Individualised dosing for HSCT conditioning

Precision dosing, Populaton PK Models,

Pharmacogenomics and Bayesian Forecasting Software

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August 2026

Queensland Government

PRECISION MEDICINE

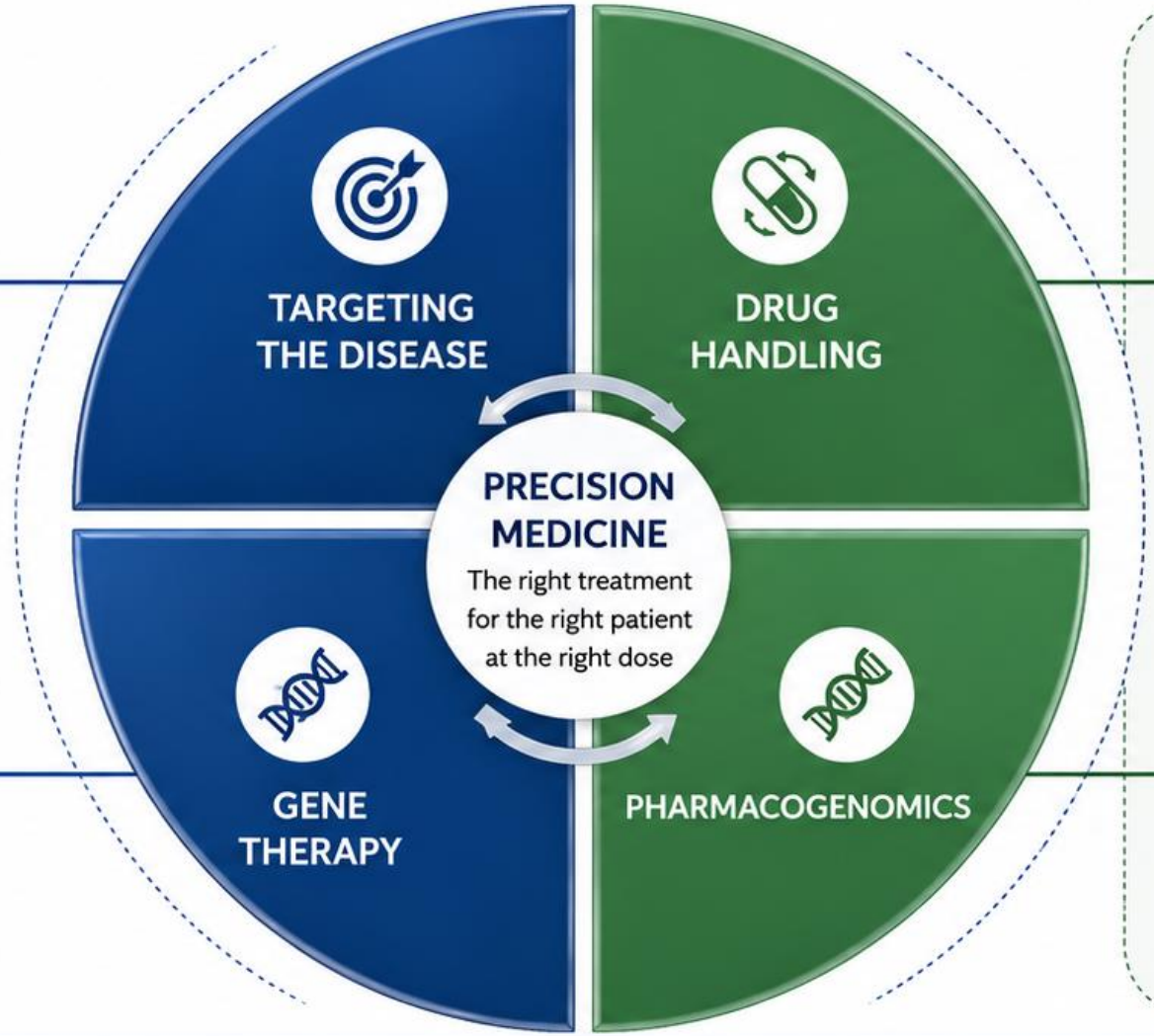
An integrated approach to understand disease, optimise treatment and improve outcomes for every individual

TARGETING THE DISEASE

- Clinical trials
- Poor/Good prognostic factors
- Individual targetable mutations
- Personalised medicine at a cellular level

GENE THERAPY

- Replace faulty gene
- Block activity of a faulty gene
- Emerging therapies



INDIVIDUALISED DOSING

(THE RIGHT DOSE FOR EACH PATIENT)

DRUG HANDLING

- Organ function
- Drug interactions
- ECMO
- Renal replacement therapy
- Bayesian Forecasting Software

PHARMACOGENOMICS

- Identify patients at risk of toxicities from medicines
- Identify patients at risk of failure of therapy
- Individualised dosing based on genetic profile

ALL FOUR PILLARS WORK TOGETHER TO DELIVER PRECISION MEDICINE.

Drug handling and pharmacogenomics provide the foundation for **individualised dosing – ensuring the right dose for each patient.**

We individualise the transplant. Why not the conditioning?

We individualise many aspects of stem cell transplantation …

Who receives a transplant

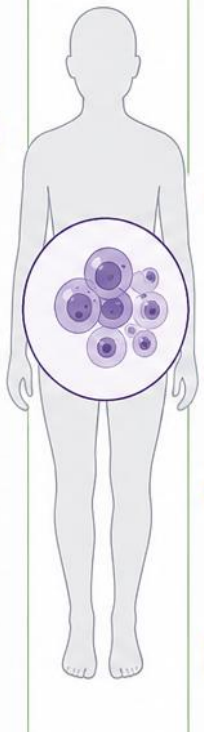
- Disease type
- Disease risk
- Prior therapies
- Performance status and comorbidities

Donor selection

- HLA match
- Donor type (MRD, MUD, Haplo)
- Donor age and sex
- CMV serostatus

Graft manipulation

- T-cell depletion
- CD34+ selection
- Cell dose



Supportive care (and beyond)

- CMV risk → letermovir
- Prior fungal infection → fungal prophylaxis
- VOD risk → Urso ± defibrotide
- Monitoring for viral reactivation (e.g. CMV, EBV, HHV-6, BK virus, adenovirus)
- GVHD risk → prophylaxis strategy

We individualise to maximise benefit and minimise harm

… yet conditioning chemotherapy dosing remains largely based on size alone

Conditioning chemotherapy dosing

Primarily weight or body surface area

Despite:

- Wide interpatient variability in drug exposure
- Narrow therapeutic windows

Toxicity | Target | Relapse

- We accept some mortality due to treatment-related toxicity

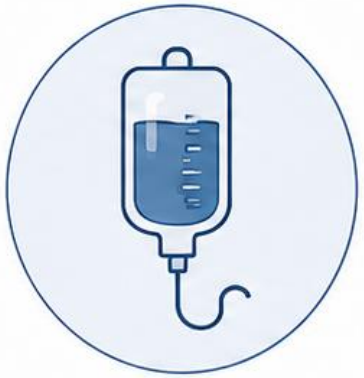
We should individualise conditioning chemotherapy dosing too

Moving from "one size fits all" dosing to exposure-guided, patient-centred therapy has the potential to improve outcomes beyond what we currently achieve.

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; VOD, veno-occlusive disease; Urso, ursodeoxycholic acid; GVHD, graft-versus-host disease.

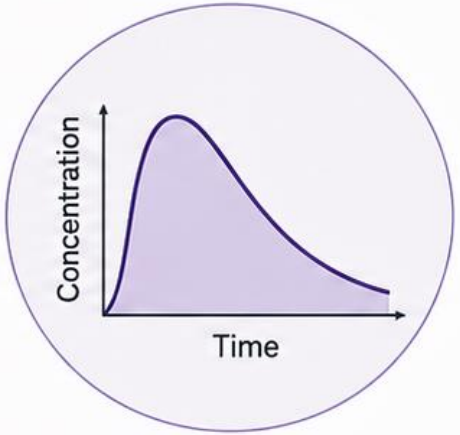
The missing variable: exposure

DOSE



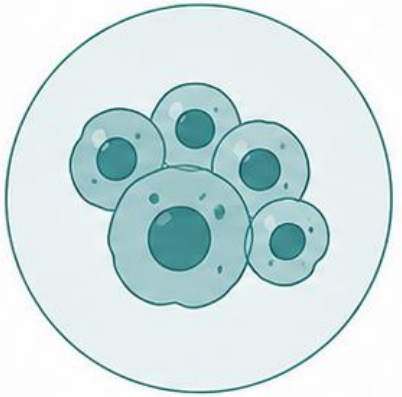
What we prescribe

EXPOSURE



What the patient actually experiences

BIOLOGICAL EFFECT



Pharmacologic effect on disease and normal tissues

OUTCOME

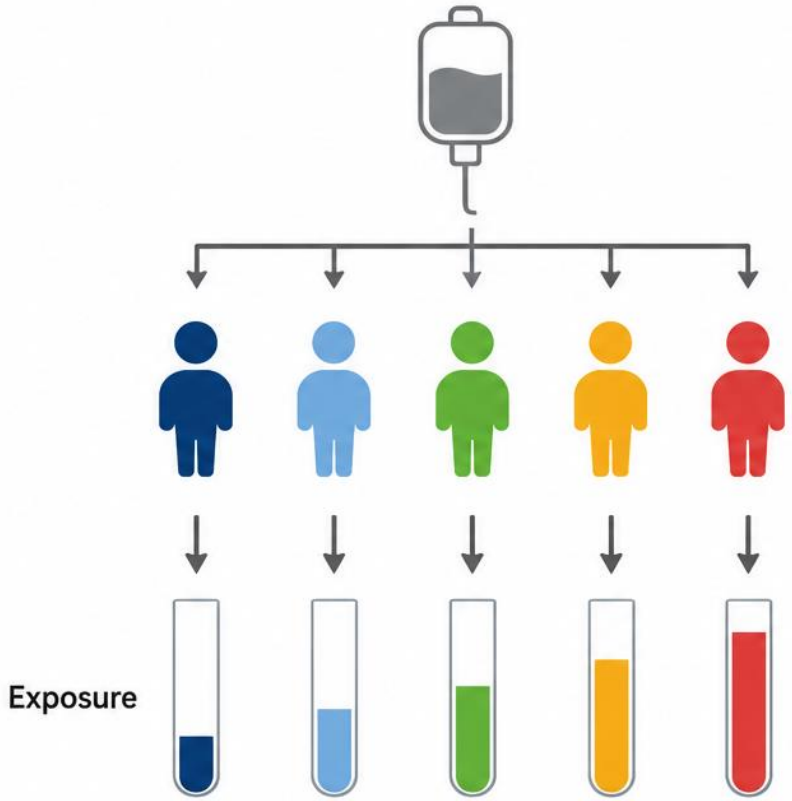
Toxicity, efficacy, survival

Dose alone is an imperfect surrogate.

Two patients given the same dose can have very different exposures—and therefore different outcomes.

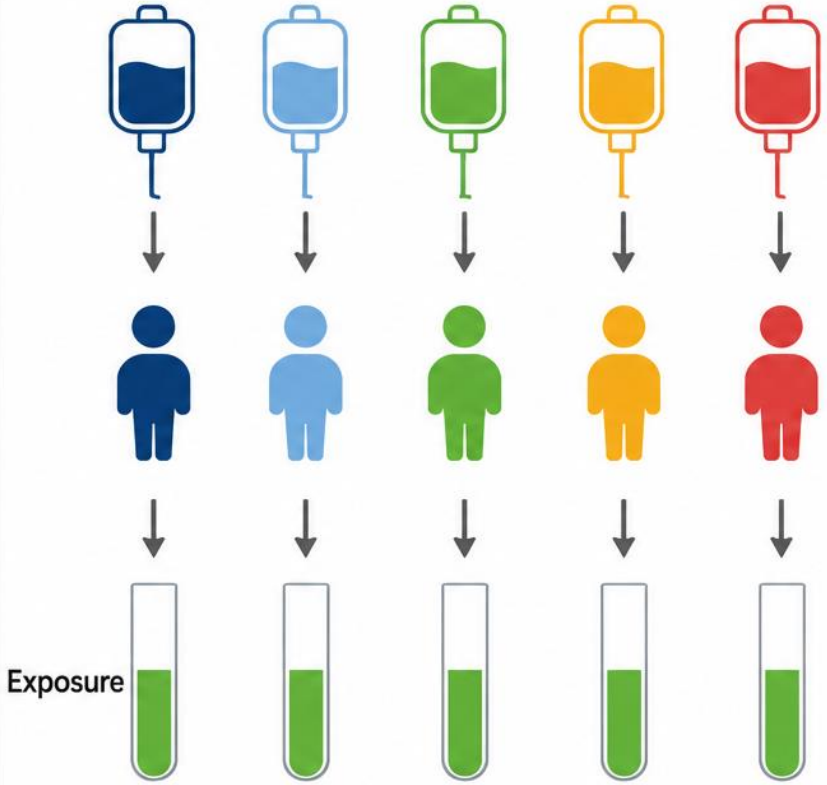
TODAY

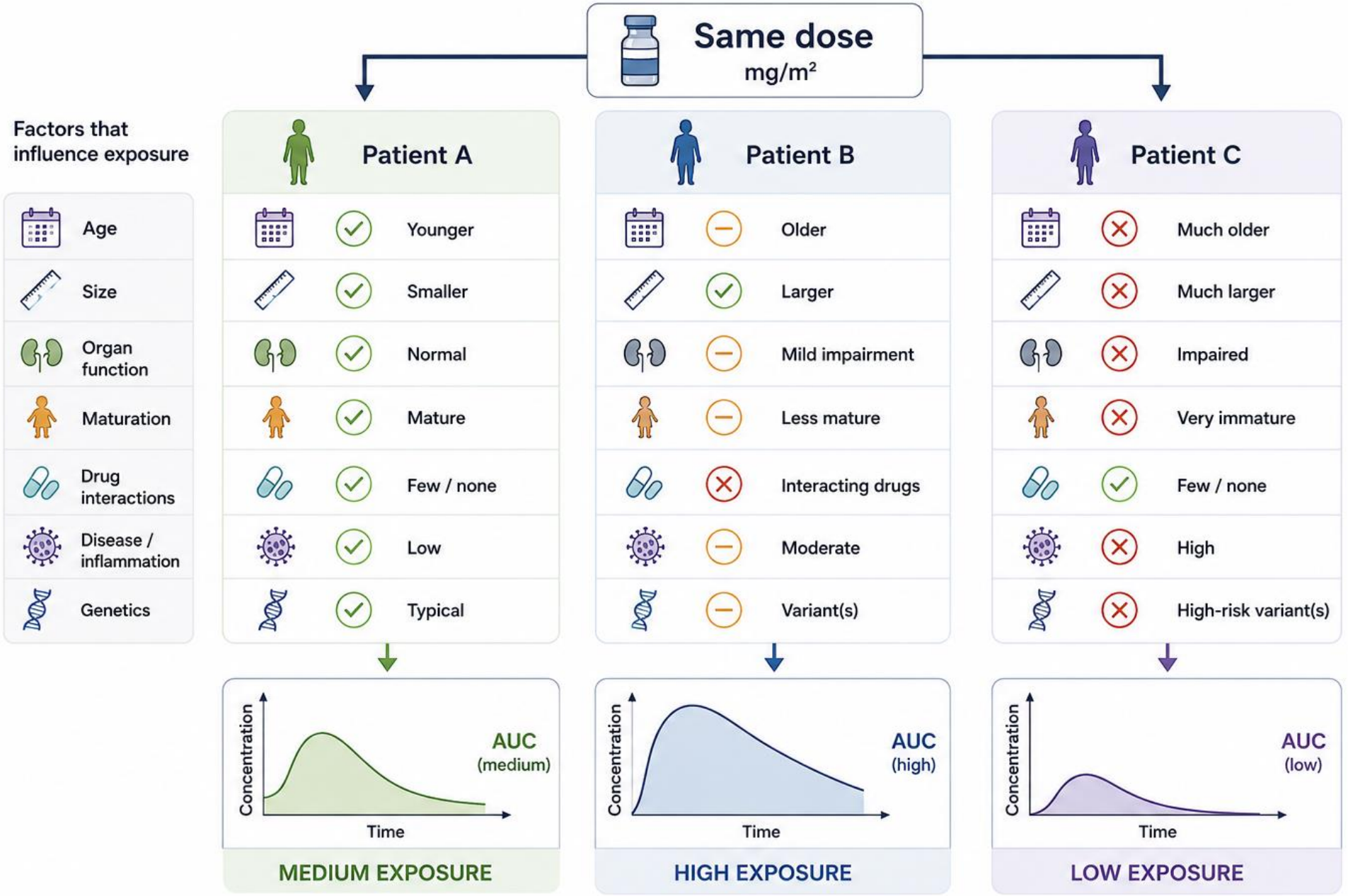
Same dose → Different exposures



FUTURE

Individualised dose → Similar exposures




Same dose
mg/m²
Factors that influence exposure
Age
Size
Organ function
Maturation
Drug interactions
Disease / inflammation
Genetics
Patient A
Younger
Smaller
Normal
Mature
Few / none
Low
Typical
Patient B
Older
Larger
Mild impairment
Less mature
Interacting drugs
Moderate
Variant(s)
Patient C
Much older
Much larger
Impaired
Very immature
Few / none
High
High-risk variant(s)
Concentration
Time
AUC
(medium)
MEDIUM EXPOSURE
Concentration
Time
AUC
(high)
HIGH EXPOSURE
Concentration
Time
AUC
(low)
LOW EXPOSURE
Same mg/m² dose → Different patients → Different exposures

To get “the right dose”
IT might require a combination of individualized dosing strategies

Exposure-response

AUC

AUCcum

Cmax

Time above MIC

Link Dose decisions to outcomes

Population PK Models

Busulfan

Fludarabine

ATG

Tacrolimus/ Cyclosporin

Estimate likely exposure

PGx

TPMT/ NUDT15

DPYD

G6PD

CYP2C19

Avoid predictable severe toxicity

Bayesian Forecasting

Busulfan

Vancomycin

Aminoglycosides

Tacrolimus

Enoxaparin

Warfarin

Individualise dose using measured concentrations

BUSULFAN EXPOSURE MATTERS

THE EVIDENCE FOR AN OPTIMAL CUMULATIVE EXPOSURE

PAEDIATRIC FOUNDATIONAL

Bartelink 2009

Biol Blood Marrow Transplant

n = 102 children and young people

Identified optimal cumulative AUC **~78 mg·h/L**

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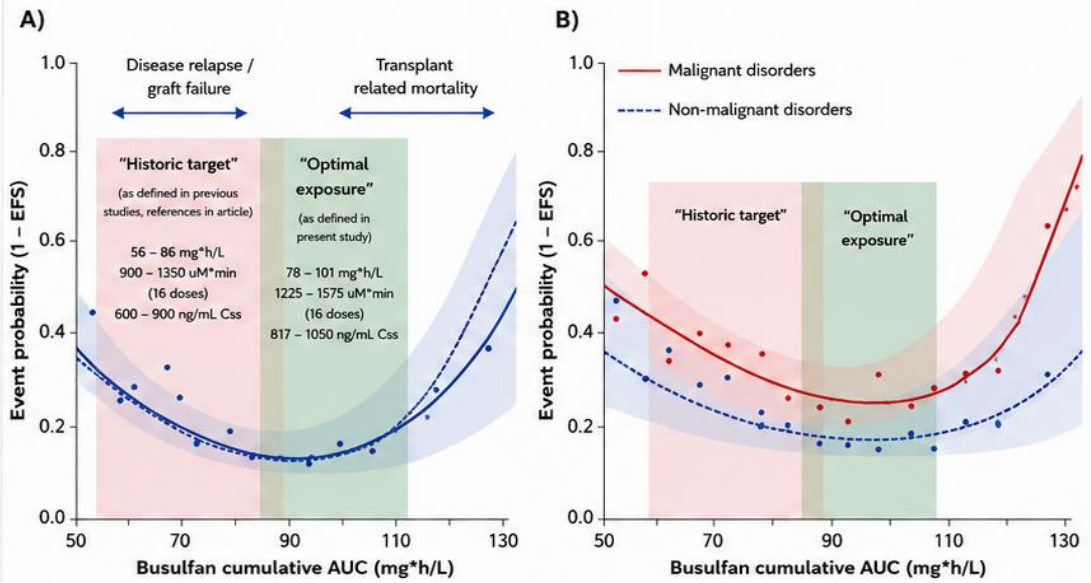
n = 674 children and young adults



- Optimal 2-year EFS with cumulative AUC **78–101 mg*h/L**
- Lower exposure ↑ graft failure/relapse; higher exposure ↑ toxicity/TRM

TARGET CUMULATIVE AUC: 78–101 mg*h/L

INDIVIDUALISE TO ACHIEVE THE RIGHT EXPOSURE FOR EACH PATIENT

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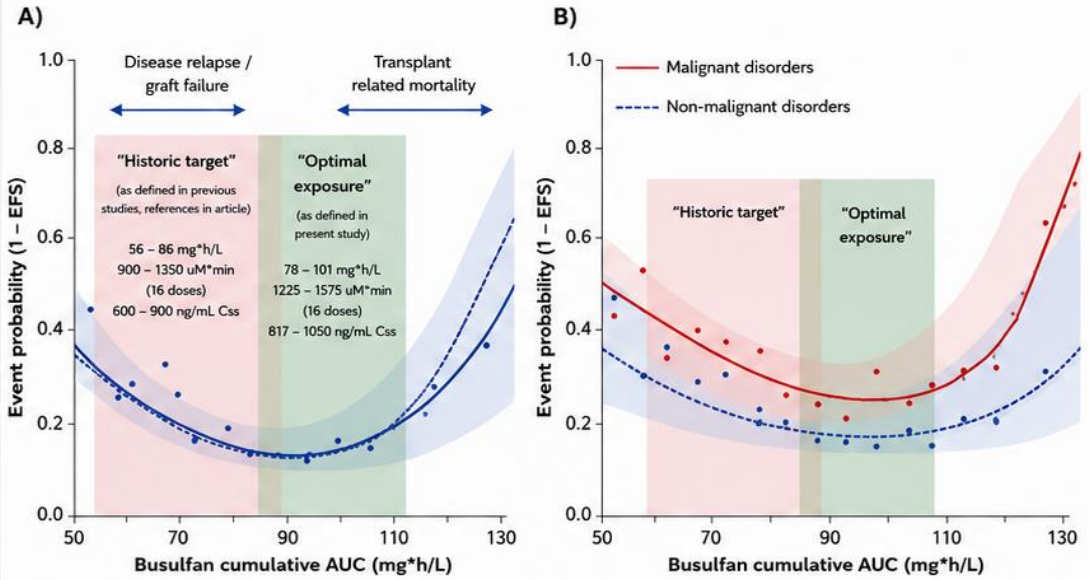

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ADULT – TOXICITY RISK

Seydoux 2022

Bone Marrow Transplant

n = 300 adults with myeloid malignancies

High AUC associated with higher non-relapse mortality (RR of death 1.9)

ADULT – UNDEREXPOSURE RISK

Tamari 2023

Blood Advances

n = 176 adults (CD34-selected HSCT)

5-year OS: **40%** (<59.5 mg*h/L) vs **67%** (≥59.5 mg*h/L)

TARGET CUMULATIVE AUC: 78–101 mg*h/L

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Chen T et al. Annals of Hematology (2022) 101:667–679

Fixed-dose administration and pharmacokinetically guided adjustment of busulfan dose for patients undergoing hematopoietic stem cell transplantation: a meta-analysis and cost-effectiveness analysis

6 observational studies
825 patients

PK-guided (n=344)
vs
Fixed-dose (n=481)

Busulfan in HSCT
myeloablative setting

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BENEFITS OF PK-GUIDED DOSING

Progression-free survival (PFS)
Better with PK-guided
RR 1.37 (95% CI 1.17–1.61), $P < 0.0001$

Overall survival (OS)
No significant difference overall
RR 1.20 (95% CI 0.96–1.51), $P = 0.11$

Allo-HSCT subgroup: better
RR 1.30 (95% CI 1.07–1.60), $P = 0.01$

Relapse rate
Lower with PK-guided
RR 0.66 (95% CI 0.51–0.85), $P = 0.001$

TRADE-OFFS / NO BENEFIT

Veno-occlusive disease (VOD)
Higher with PK-guided
RR 2.41 (95% CI 1.09–5.30), $P = 0.03$

Acute GVHD (grade ≥2)
No significant difference
RR 0.85 (95% CI 0.33–2.16), $P = 0.73$

Non-relapse mortality (NRM)
Not pooled
Individual studies consistently lower with PK-guided
10 years: 20% vs 28%
1 year: 7% vs 9%
475 days: 15% vs 37%

KEY TAKEAWAYS

PK-guided dosing improves disease control
PFS and relapse reduced

No overall OS advantage
Benefit seen in allo-HSCT subgroup only

VOD increased
Potentially related to high exposure/peak levels

Target the right exposure, not just do PK-guided dosing

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Target the right exposure, not just do PK-guided dosing

KEY MESSAGES

- PK-guided busulfan dosing improves PFS and reduces relapse compared with fixed-dose dosing.
- Overall survival is not significantly different in the total population, but is improved in allo-HSCT patients.
- PK-guided dosing is associated with a higher incidence of VOD.
- No significant difference in acute GVHD; NRM is consistently lower with PK-guided dosing (individual studies).

BUSULFAN PEAK CONCENTRATION (C_{MAX}) MATTERS

EXPOSURE–RESPONSE EVIDENCE FOR BUSULFAN C_{MAX}

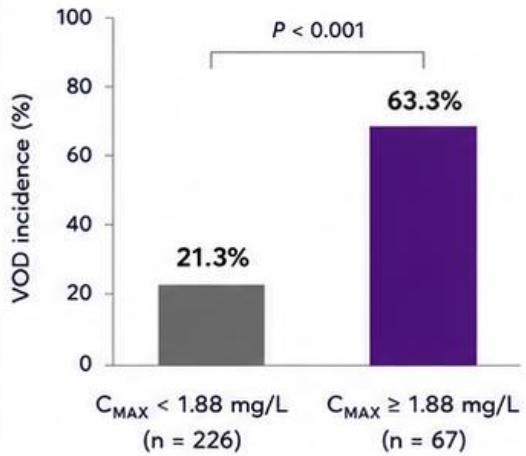
1 Philippe 2019

Biol Blood Marrow Transplant

n = 293 children

IV busulfan (q6h or daily)

INCIDENCE OF VOD BY C_{MAX}



↑ Higher C_{MAX} (≥1.88 mg/L) associated with ↑ VOD (63.3% vs 21.3%)

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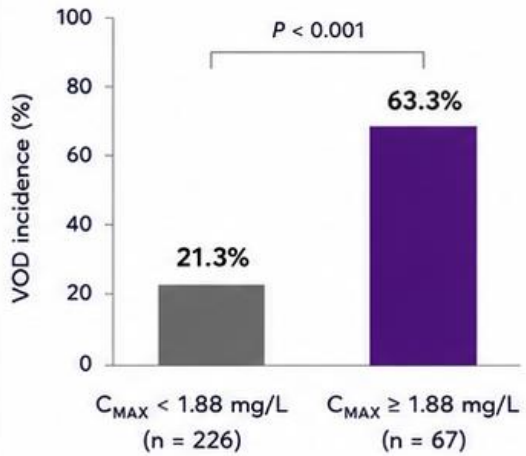

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2 Bognár 2022

Bone Marrow Transplantation

n = 697 children & young adults

IV busulfan (q6h or once daily)

VOD/SOS BY C_{MAX} (BUSULFAN + ADDITIONAL ALKYLATOR) n = 444

C_{MAX} (µg/L)	VOD/SOS incidence % (n)
< 1450 n = 148	16.7% (23)
1450 – 2250 n = 159	10.7% (17)
> 2250 n = 147	19.0% (28)

⊖ No significant association between C_{MAX} and VOD/SOS in either treatment subgroup

(Cohort included both q6h and once-daily dosing)

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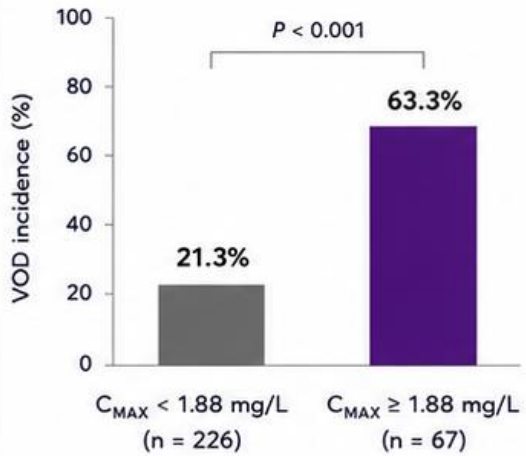

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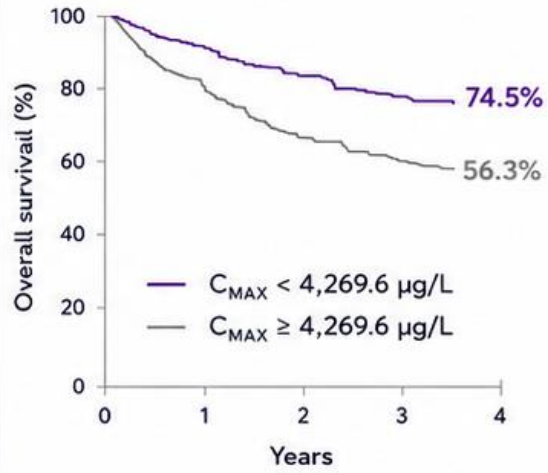
3 Bae 2026

Bone Marrow Transplantation

n = 334 children & young adults

Once-daily IV busulfan

4-YEAR OVERALL SURVIVAL BY C_{MAX}



↓ Lower C_{MAX} associated with better 4-year survival (74.5% vs 56.3%)

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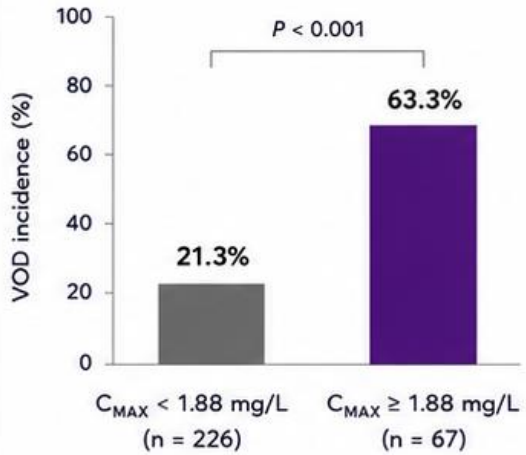

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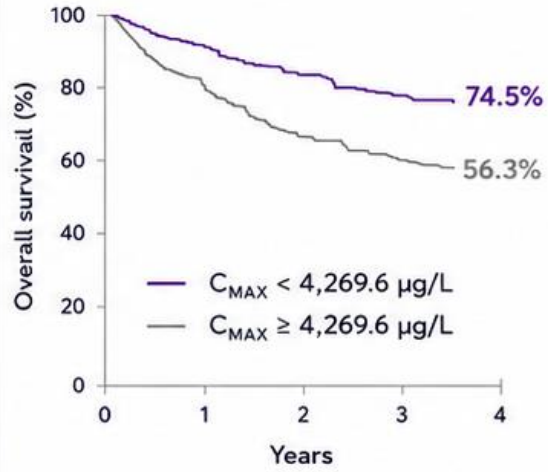

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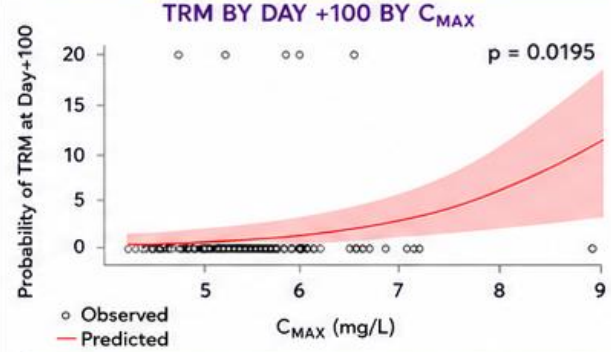
4 QCH (Unpublished)

n = 96 children

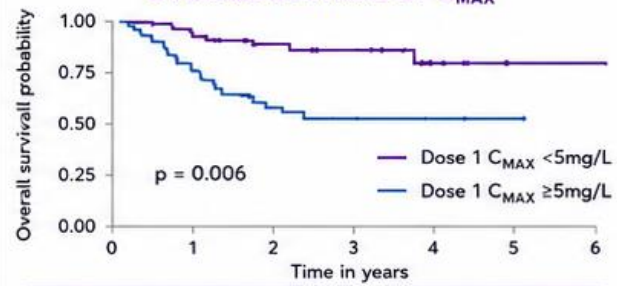
IV busulfan (once daily)

Pharmacokinetic sampling each day

TRM BY DAY +100 BY C_{MAX}



OVERALL SURVIVAL BY C_{MAX}



↑↓ Higher C_{MAX} associated with ↑ TRM and ↓ OS

KEY MESSAGE

- Evidence for C_{MAX} is mixed in cohorts including both q6h and once-daily dosing (Bognár 2022).
- In once-daily dosing, higher C_{MAX} is associated with ↑ VOD (Philippe 2019), ↓ survival (Bae 2026) and ↑ TRM with ↓ OS (QCH unpublished).

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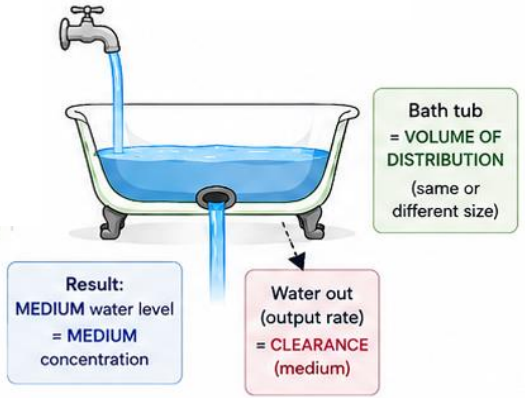
Population PK model dosing- Mathematical equations to describe data

BATHTUB ANALOGY FOR DRUG DOSING

Why the same input can lead to different levels (concentration)

- DOSE ADMINISTERED (input)
- VOLUME OF DISTRIBUTION (the bathtub)
- CLEARANCE (output)



In drug dosing:
DOSE ADMINISTERED (input) fills the VOLUME OF DISTRIBUTION (the bathtub), and CLEARANCE (output) drains the drug from the body.

WE CAN DESCRIBE THIS WITH A MATHEMATICAL EQUATION

Dose administered (input rate) (water in) D_{in} − Clearance (output rate) (water out) CL = Amount of drug in the body (volume in tub) A Change in amount of drug over time (how level changes) $\frac{dA}{dt}$

where:

- D_{in} = rate of drug input (dose administration rate)
- CL = clearance (rate of drug elimination)
- A = amount of drug in the body (in the volume of distribution)
- dA/dt = how the amount of drug changes over time

THE EQUATION: $\frac{dA}{dt} = D_{in} - CL$

This tells us that the amount of drug in the body (A) changes over time depending on how much dose is given (D_{in}), how much drug is cleared (CL), and how big the volume of distribution is (A for a given concentration).

By solving this equation, we can **estimate the drug concentration** ($C = A / V_d$) and how it changes over time.
(where V_d = volume of distribution)

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BATHTUB 1

Small drain
(low clearance)

Water in (input rate) = DOSE ADMINISTERED

Bath tub = VOLUME OF DISTRIBUTION (size of tub determines how much it holds)

Result: HIGH water level = HIGH concentration

Water out (output rate) = CLEARANCE (low)

BATHTUB 2

Medium drain
(medium clearance)

Bath tub = VOLUME OF DISTRIBUTION (same or different size)

Result: MEDIUM water level = MEDIUM concentration

Water out (output rate) = CLEARANCE (medium)

BATHTUB 3

Large drain
(high clearance)

Bath tub = VOLUME OF DISTRIBUTION

Result: LOW water level = LOW concentration

Water out (output rate) = CLEARANCE (high)

In drug dosing:
DOSE ADMINISTERED (input) fills the VOLUME OF DISTRIBUTION (the bathtub), and CLEARANCE (output) drains the drug from the body.

WE CAN DESCRIBE THIS WITH A MATHEMATICAL EQUATION

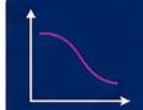
Dose administered (input rate) (water in) D_{in} −  Clearance (output rate) (water out) CL =  Amount of drug in the body (volume in tub) A Change in amount of drug over time (how level changes) $\frac{dA}{dt}$

where:

- D_{in} = rate of drug input (dose administration rate)
- CL = clearance (rate of drug elimination)
- A = amount of drug in the body (in the volume of distribution)
- dA/dt = how the amount of drug changes over time

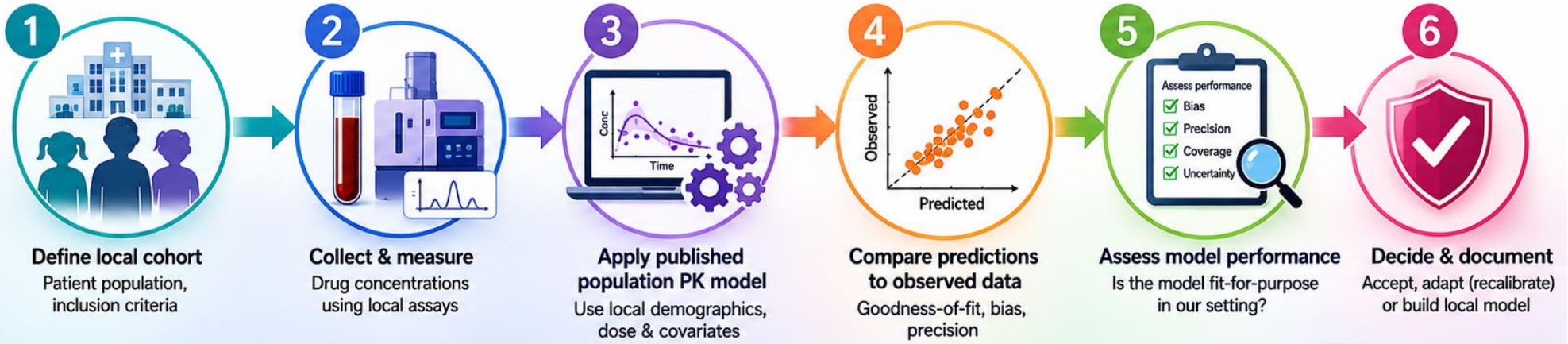
THE EQUATION: $\frac{dA}{dt} = D_{in} - CL$

This tells us that the amount of drug in the body (A) changes over time depending on how much dose is given (D_{in}), how much drug is cleared (CL), and how big the volume of distribution is (A for a given concentration).



By solving this equation, we can **estimate the drug concentration** ($C = A / V_d$) and how it changes over time.
(where V_d = volume of distribution)

Local validation of a population PK model



Define local cohort
Patient population, inclusion criteria

Collect & measure
Drug concentrations using local assays

Apply published population PK model
Use local demographics, dose & covariates

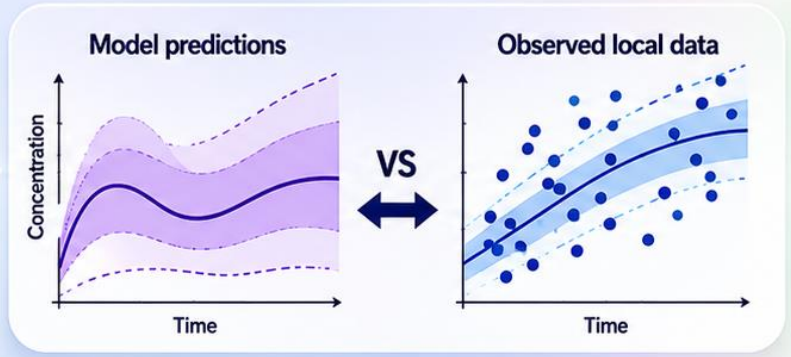
Compare predictions to observed data
Goodness-of-fit, bias, precision

Assess model performance
Is the model fit-for-purpose in our setting?

Decide & document
Accept, adapt (recalibrate) or build local model

What we check

- Predicted vs observed concentrations
- Bias (over/under prediction)
- Precision (closeness of fit)
- Coverage (uncertainty intervals capture data)
- External validation metrics (e.g. RMSE, MAE, R^2, VPC)



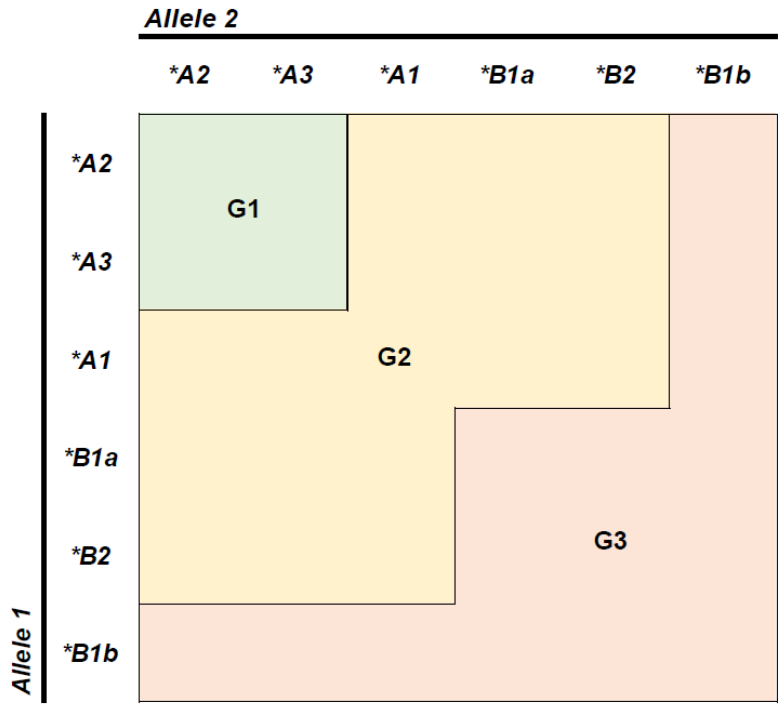
Validated
Model fit-for-purpose in our setting

Ongoing monitoring & re-validation
Update as practice, assays or patient mix changes

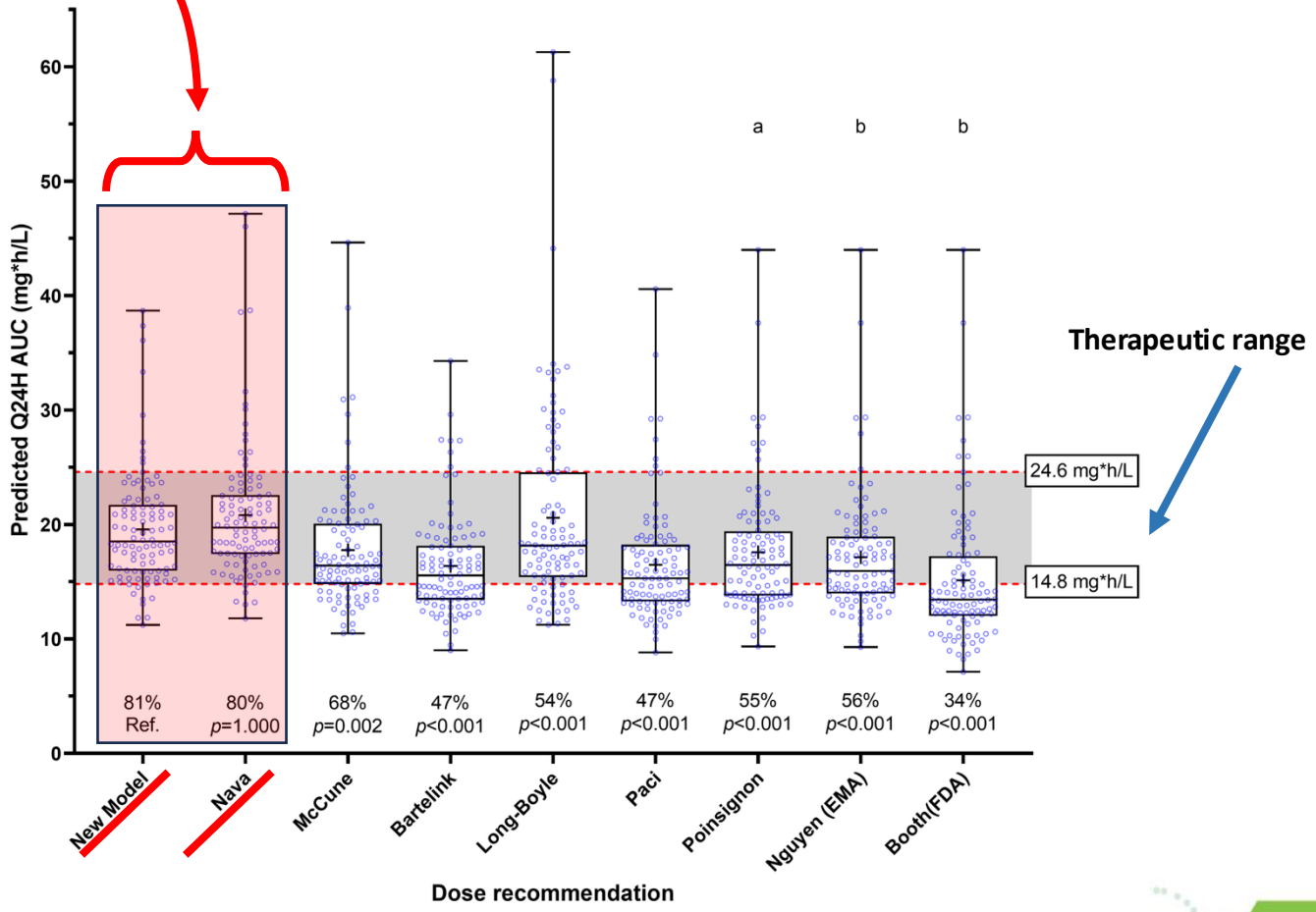
Why mismatch occurs in local populations

Incorporation of the *GSTA1*-based metabolic groups into the dosing recommendation of busulfan

***GSTA1* diplotype composition**



Resulting AUC after the first dose of busufan

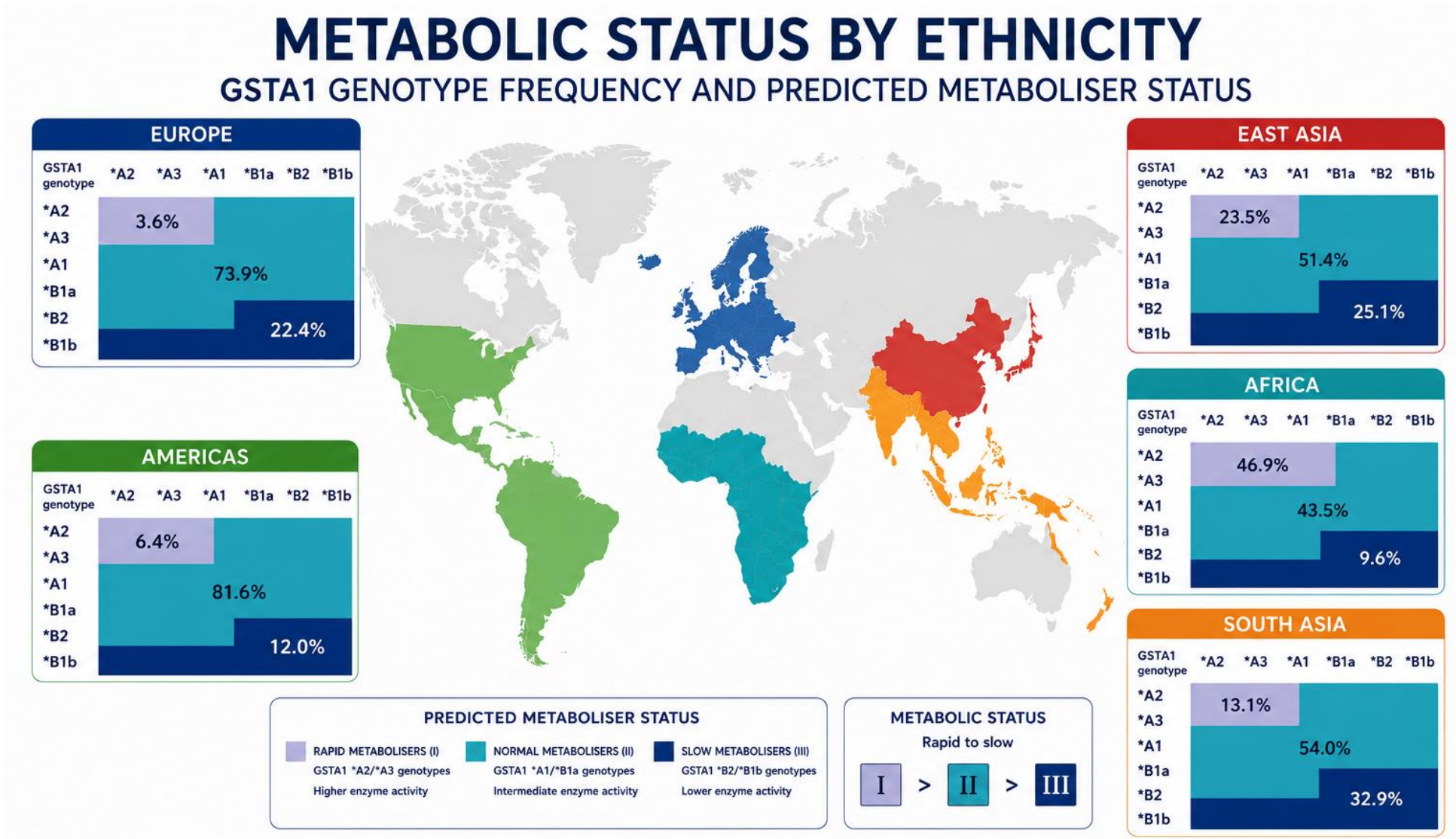


Nava et al. *Br J Clin Pharmacol*. 2018 Jul;84(7):1494 / Hassine KB et al. *CPT Pharmacometrics Syst Pharmacol. 2021*

Mlakar et al, Sci Rep 2021

METABOLIC STATUS BY ETHNICITY

GSTA1 GENOTYPE FREQUENCY AND PREDICTED METABOLISER STATUS



Hassine 2022, CPIC

Impact of GSTA1 Metaboliser Status on Busulfan Exposure

Population PK model predictions for the first once-daily dose of busulfan infused over 3 hours (IV)

Patient
4-year-old child
Weight: 15 kg

Initial Dose
4.8 mg/kg/dose
(Total dose = 72 mg)

Infusion
Once daily
infused over 3 hours (IV)

Hassine et al. 2024
Busulfan PopPK model for CL

Model clearance (CL) equation

$$CL = \theta_1 \times \left(\frac{WT}{70}\right)^{\theta_2} \times \left(\frac{Age}{1}\right)^{\theta_3} \times \left(\frac{eGFR}{90}\right)^{\theta_4} \times GSTA1 \times D_{drug}$$

where:

- WT = weight (kg)
- Age = age (years)
- eGFR = glomerular filtration rate (mL/min/1.73m²)
- GSTA1 = genotype factor
- D_{drug} = drug interaction factor (product of interacting drugs)

Covariates included in the model

- Weight
- Age
- Renal function (eGFR)
- GSTA1 genotype
- Concomitant drugs (enzyme inducers, azole antifungals & others)

Model performance

Good predictive performance in children & adults (bootstrapping & external validation)

FROM MEASURING EXPOSURE TO PREDICTING EXPOSURE

Comparing Non-Compartmental Analysis (NCA) vs Bayesian Forecasting Software (BFS)

1. NON-COMPARTMENTAL ANALYSIS (NCA)

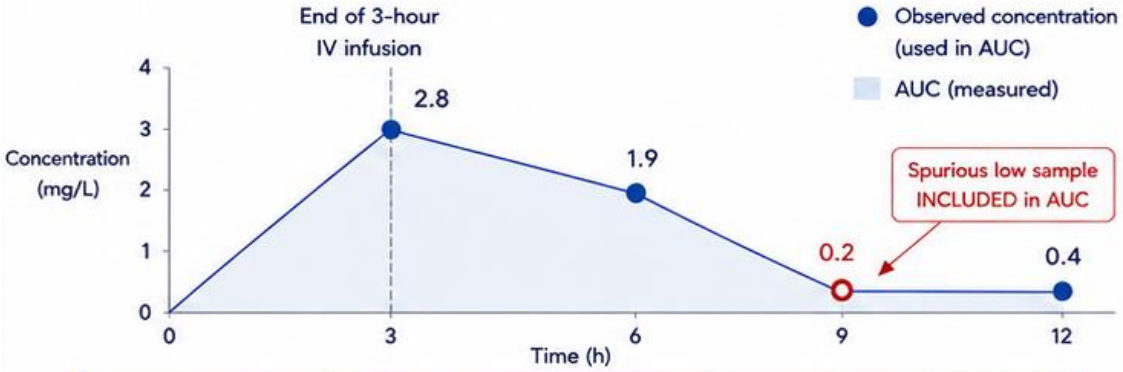
What happened (observed data only)

1 Give dose — Dose administered to the patient

2 Measure concentrations — Drug concentrations measured at several time points

3 Map & calculate AUC — Concentrations are plotted and AUC is calculated (trapezoidal method)

All samples collected after the infusion (0–3 h)



AUC is calculated from the observed concentrations only.
Includes all measured data (including outliers).
No assumptions about the body (PK) are made.

NON-COMPARTMENTAL ANALYSIS (NCA)

- Uses measured concentrations only
- Describes past exposure
- Cannot predict beyond last sample
- AUC calculated from the observed data
- Sensitive to outliers and missing early peak

VS.

FROM MEASURING EXPOSURE TO PREDICTING EXPOSURE

Comparing Non-Compartmental Analysis (NCA) vs Bayesian Forecasting Software (BFS)

1. NON-COMPARTMENTAL ANALYSIS (NCA)

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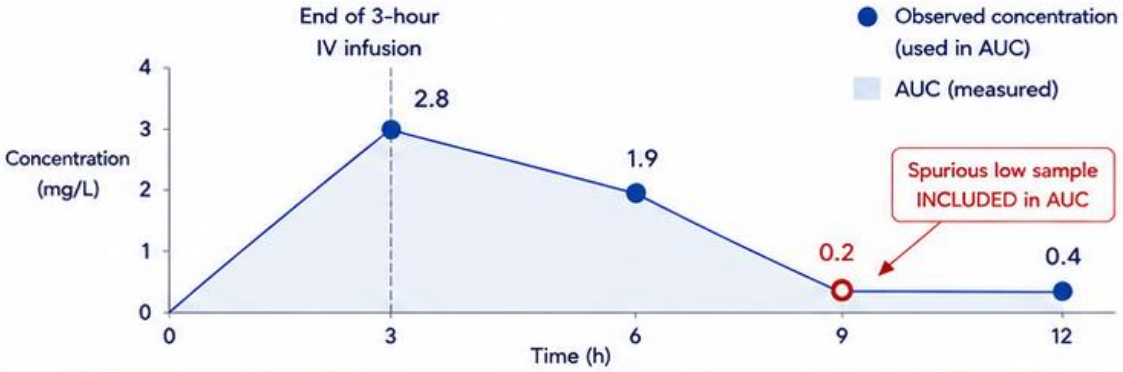


AUC is calculated from the observed concentrations only.
Includes all measured data (including outliers).
No assumptions about the body (PK) are made.

2. BAYESIAN FORECASTING SOFTWARE (BFS)

What will happen (model-informed prediction)

1 Give dose
Dose administered to the patient

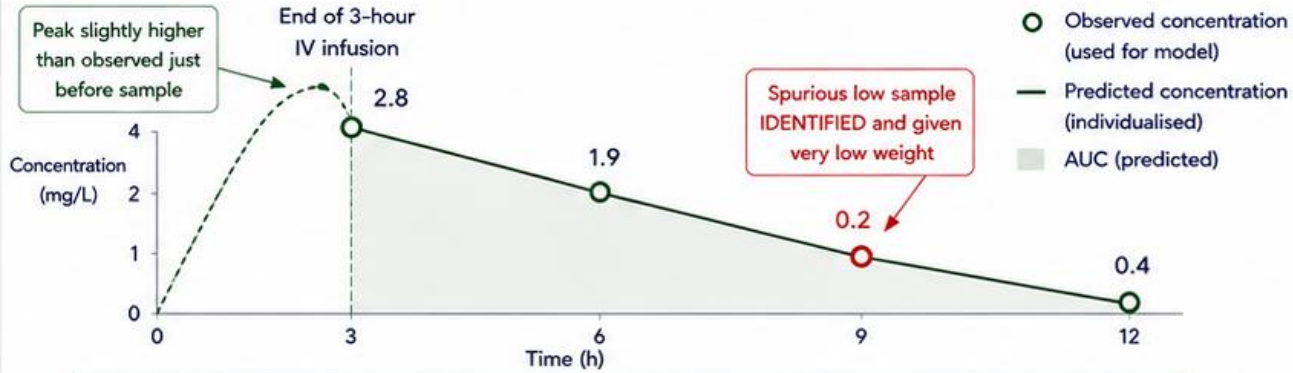
2 Measure some concentrations
Concentrations measured at a few time points

3 Estimate PK parameters
Software uses a population PK model + patient data

4 Predict full concentration profile
Individualised concentration–time curve estimated

5 Estimate AUC
AUC is calculated from the predicted concentration profile

All samples collected after the infusion (0–3 h)



PK parameters (e.g., clearance, volume of distribution) are estimated for the individual patient using a population model + measured data.
Dose + estimated PK → predicted concentrations → predicted AUC.

NON-COMPARTMENTAL ANALYSIS (NCA)

- Uses measured concentrations only
- Describes past exposure
- Cannot predict beyond last sample
- AUC calculated from the observed data
- Sensitive to outliers and missing early peak

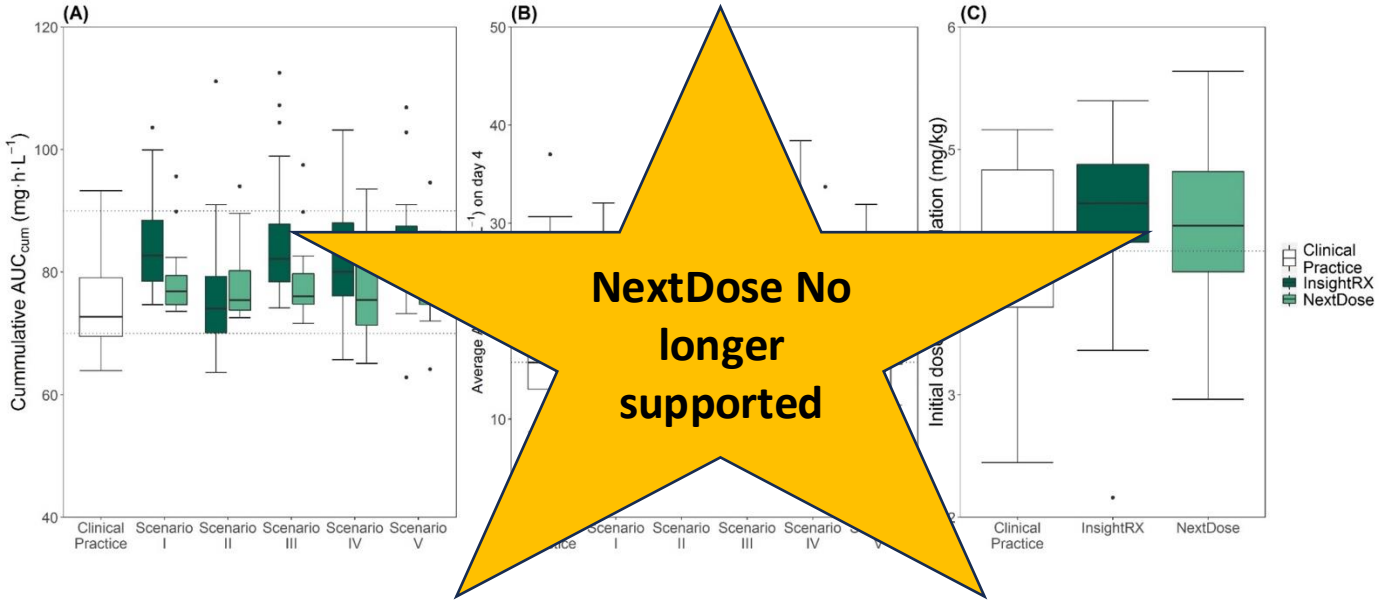
VS.

BAYESIAN FORECASTING SOFTWARE (BFS)

- Estimates individual PK parameters
- Predicts full concentration–time profile (including peak)
- Can predict future exposure and alternate dosing
- AUC calculated from the predicted profile
- Robust to outliers and sparse sampling

BFS provides insight into what will happen and helps optimise dosing for each individual.

Review of software available and validation of models- InsightRx/ NextDose



BE AWARE: Different platforms implement different models and often may produce different outputs even with the same data

Thompson et al 2025, Lawson et al 2021

Evidence Supporting Implementation-Ready Agents for Model Informed Individualised Dosing in Paediatric HSCT

Agent	Population PK Model Available	Exposure–Response Evidence	Clinical Outcomes Associated with Exposure	Implementation Readiness
Busulfan	✓	✓✓✓	Survival, relapse, graft failure, toxicity, TRM	Very High
Fludarabine	✓	✓	Survival, relapse, NRM, immune reconstitution	Medium
Treosulfan	✓	✓	Toxicity, engraftment, survival outcomes	Medium
Alemtuzumab	✓	✓	GVHD, immune reconstitution, infection risk, survival	Medium
Anti-thymocyte globulin (ATG)	✓	✓	GVHD, relapse, immune reconstitution, survival	Medium
Cyclophosphamide	Partial	Emerging	Toxicity and metabolite exposure relationships reported	Low (emerging)
Etoposide	Partial	Emerging	Limited exposure–response data available	Low (emerging)
Melphalan	Partial	Emerging	Exposure–toxicity relationships reported	Low (emerging)

BEYOND SINGLE-DRUG THINKING

A “safe” exposure to one drug may not be safe in the context of high exposure to another.

Is the future target a single-drug therapeutic window or an optimal multidrug exposure profile?

SINGLE-DRUG VIEW

Each drug considered in isolation

Drug exposures assessed one at a time. If each drug is within its target range, it is considered “safe”.

Looks safe for each drug...

vs.

MULTIDRUG VIEW

Drug exposures interact

The combination of drug exposures matters. A “safe” exposure to one drug may not be safe in the context of high exposure to another.

May be unsafe together

BUSULFAN + FLUDARABINE:

Perhaps looking at each drug independently is no longer enough.

The future target may be an optimal multidrug exposure profile.

THE WAY FORWARD: FOUR PATHS, ONE GOAL

Advancing precision dosing through integrated science and technology

1. EXPOSURE–RESPONSE ANALYSES (INCLUDING MULTIAGENT EXPOSURES)

- Define optimal exposure ranges
- Understand benefit–risk relationships
- Evaluate combined drug exposures

2. POPULATION PK MODELS – EXPANDED COVARIATE EXPLORATION

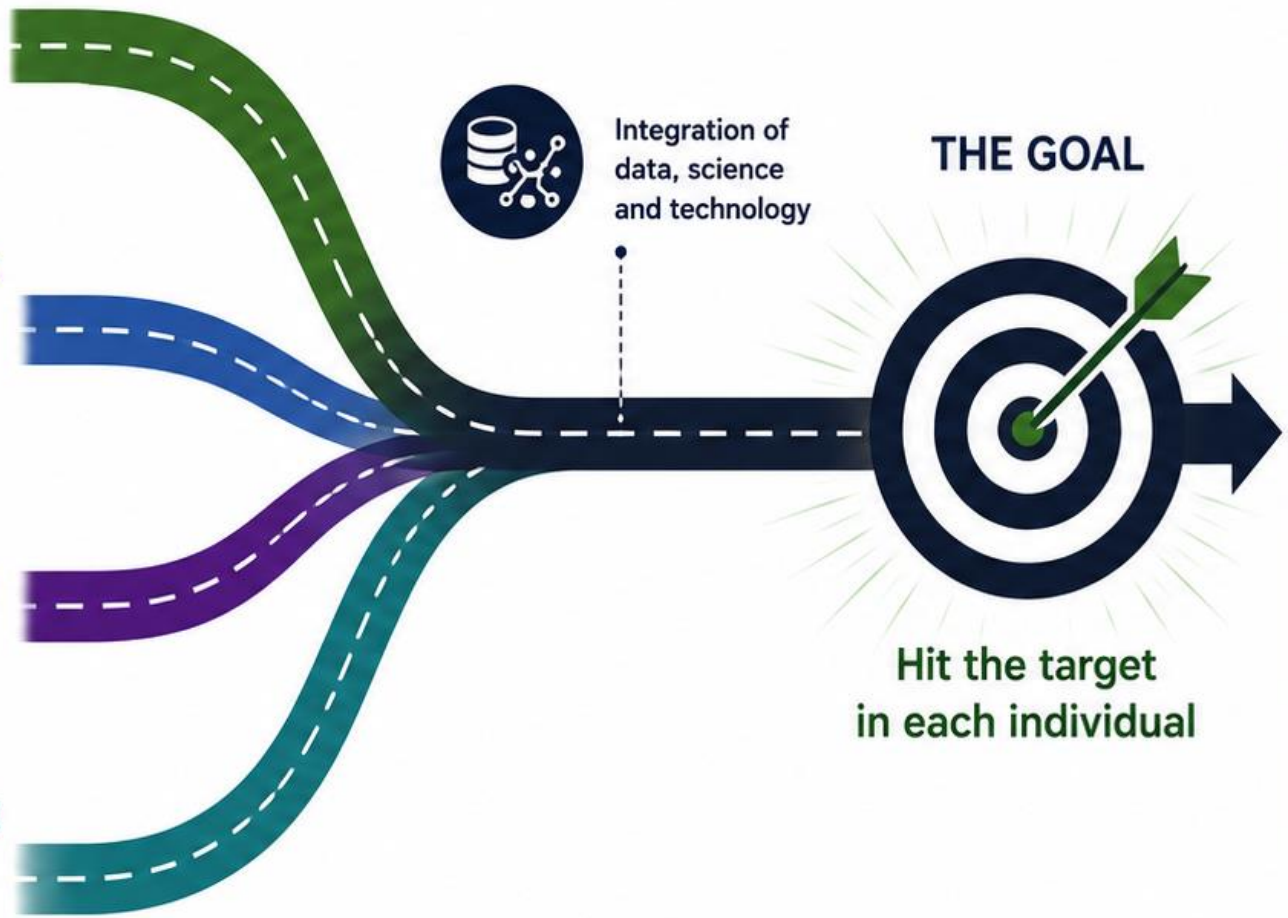
- Build robust population models
- Explore clinical, demographic and disease covariates
- Improve initial dosing and predictions

3. PHARMACOGENOMICS (INTER-PLAY BETWEEN MULTIPLE GENES)

- Identify genetic variants impacting PK/PD
- Understand gene–gene interactions
- Refine prediction of variability and risk

4. BAYESIAN FORECASTING SOFTWARE AND INTEGRATION OF AI

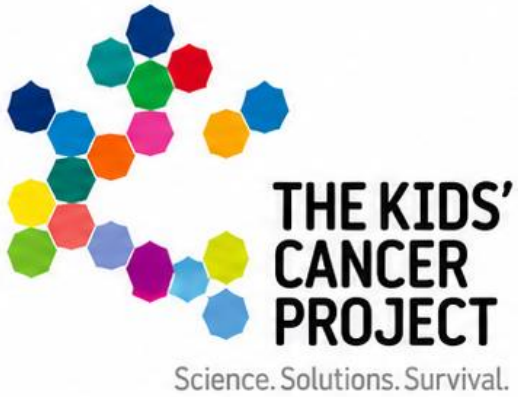
- Real-time individualised dosing
- Continuous learning from outcomes
- AI-enhanced insights and decision support



IMPROVED PATIENT OUTCOMES

- Better efficacy
- Fewer toxicities
- Reduced variability
- Improved survival
- Better quality of life

Thankyou



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