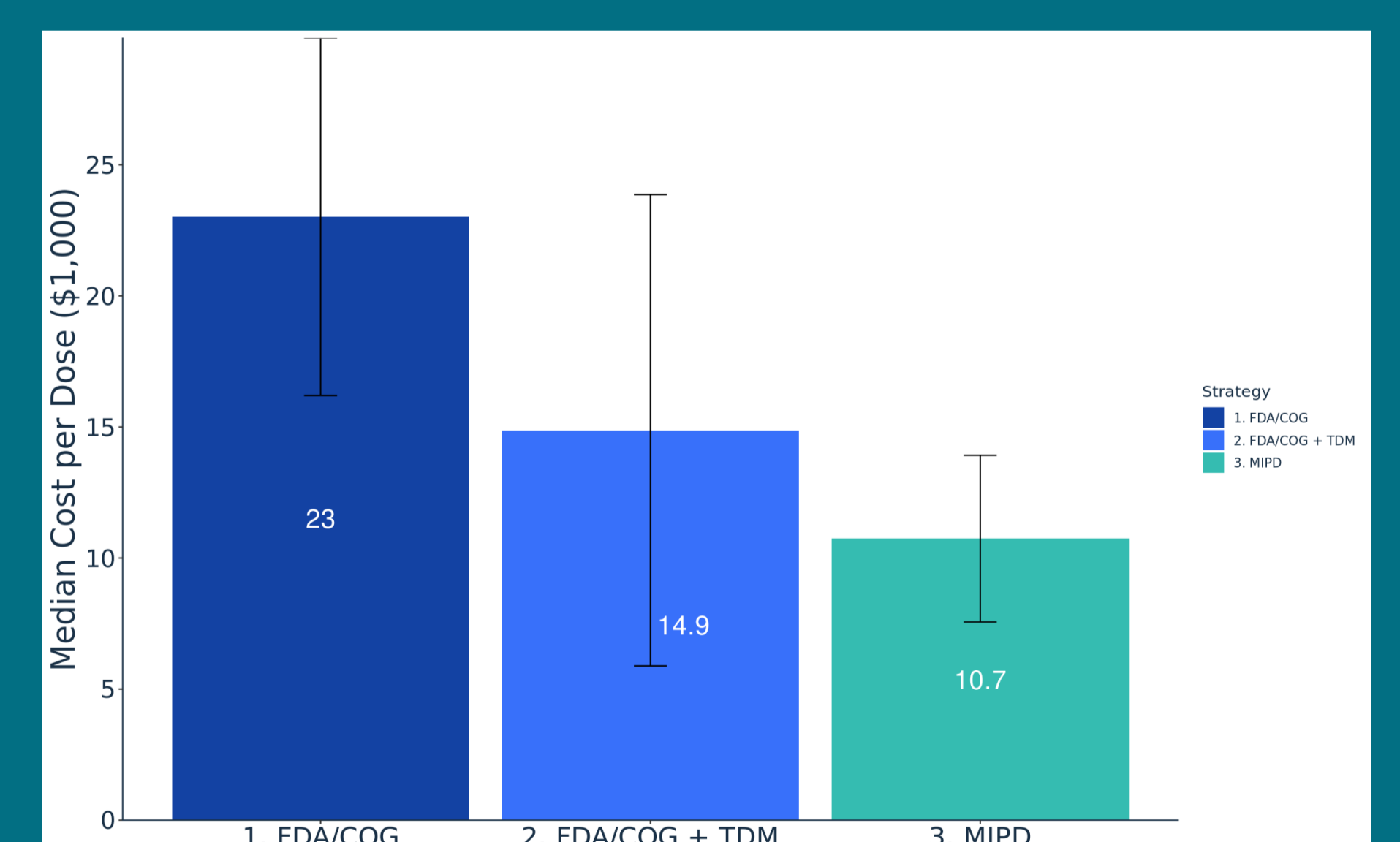**Figure 3.** Percentages of steady state trough AAL by target group for each dosing strategy.

Figure 4. Idealized median cost per dose of PEG-ASNase by dosing strategy with error bars reflecting standard deviation.

Conclusion

- Adoption of MIPD in the routine clinical use of PEG-ASNase in children and young adults being treated for ALL has potential to improve therapeutic level attainment and minimize treatment costs.

- Furthermore, this study externally validates an existing PopPK model, highlighting that the tools for implementing MIPD in clinical care are available.

- **Future Steps:** Deeper investigation to the relationship between PEG-ASNase PK and treatment-limiting toxicities is necessary to lend veracity to any AAL target and toxicity threshold.

References

1. Huynh V et al. Asparaginase-Associated Toxicities and Hypersensitivity Reactions in Pediatric and Adolescent Down Syndrome Patients with Acute Lymphoblastic Leukemia or Lymphoma. *Blood* 2023; 142 (Supplement 1): 5809. doi: https://doi.org/10.1182/blood-2023-190734
2. Bender C et al. Clinical Utility of Pegaspargase in Children, Adolescents and Young Adult Patients with Acute Lymphoblastic Leukemia: A Review. *Blood Lymphat Cancer.* 2021 Apr 19;11:25-40. doi: 10.2147/BLCTT.S245210.
3. Würthwein G et al. AIEOP-BFM ALL 2009 Asparaginase Working Party. Population Pharmacokinetics of PEGylated Asparaginase in Children with Acute Lymphoblastic Leukemia: Treatment Phase Dependency and Predictivity in Case of Missing Data. *Eur J Drug Metab Pharmacokinet.* 2021 Mar;46(2):289-300. doi: 10.1007/s13318-021-00670-8.
4. Kloos RQH et al. Individualized Asparaginase Dosing in Childhood Acute Lymphoblastic Leukemia. *J Clin Oncol.* 2020;38(7):715-724. doi:10.1200/JCO.19.02292
5. Jasmine Hughes. *mipdtrial:* Simulate MIPD trials. R package version 0.0.0.1. https://github.com/InsightRX/mipdtrial