

Enhancing Methotrexate Pharmacotherapy in Children with Cancer

Jeffrey S. Barrett, PhD, FCP



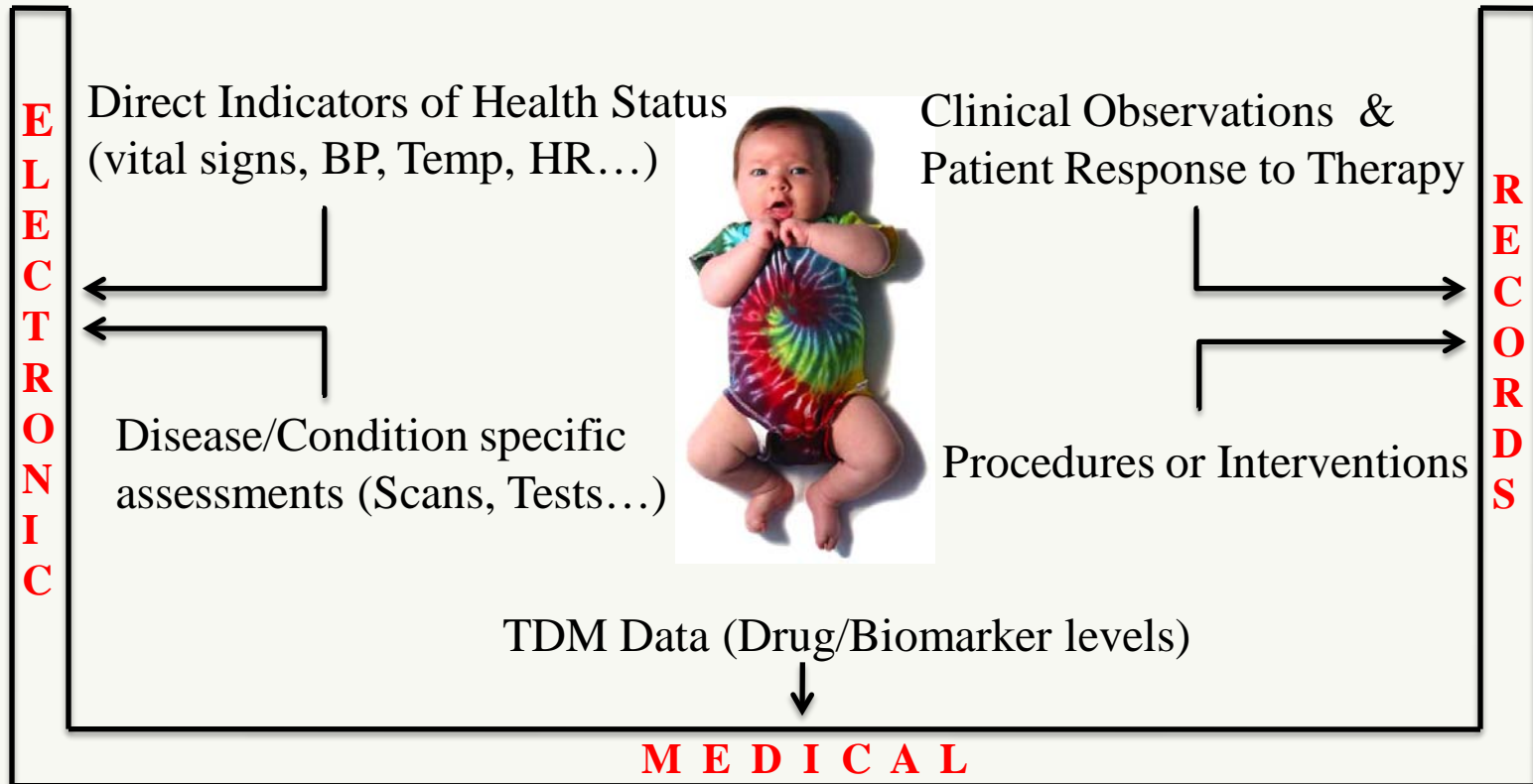
 The Children's Hospital of Philadelphia[®]

A Decision Support System Integrating Real-time PK/PD Modeling
and Simulation with Patient Medical Records

PAGE 2010

Berlin, Germany, June 9-11, 2010

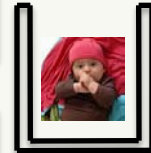
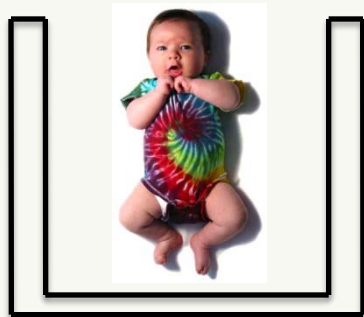
What is the PKB?



Opportunities for PKB

Opportunities for:

- Disease progression
- Population analysis
- Meta analyses . . . correlation



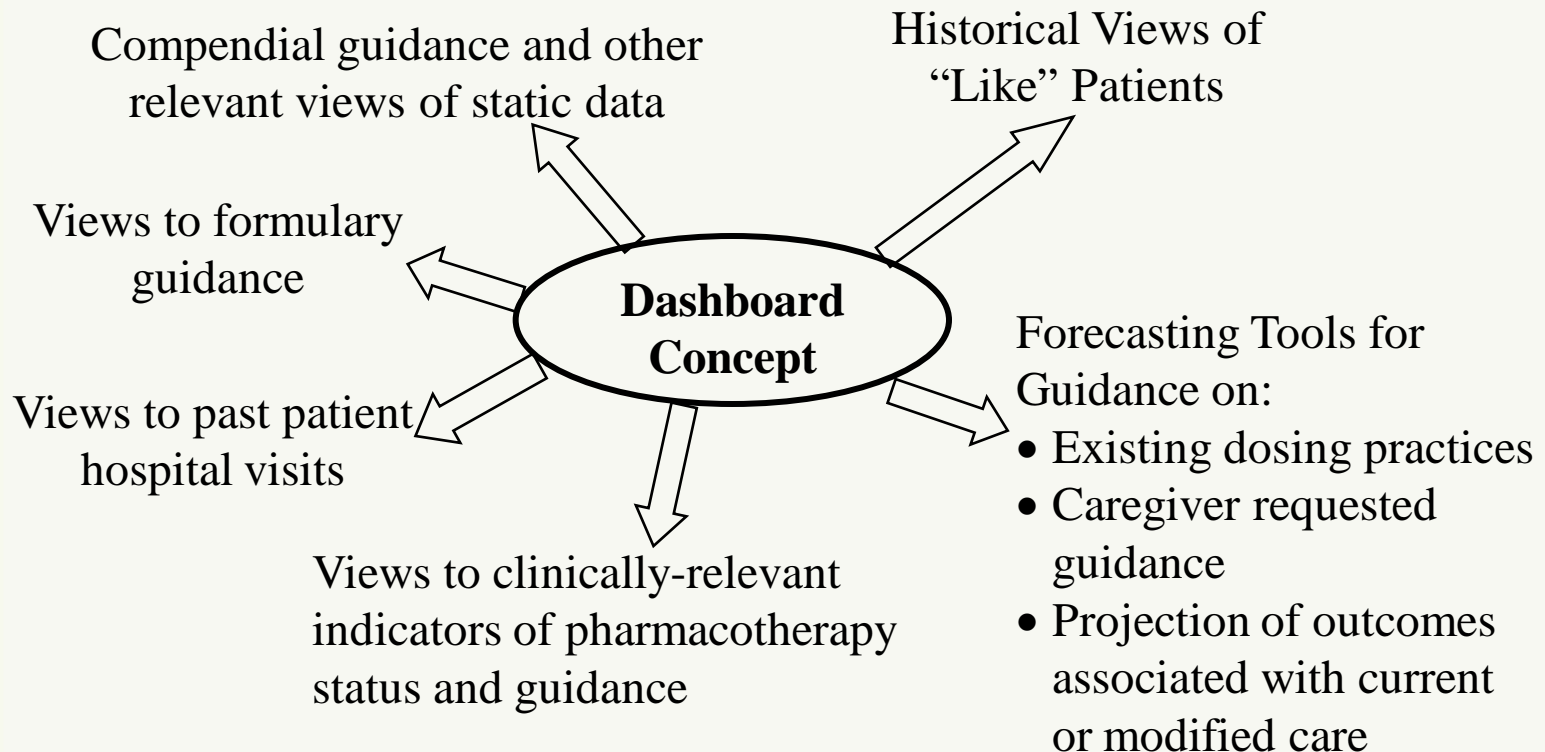
Longitudinal: within patient

Data Mining: across patients



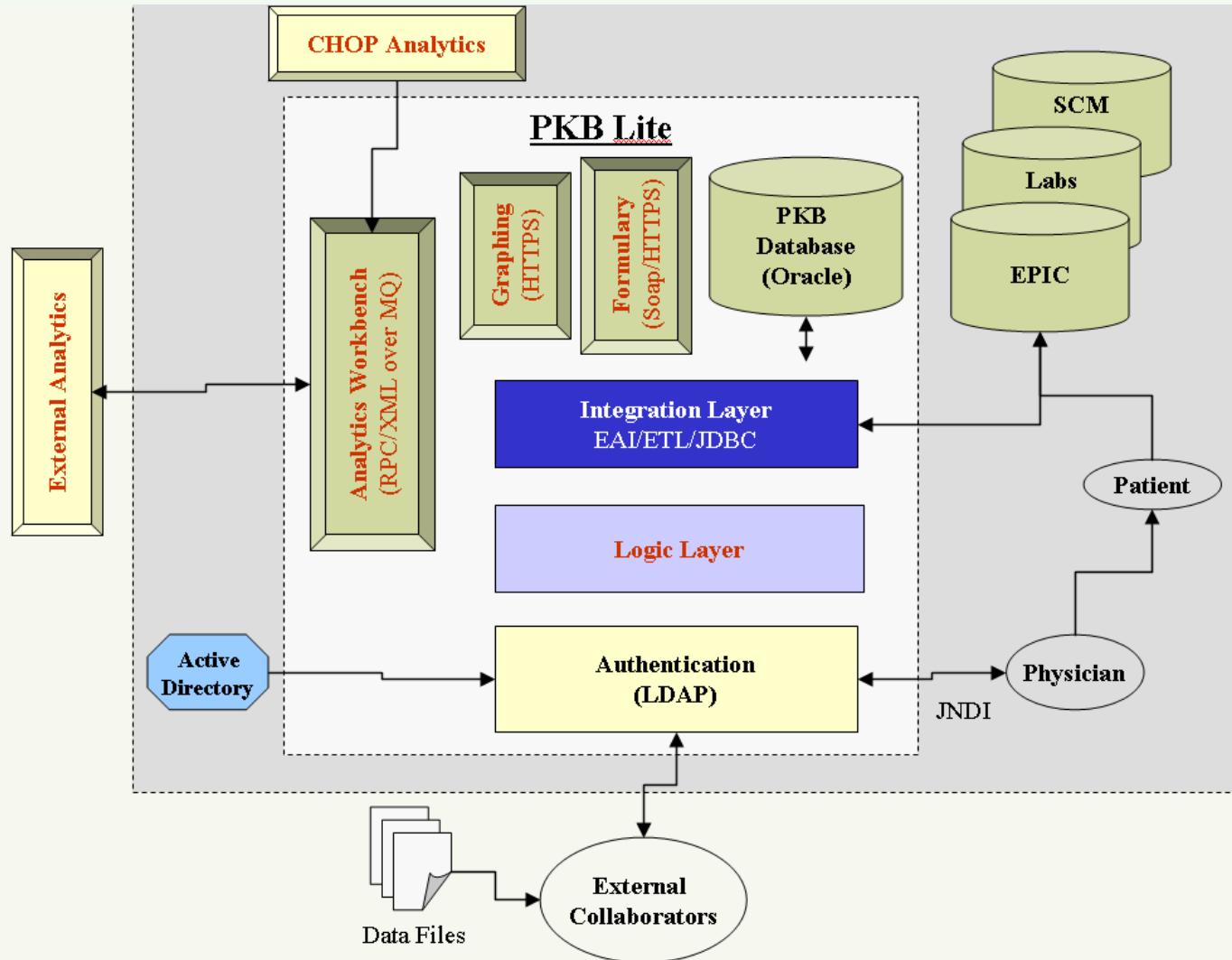
Dashboard Concept

Functionality



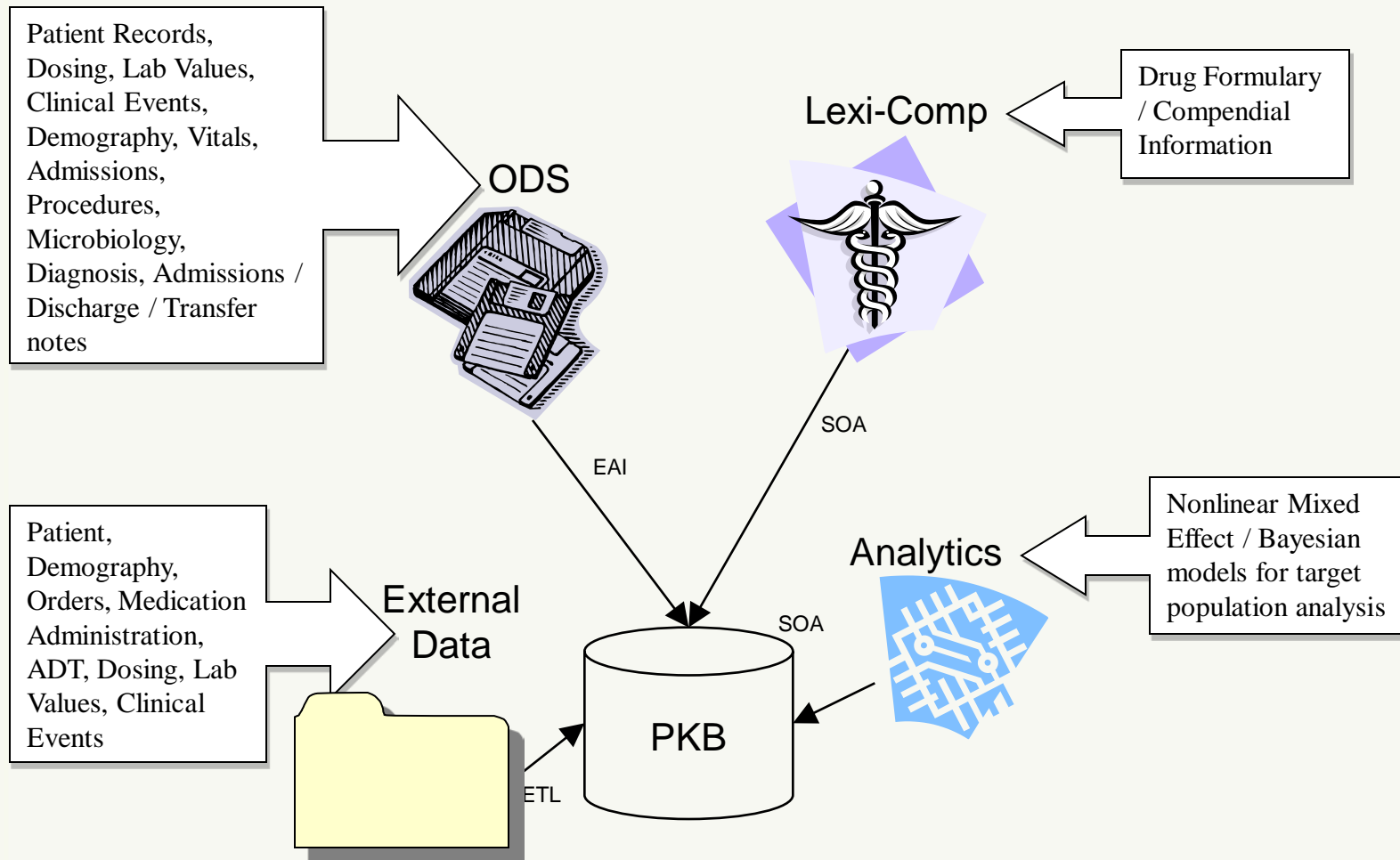
Pediatric Knowledgebase Architecture

- Service-oriented architecture
- Compliant with HL7 CDA



Pediatric Knowledgebase

Source Data / Integration Challenges



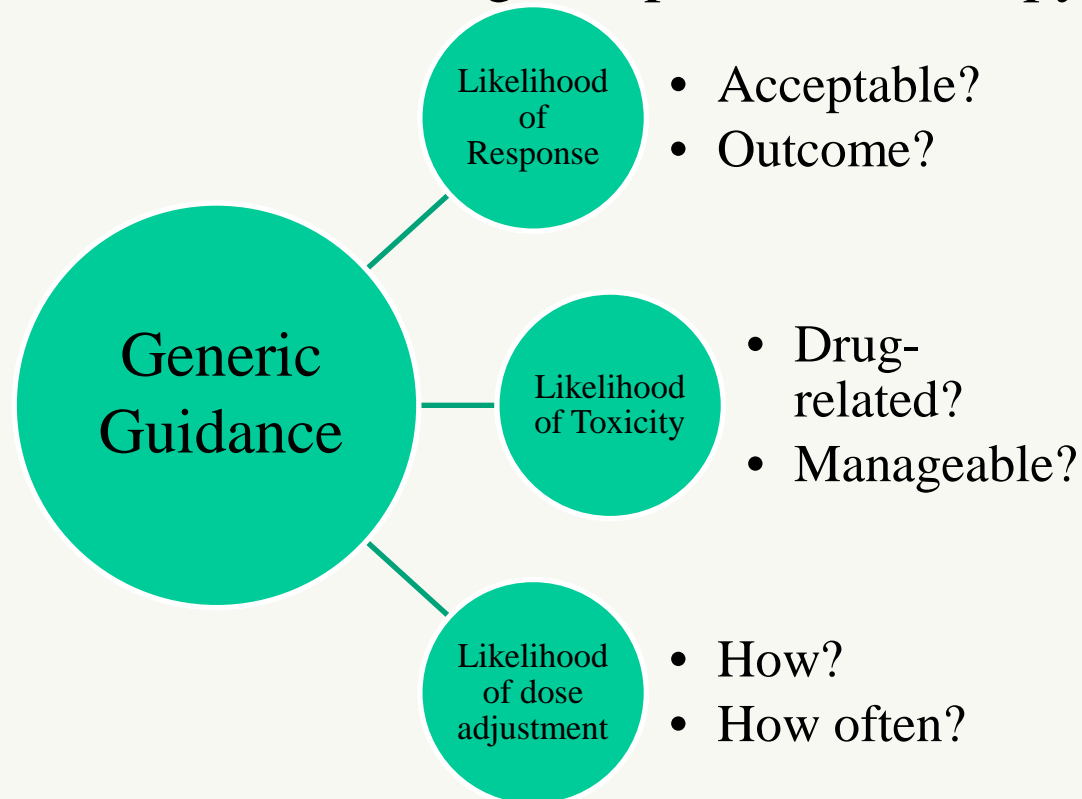
Fundamental Truisms About the Pediatric Caregiver

- The common practice in managing pharmacotherapy may not be the best practice
- The process of collecting EHR data may not ensure that relevant patient response(s) are being captured / assessed
- Even if you deliver exactly what the caregiver wants, there is no guarantee that they will use it.



The Patient Presents . . .

- Data collected to diagnose patient
- Value of information to guide pharmacotherapy?



The Ultimate Customer

Who are we treating with MTX?

Abstracted from Electronic Medical Records . . .

Age: 16 Months

Sex: Male

Race: Asian

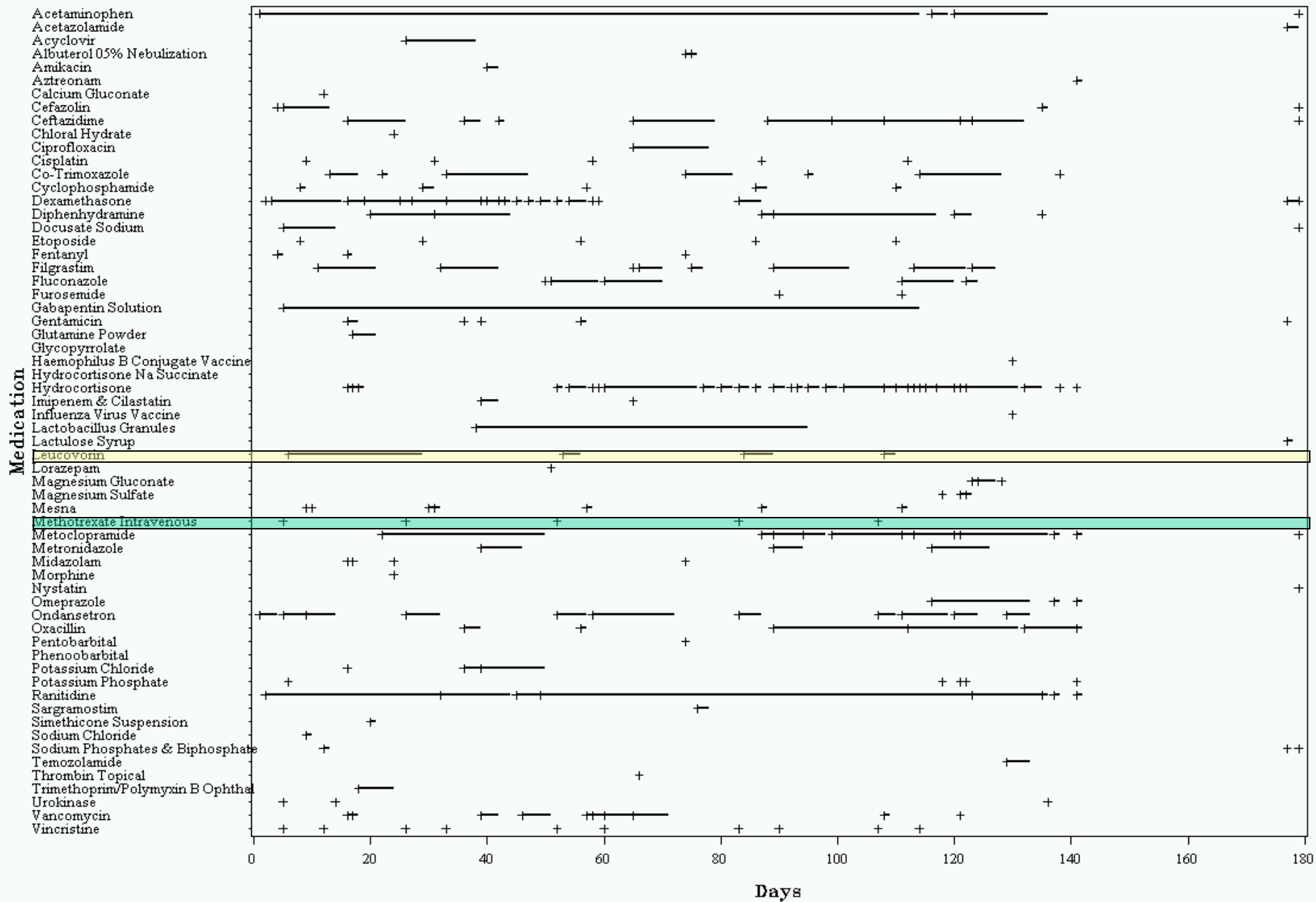
WT: 8.73 kg

HT: 76 cm

Diagnosis: Patient was diagnosed with Medulloblastoma with metastases to the spinal cord. Other complications include tumor, flaccid lower extremity diplegia, amblyopia, hearing loss, and oral aversion.



Co-Medication in a Single Pediatric Oncology Patient



MTX

Administration

- Urine pH must be ≥ 7
- 25 mg/ml solution in Dextrose 5% in water (D5W)
- Maximum absolute dose: 20g

MTX TDM

- Begins 24 hours after the start of MTX infusion
- Results plotted on protocol-specific nomogram
- Continues daily until MTX level $\leq 0.1 \mu\text{M}$

MTX Cleared

- MTX level $\leq 0.1 \mu\text{M}$
- Patient can be discharged

Before Administration

0 – 24 Hours

24 Hours -
Discharge

Prehydration

- 750 ml/m² of D5 0.22% NaCl with 40 mEq/L NaHCO₃ is given over 1 hour
- If urine pH < 7, 0.5 mEq/L NaHCO₃ is given over 30 minutes. Repeated if urine pH is < 7 after 1 hour

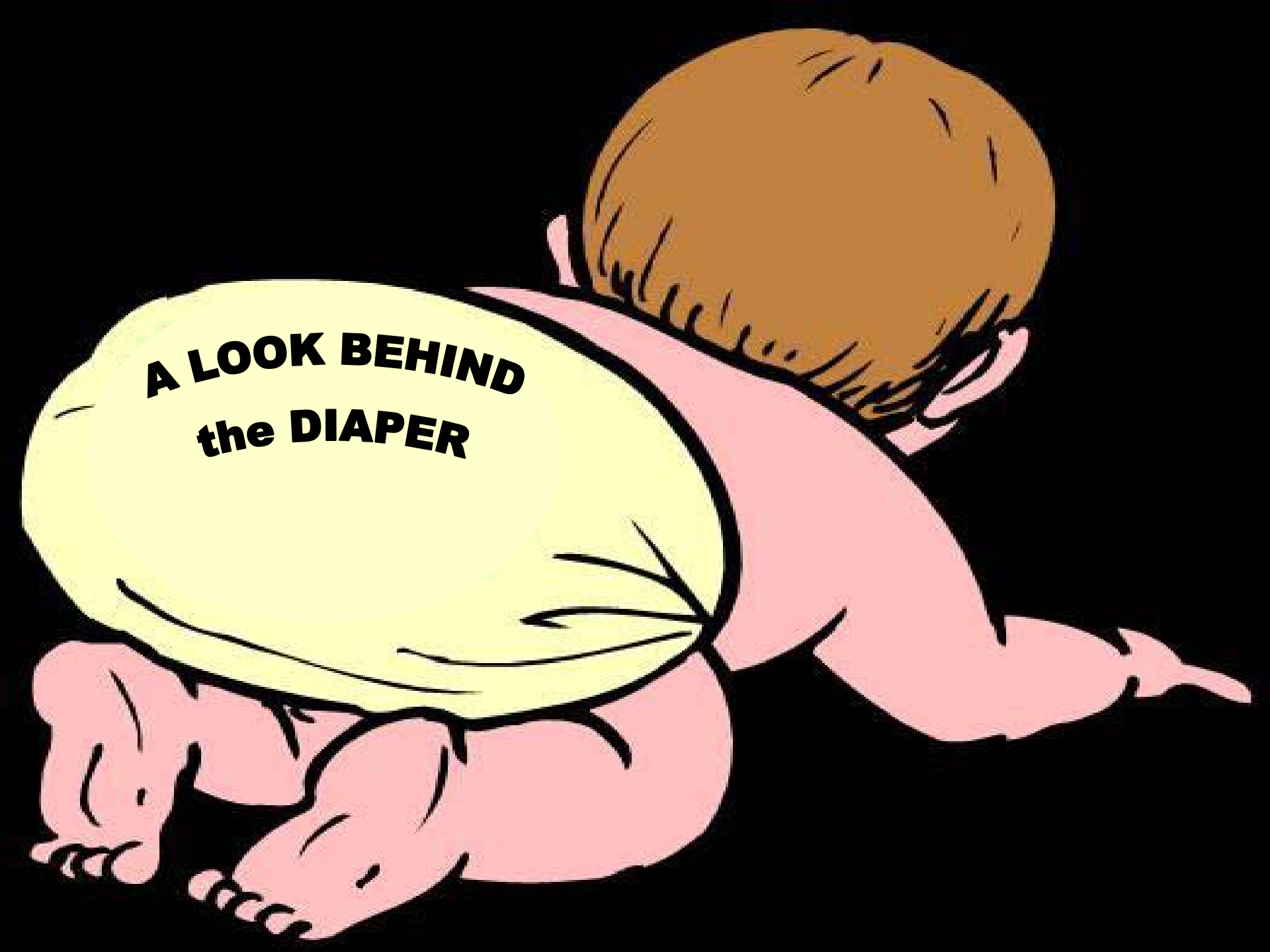
Continuing Hydration

- D5 0.22% NaCl with 40 mEq/L NaHCO₃ at 100 ml/m²/hr
- Urine pH is measured every 8 hours. If pH < 7, 10 ml/kg hydration fluid is given over 30 minutes and pH measurements are taken
- Lasts until MTX level $\leq 0.1 \mu\text{M}$

LVR

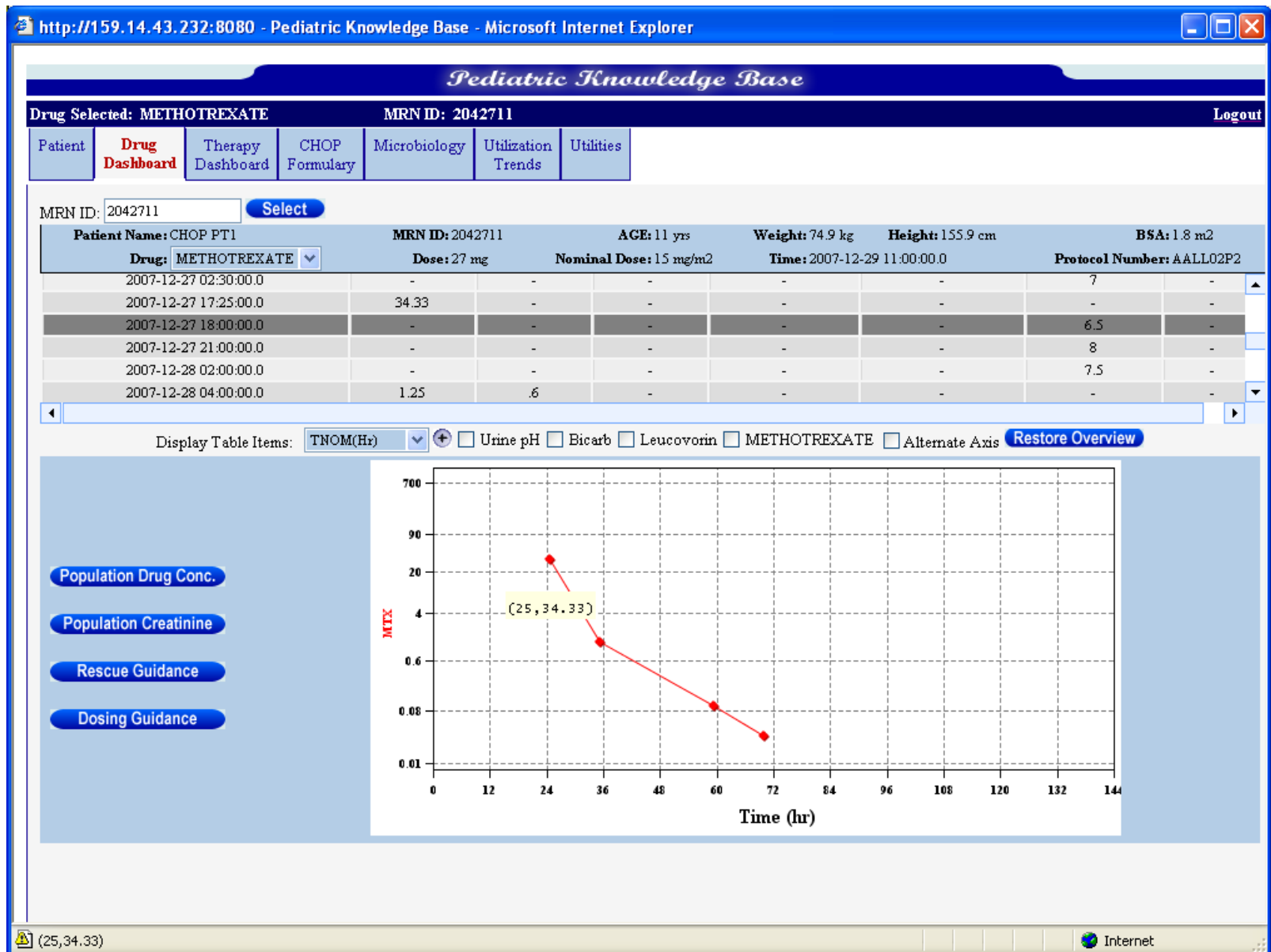
Administration

- LVR starts 24 - 42 hours after the start of MTX infusion as 15 mg/m² IVSS over 15 minutes, every 6 hours
- Dose can be modified based on protocol-specific nomogram because of excretion delay
- Lasts until MTX level $\leq 0.1 \mu\text{M}$



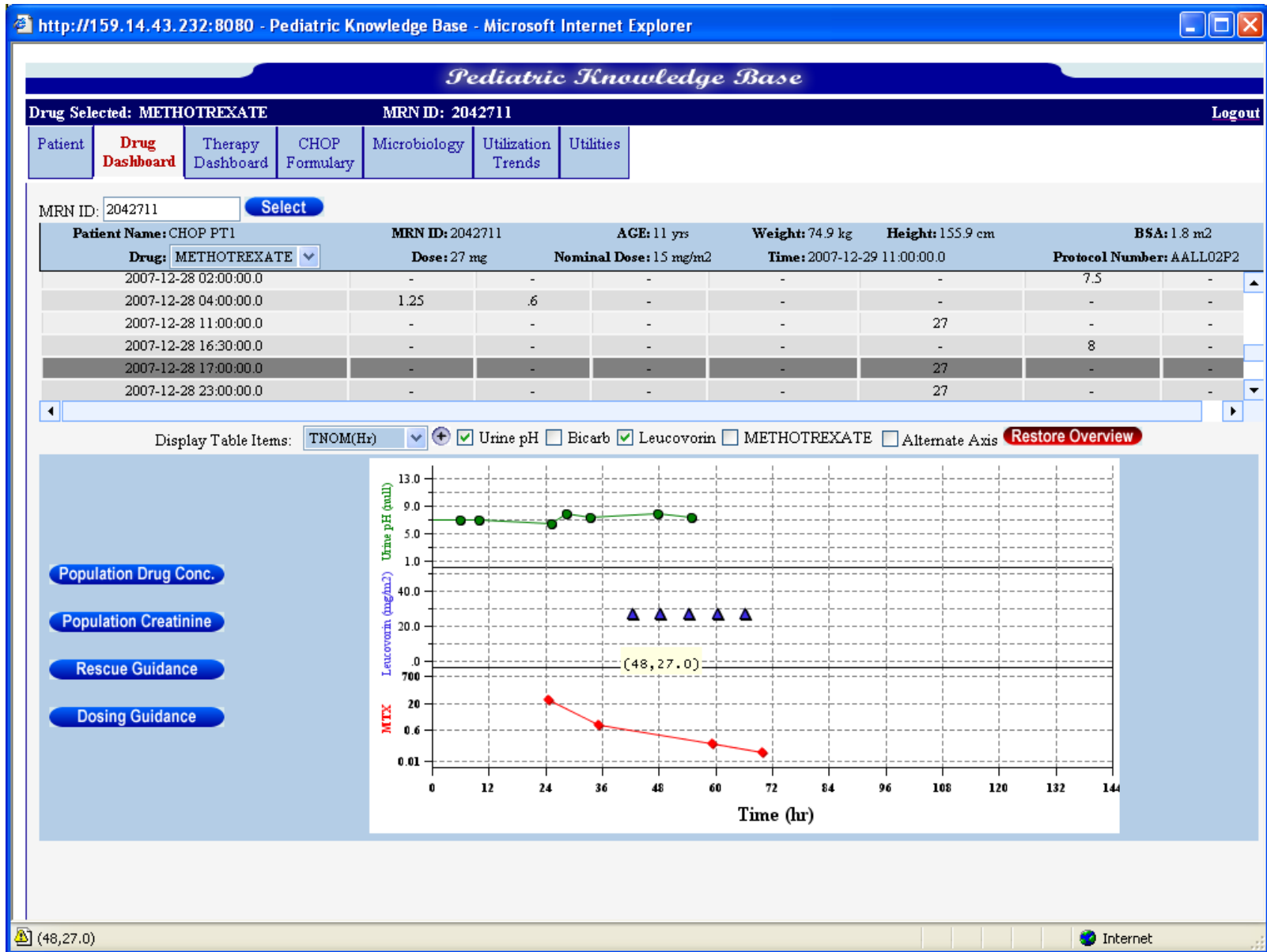
**A LOOK BEHIND
the DIAPER**

MTX Drug Exposure



The rows highlight when you mouse over a concentration point

A Broader Patient View with Clinical Biomarkers



Views to Historical Controls

http://159.14.43.232:8080 - Pediatric Knowledge Base - Microsoft Internet Explorer

Pediatric Knowledge Base

Drug Selected: METHOTREXATE MRN ID: 2042711 [Logout](#)

[Patient](#) **Drug Dashboard** [Therapy Dashboard](#) [CHOP Formulary](#) [Microbiology](#) [Utilization Trends](#) [Utilities](#)

MRN ID: [Select](#)

Patient Name: CHOP PT1	MRN ID: 2042711	AGE: 11 yrs	Weight: 74.9 kg	Height: 155.9 cm	BSA: 1.8 m2
Drug: METHOTREXATE	Dose: 27 mg	Nominal Dose: 15 mg/m2	Time: 2007-12-29 11:00:00.0	Protocol Number: AALL02P2	
2007-12-27 18:00:00.0	-	-	-	-	6.5
2007-12-27 21:00:00.0	-	-	-	-	8
2007-12-28 02:00:00.0	-	-	-	-	7.5
2007-12-28 04:00:00.0	1.25	.6	-	-	-
2007-12-28 11:00:00.0	-	-	-	27	-
2007-12-28 16:30:00.0	-	-	-	-	8

Display Table Items: TNOM(Hr) Urine pH Bicarb Leucovorin METHOTREXATE Alternate Axis [Restore Overview](#)

[Population Drug Conc.](#)

[Population Creatinine](#)

[Rescue Guidance](#)

[Dosing Guidance](#)

Comparison across CHILDREN, MALE for Dose = 15 mg/m2

Time (hr)	Population Creatinine (mg/dL)	Population Drug Conc. (mg/dL)
0	3.5	0.5
24	3.7	0.6
48	3.7	0.6
72	4.4	0.6
96	5.5	0.6
120	5.5	0.6
144	5.5	0.6
168	5.5	0.6
192	5.5	0.6
216	5.5	0.6
240	5.5	0.6
264	5.5	0.6
288	5.5	0.6
312	4.4	0.6

4.4

4.4

Internet

Rescue Guidance

http://159.14.43.232:8080 - Pediatric Knowledge Base - Microsoft Internet Explorer

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Pediatric Knowledge Base

Drug Selected: METHOTREXATE MRN ID: 1084261 [Logout](#)

[Patient](#)
 [Drug Dashboard](#)
 [Therapy Dashboard](#)
 [CHOP Formulary](#)
 [Microbiology](#)
 [Utilization Trends](#)
 [Utilities](#)

MRN ID: [Select](#)

Patient Name:	MRN ID:	AGE:	Weight:	Height:	BSA:
PATIENT 3 CHOP	1084261	15 yrs	46.2 kg	171.5 cm	1.48 m ²

Drug:	Dose:	Nominal Dose:	Time:	Protocol Number:
METHOTREXATE	12000 mg	8090 mg/m ²	2006-07-03 21:00:00.0	(L) ANHL01P1
2006-07-06 15:00:00.0	-	-	-	-
2006-07-06 16:00:00.0	-	-	-	8
2006-07-06 21:00:00.0	-	-	-	-
2006-07-07 03:00:00.0	-	-	-	22
2006-07-07 04:00:00.0	0.11	0.6	-	8
2006-07-07 09:00:00.0	-	-	-	22
				7.5

Display Table Items: Urine pH Bicarb Leucovorin METHOTREXATE Alternate Axis [Restore Overview](#)

[Population Drug Conc.](#)

[Population Creatinine](#)

[Rescue Guidance](#)

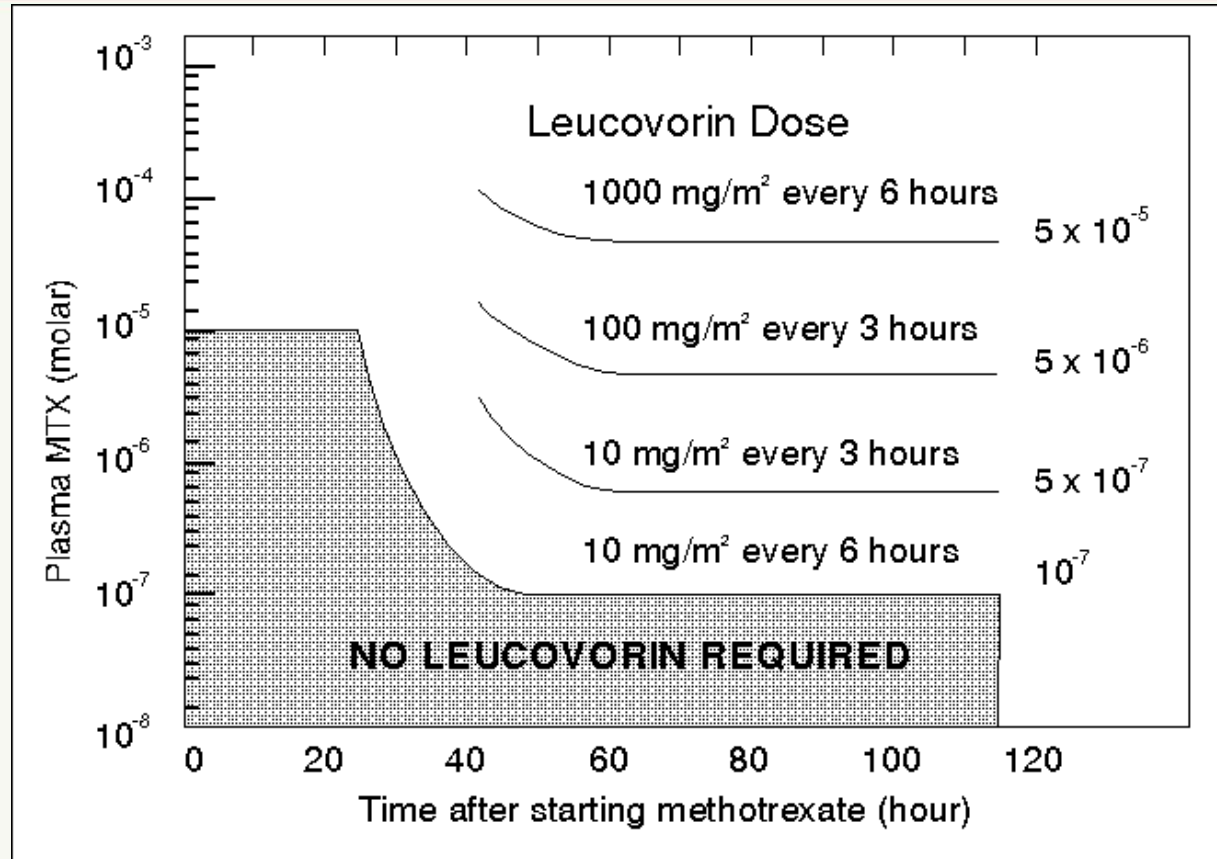
[Dosing Guidance](#)

1000 mg/m² - q₆

 Internet

Therapeutic Window

Leucovorin Rescue



Current procedure is to photocopy “master” nomogram for specific protocols and hand plot individual data

Dosing Guidance

http://159.14.43.232:8080 - Pediatric Knowledge Base - Microsoft Internet Explorer

Pediatric Knowledge Base

Drug Selected: METHOTREXATE MRN ID: 1084261 [Logout](#)

[Patient](#)
[Drug Dashboard](#)
[Therapy Dashboard](#)
[CHOP Formulary](#)
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[Utilization Trends](#)
[Utilities](#)

MRN ID: 1084261 [Select](#)

Patient Name:	MRN ID:	AGE:	Weight:	Height:	BSA:
PATIENT 3 CHOP	1084261	15 yrs	46.2 kg	171.5 cm	1.48 m ²

Drug:	Dose:	Nominal Dose:	Time:	Protocol Number:
METHOTREXATE	12000 mg	8090 mg/m ²	2006-07-03 21:00:00.0	(L) ANHLO1P1

Time	MTX Conc (Micro M)	Urine pH	Bicarb	Leucovorin	METHOTREXATE	Alternate Axis
2006-07-06 15:00:00.0	-	-	-	-	-	-
2006-07-06 16:00:00.0	-	-	-	-	-	-
2006-07-06 21:00:00.0	-	-	-	-	-	-
2006-07-07 03:00:00.0	-	-	-	-	-	-
2006-07-07 04:00:00.0	0.11	0.6	-	-	-	-
2006-07-07 09:00:00.0	-	-	-	-	-	-

Display Table Items: TNOM(Hr) Urine pH Bicarb Leucovorin METHOTREXATE Alternate Axis [Restore Overview](#)

[Population Drug Conc.](#)

[Population Creatinine](#)

[Rescue Guidance](#)

[Dosing Guidance](#)

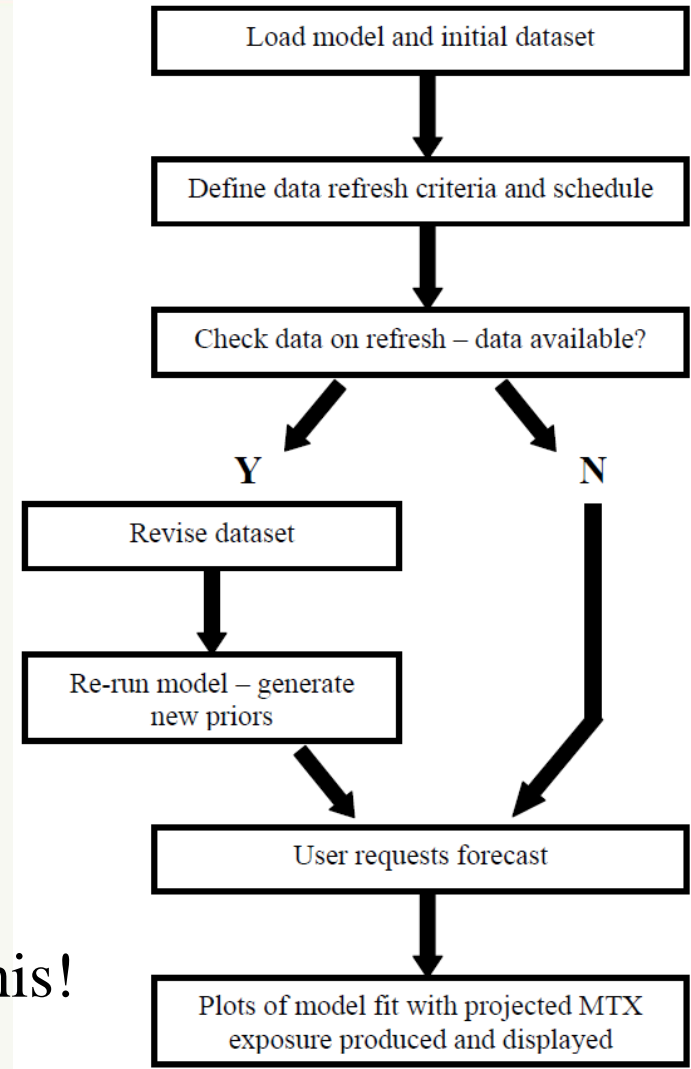
Time (hr)	Observed MTX Conc (Micro M)	LVR 1000 mg/m ² - q6 (Predicted)	LVR 100 mg/m ² - q3 (Predicted)	LVR 10 mg/m ² - q3 (Predicted)	LVR 10 mg/m ² - q6 (Predicted)
24	~30	-	~20	~10	~10
36	~10	-	~10	~10	~10
48	-	~100	~10	~10	~10
60	~3	-	~5	~10	~10
84	~0.1	-	~5	~10	~10
96	~0.05	-	~5	~10	~10

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Forecasting MTX Exposure

Model and Forecasting Routine

- Population-based PK model specified in NONMEM
- Bayesian forecasting (simulation) model for individualized MTX exposure prediction (also in NONMEM)



We could do a lot more than this!



Model Development Progression

- | | |
|------------------------------------|---|
| Structural Model(s) | <ul style="list-style-type: none">• Literature, drug-specific properties; data in adults, animals, etc |
| Population Model | <ul style="list-style-type: none">• Targeted studies in specific patient populations |
| Patient Individualization Model(s) | <ul style="list-style-type: none">• TDM data; observational studies; studies with linkages to outcomes, lifestyle and patient management |
| Forecasting Model(s) | <ul style="list-style-type: none">• DSS interface; prospective evaluation; emphasis on prediction |
| Operational Model | <ul style="list-style-type: none">• Validation of performance under typical usage conditions: missing covariates; time and dose uncertainty; range checking considerations, etc |



MTX - TDM Model

- Serum creatinine and age were significant predictors of CL, reducing the BSV of CL approximately 19.5%.
- Height was a significant predictor of Vc, reducing the BSV of Vc approximately 18.5%.

Figure 1: Observations vs. Population predictions

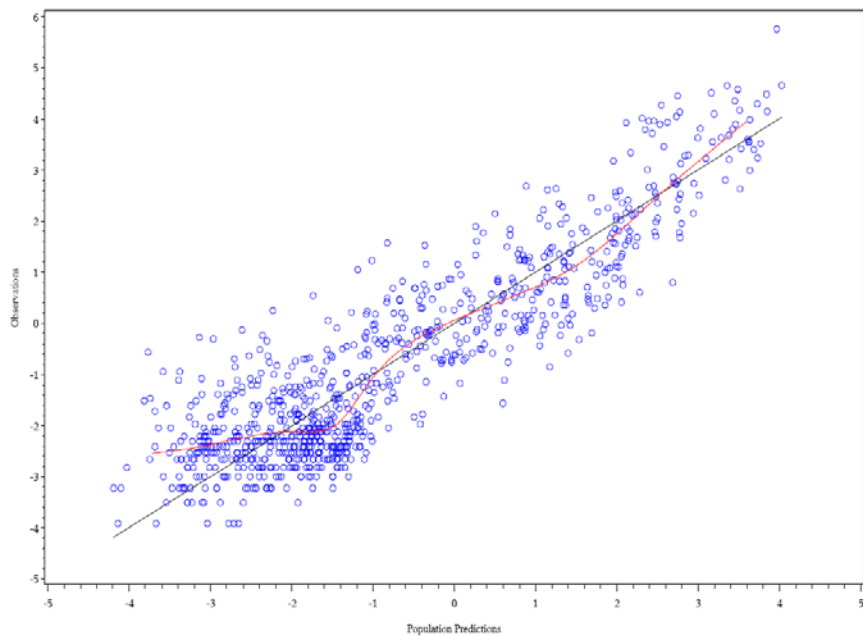
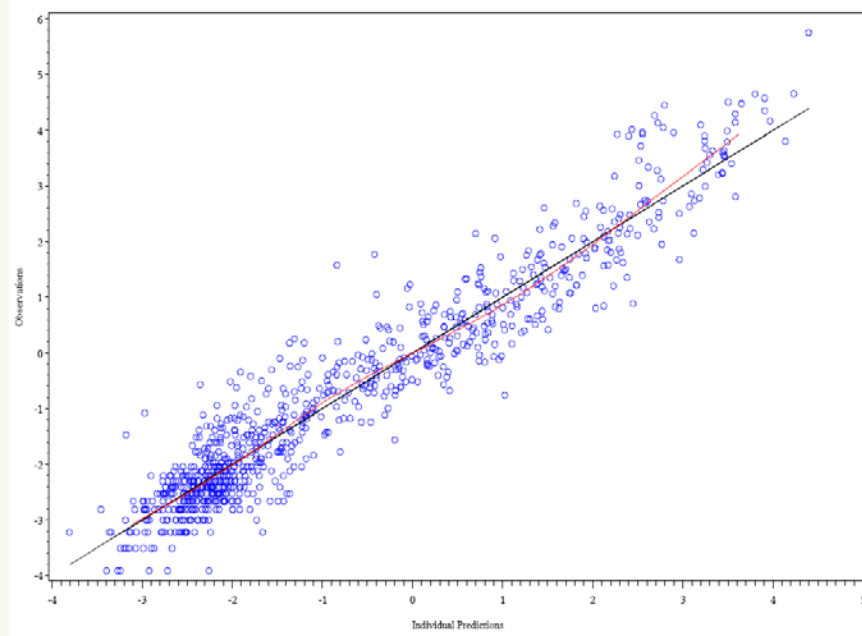
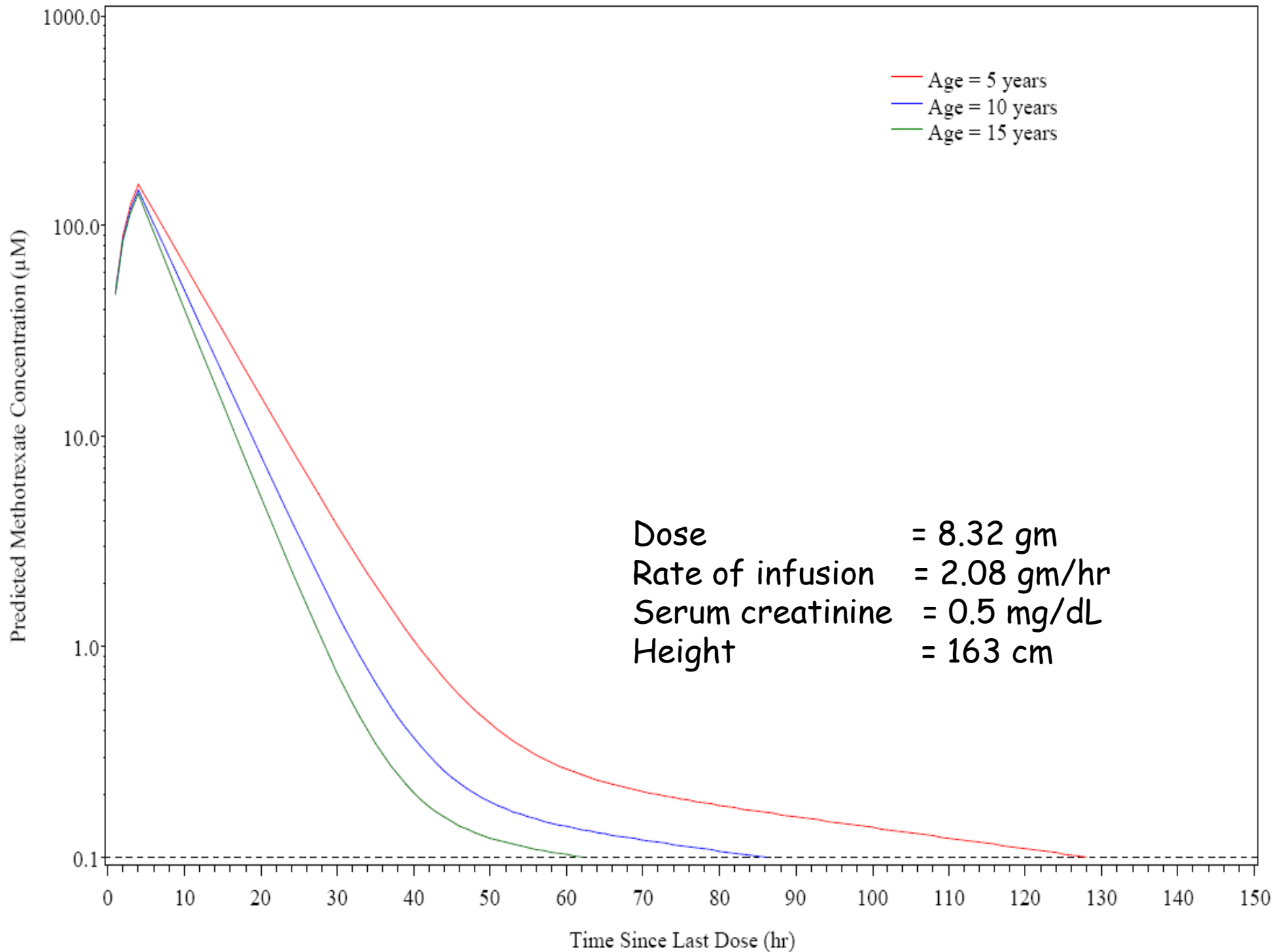
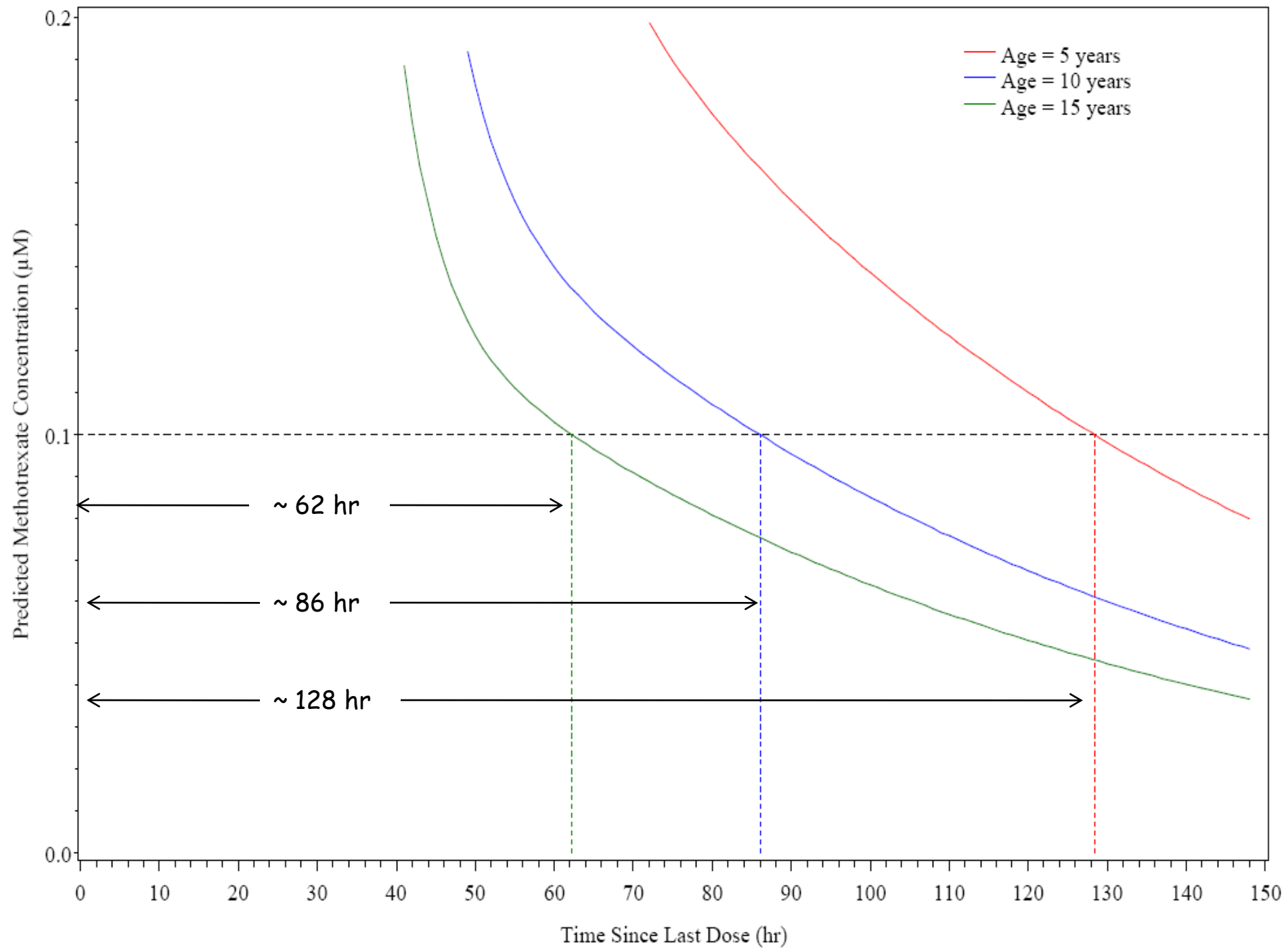


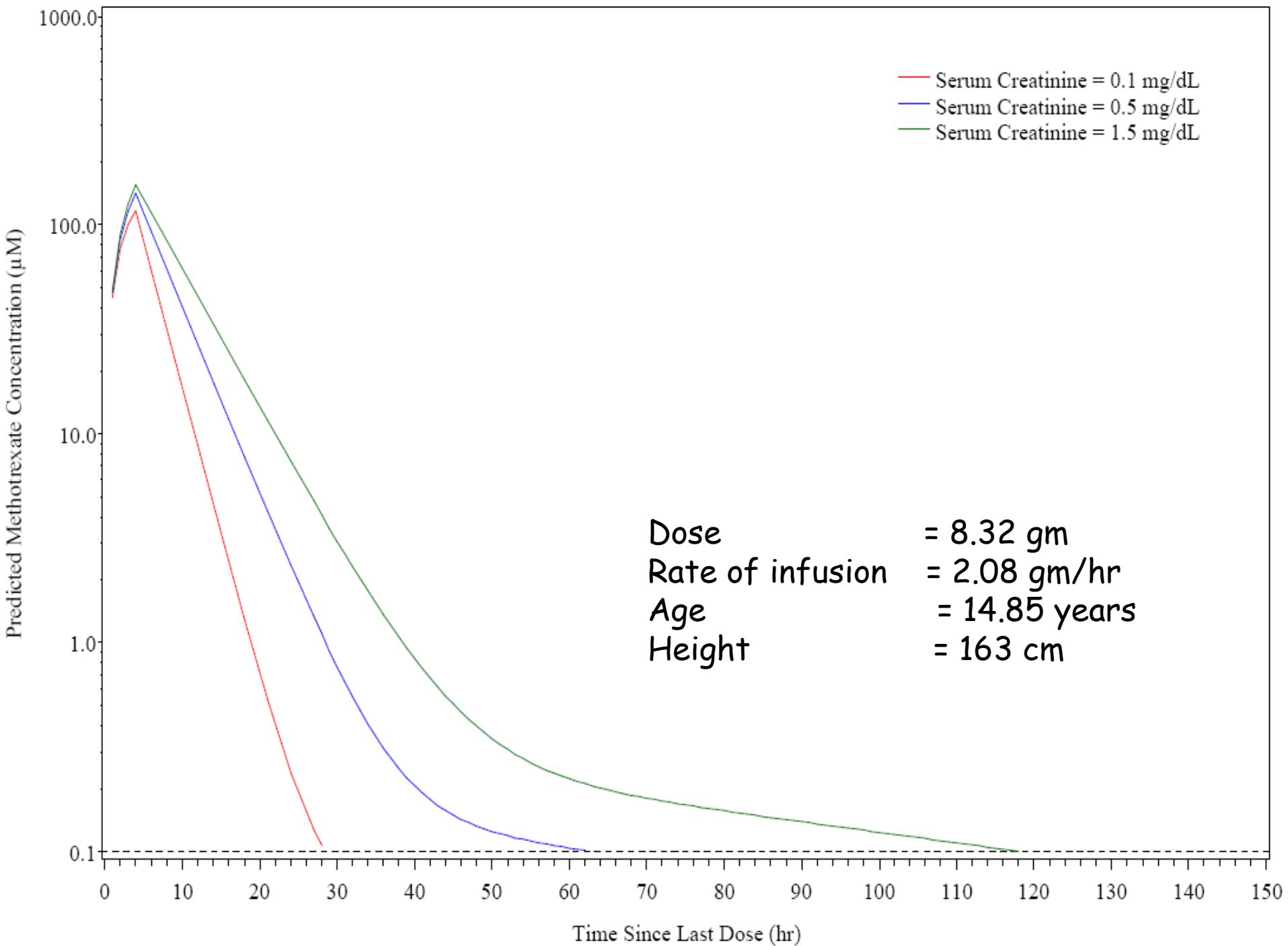
Figure 2: Observations vs. Individual predictions

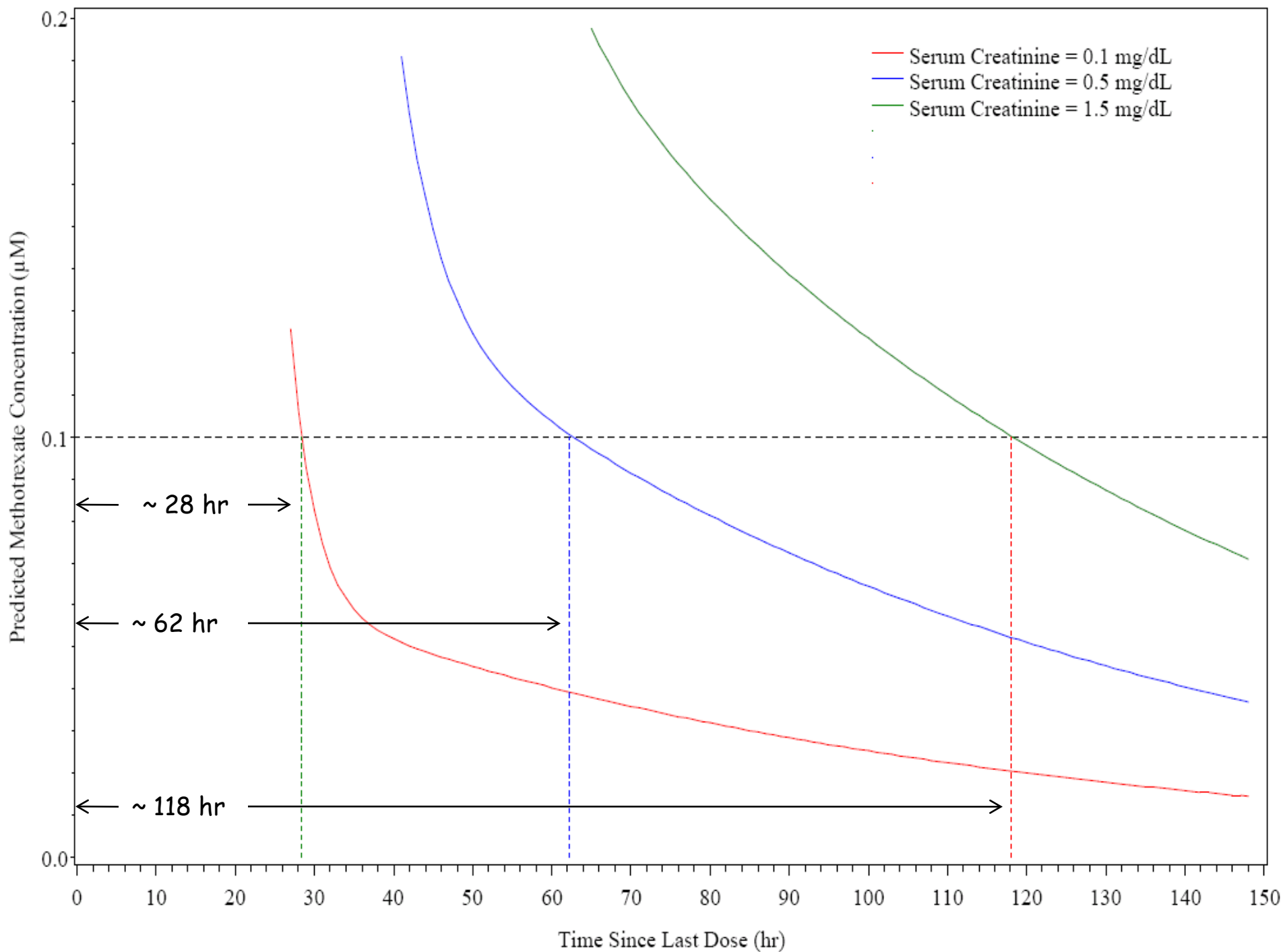


Parameter	Population Mean (%RSE)		BSV (%CV) (%RSE)	
	Base Model	Final Model	Base Model	Final Model
CL (L/hr)	6.96 (15.4)	8.17 (13.1)	35.6 (21.4)	28.7 (23.2)
Vc (L)	33.3 (20.3)	39.8 (17.7)	47.2 (23.4)	38.5 (29.8)
Q (L/hr)	0.123 (25)	0.126 (24.1)	-	-
Vp (L)	9.7 (28.9)	10.7 (27.8)	-	-
Power for SCr on CL	-	-0.279 (29.7)	-	-
Power for age on CL	-	0.331 (12.1)	-	-
Power for height on Vc	-	1.1 (13.3)	-	-
Residual variability	0.373 (12.7)	0.342 (10.4)	-	-







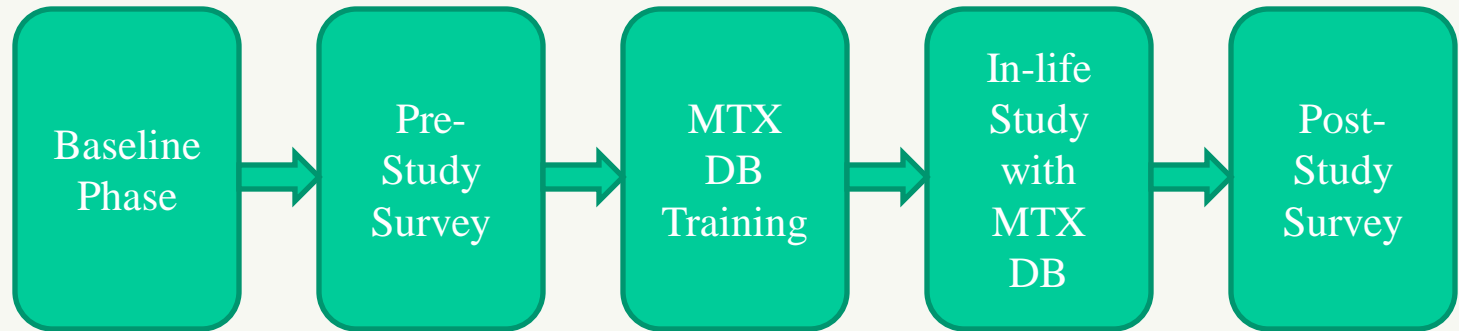


Methotrexate Pilot

By Study Phase Evaluations

Not yet live
with EHR
data

Source data
from SCM,
EPIC and
EDW (egate
HL7 feed)
into PKB
data model



- MTX management assessment from historical controls
 - Indications and usage
 - Toxicity (frequency and severity)
 - Dosing adjustments and patterns
 - ADR frequency and severity

- Pediatric caregiver assessment of MTX management in children with cancer
 - % well-managed
 - % ADRs associated with dosing
 - % avoidable toxicity
 - etc

- Hands-on user training and scenario testing
 - Mock patient scenarios
 - Function testing - SOPs

- MTX management with access to MTX DB (duration of in-life TDB)
 - User tracking of DB functionality (function and duration recorded per session)
 - Objective metrics: LOS, # toxicities, #ADRs, adjustments recommended, etc
 - Subjective metrics: usability, patient outcomes

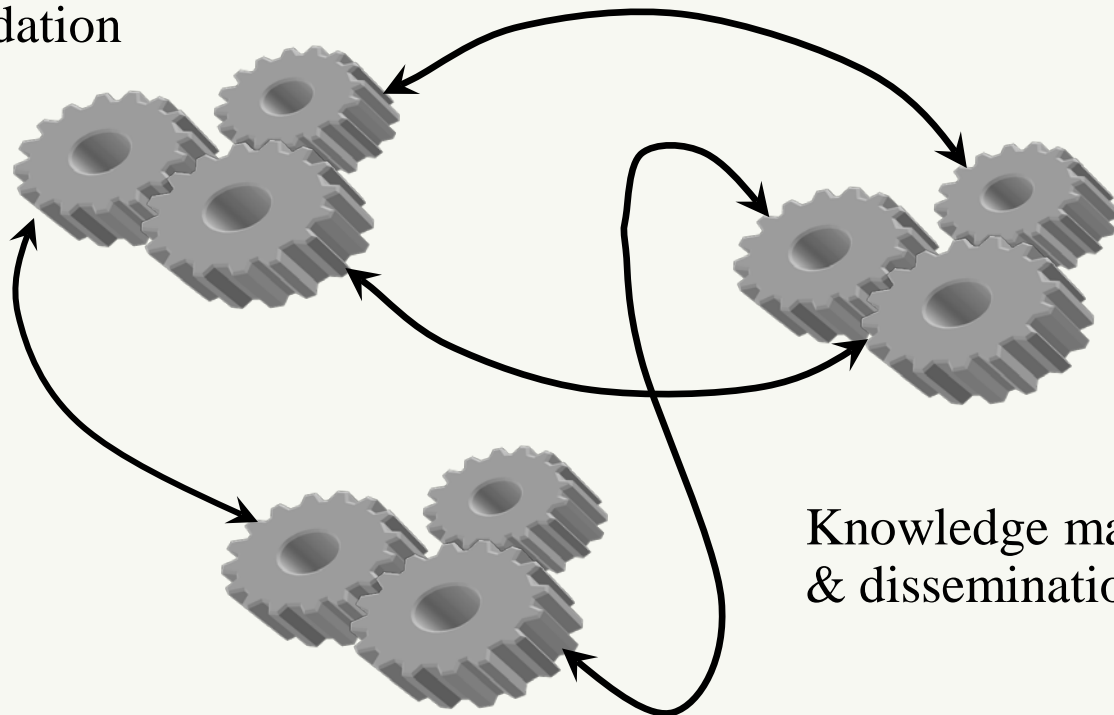
- Caregiver assessment with access to MTX DB
 - Value of MTX DB
 - % well-managed
 - % ADRs associated with dosing
 - % avoidable toxicity
 - etc



Vision for PKB

Interacting Life Cycles

Knowledge generation & validation



Knowledge management & dissemination

Dashboard implementation & evaluation



The Vision for PKB

- An international consortium of pediatric centers of excellence that support and drive the development of the PKB
 - PKB-lite development for clinics, institutions without EMRs and small physician offices
 - Global connectivity that accommodates regional and global best practices with guidance options
 - Guidance for developing countries / institutions

