**Figure S1:** Architecture of MTXPK.org. MTXPK.org (left) is a web application that uses a Web API interface to interact with the end user. Commands are entered by the user then are automatically translated down a layer to the MTXPK business logic, where they undergo command processing. The logic string will call upon the general PKPD modeling engine, which uses a PKPD modeling repository to provide proper Bayesian estimation and simulation of the elimination curves. Processed information is sent back up the layering to the Web API to be presented to the end user. MtxSim (right) follows a similar logic string but lacks the Web API interface to interact publicly with the end user.

API: Application programming interface
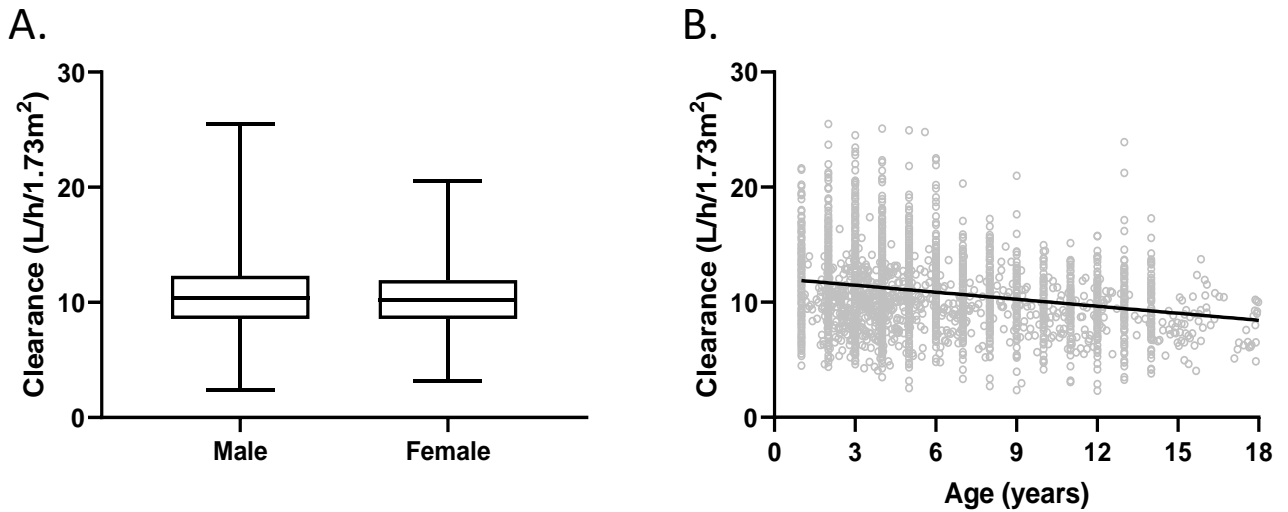PKPD: Pharmacokinetic/Pharmacodynamic

**Figure S2:** Additional covariate analysis. Once clearance was normalized to BSA, there was no significant effect of sex (A) on clearance estimates ($p = 0.39$). Age did not share a significant linear relationship with normalized clearance (B). The line within the box represents the median, the box represents the inter-quartile range, with the whiskers representing the minimum and maximum values. Gray circles depict the estimated clearance values at the given age at the start of treatment. The black line represents a linear regression.
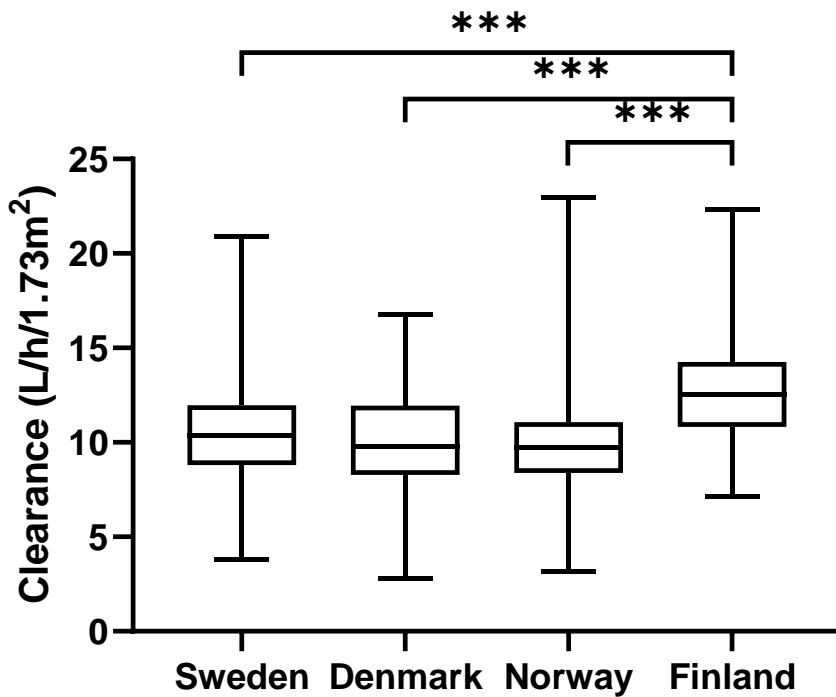
**Figure S3:** Impact of country of treatment on clearance estimates. Finnish patients had an estimated 26% faster clearance compared to Swedish, Danish, and Norwegian patients (p < 0.001). The line within the box represents the median value. The box represents the inter-quartile range with the whiskers representing the minimum and maximum values.
*** corresponds to a p < 0.0001

| Model Name | Trevino [a] (18) | | Kawakatsu [ab] (28) | | NOPHO [b] - 3CP | |
|---|---|---|---|---|---|---|
| CL | 111.9 [c] | ml/min/m² | 12 | L/h/70kg | 11 | L/h/1.73m² |
| | 10.9 [de] | L/h/1.73m² | 10.51 | L/h/1.73m² | | |
| V(1) | - | - | 52 | L/70kg | 16.5 | L/1.73m² |
| | - | - | 45.54 | L/1.73m² | | |
| Q(2) | - | - | 0.1 | L/h/70kg | 0.602 | L/h/1.73m² |
| | - | - | 0.087 | L/h/1.73m² | | |
| V2 | - | - | 5.6 | L/70kg | 4.55 | L/1.73m² |
| | - | - | 4.9 | L/1.73m² | | |
| Q3 | - | - | - | - | 0.111 | L/h/1.73m² |
| | - | - | - | - | | |
| V3 | - | - | - | - | 13.1 | L/1.73m² |
| | - | - | - | - | | |
| Vc | 9 | L/m² | - | - | - | - |
| Ke | 0.7 | hour⁻¹ | - | - | - | - |
| Kcp | 0.08 | hour⁻¹ | - | - | - | - |
| Kpc | 0.11 | hour⁻¹ | - | - | - | - |
| Rationale | Two-compartment model used by St. Jude and mtx.stjude.org | | Two-compartment model with eGFR included in the model | | Novel three-compartment model using NOPHO PK data | |

Note: Ke, Kcp, Kpc units shown as hour$^{-1}$; Vc as $L/m^2$; clearances as $ml/min/m^2$, $L/h/70kg$, $L/h/1.73m^2$; volumes as $L/70kg$, $L/1.73m^2$.

**Table S1:** Model parameters for evaluation

[a] PK parameters were estimated to a normalized $1.73m^2$

[b] Additional population PK model parameters exist for this model

[c] Value was pulled from the mtx.stjude.org website

[d] Calculated value derived from Ke and Vc

[e] $11.61 L/h/1.73m^2$ would be the value if derived from mtx.stjude.org

Cl: Clearance of methotrexate from the central compartment

V1: Volume of distribution of methotrexate in the central compartment

Q2: Inter-compartmental clearance for vascular peripheral compartment

V2: Volume of distribution of methotrexate in the vascular compartment

Q3: Inter-compartmental clearance for the non-vascular compartment

V3: Volume of distribution of methotrexate in the non-vascular compartment

Vc: Volume of distribution of the centralcompartment

Ke: Elimination rate constant from the central compartment

Kcp: Elimination rate constant from the central compartment to peripheral compartment

Kpc: Elimination rate constant from the peripheral compartment to central compartment

CP: Compartment

NOPHO: Nordic Society of Pediatric Hematology and Oncology

| | Population | | Individual | |
|---|---|---|---|---|
| Model | Bias (%) | Prec (%) | Bias (%) | Prec (%) |
| Trevino et al. (18) | -38 | 87 | 0.3 | 20 |
| Kawakatsu et al. (28) | 7 | 60 | 0.4 | 12 |
| NOPHO (3-CP) | -15 | 55 | -0.2 | 9 |

**Table S2:** Evaluations of MTX population PK models
Prec: Precision
CP: Compartment

| Model | Number of: Patients, Concentrations | $R^2$: IPRED vs Observed | $R^2$: PRED vs Observed | RMSE |
|---|---|---|---|---|
| NOPHO | 772, 31672 | 0.99 | 0.83 | 0.91 |
| CCHMC: Lymph | 50, 343 | 0.98 | 0.65 | 0.78 |
| CCHMC: OS | 38, 1336 | 0.99 | 0.90 | 0.99 |
| CCHMC: ALL [29] | 124, 2365 | 0.99 | 0.90 | 0.77 |
| UCSD – Total [28] | 331, 5115 | 0.98 | 0.82 | 1.14 |
| UCSD – ALL | 173, 2651 | 0.96 | 0.80 | 1.14 |
| UCSD – Lymph | 111, 1239 | 0.97 | 0.71 | 1.13 |
| UCSD – Other | 26, 449 | 0.99 | 0.83 | 1.41 |
| UCSD – OS | 21, 776 | 0.99 | 0.95 | 0.95 |
| UCSD – Age > 18 | 154, 1951 | 0.96 | 0.73 | 1.22 |

**Table S3:** External validation of MTXPK.org tool
CCHMC, Lymph: median age, 11.1; median dosage, 3165 mg
CCHMC, OS: median age, 16.1; median dosage, 20000 mg
CCHMC, ALL: median age, 8.23; median dosage, 4700 mg
Lymph: Lymphoma
OS: Osteosarcoma
ALL: Acute lymphoblastic leukemia
UCSD: University of California San Diego
IPRED: Individual Predictive Concentration
PRED: Population Predictive Concentration