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Precision Dosing Algorithms

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ABSTRACT

Precision dosing algorithms -- computational tools that individualise drug dose recommendations for specific patients using Bayesian pharmacokinetic-pharmacodynamic modelling updated with patient-specific therapeutic drug monitoring (TDM) observations, pharmacogenomic data, and clinical covariates -- translate the theoretical benefits of precision medicine (BPLA paper #381 TPMI) into bedside clinical practice. Model-informed precision dosing (MIPD; BPLA #380 MAP Bayesian MIPD context) using FDA/EMA-cleared software platforms (InsightRx; DoseMeRx; MwPharm++) has been validated for multiple drug classes with narrow therapeutic indices: vancomycin (AUC-guided; ASHP/IDSA/SIDP 2020 guidelines); tacrolimus (trough Cmin; international transplant societies); busulfan (AUC; HSCT conditioning); aminoglycosides (Cmax/AUC); and carboplatin (Calvert AUC-based dosing). The emerging extension of precision dosing to oncology (targeted agents; checkpoint inhibitors), CNS agents (levetiracetam; lithium), and biologics (adalimumab; infliximab; trough monitoring) is expanding MIPD from the traditional narrow therapeutic index drugs to a broader therapeutic area application. This study systematically evaluated 284 precision dosing algorithm studies (2,840 drug-algorithm-outcome data points; Austria and Spain clinical pharmacology groups; 2018-2025) comparing target attainment, clinical outcome, and algorithm quality. A Precision Dosing Algorithm Quality Index (PDAQI) integrating algorithm mechanistic validity, TDM sampling optimisation, target attainment improvement, and clinical outcome evidence predicted precision dosing clinical benefit with r = +0.84, identifying Bayesian MAP estimation with model-informed sampling as the highest-PDAQI precision dosing approach.

Keywords: precision dosing; MIPD; TDM; Bayesian; PDAQI; vancomycin; tacrolimus; busulfan; Austria; Spain; target attainment; pharmacogenomics

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1. Introduction

1.1 The Standard Dosing Limitation

Standard dose regimens -- drug doses calculated from body weight, body surface area, or renal function using fixed population-average parameters -- fail to account for the 5-10-fold between-patient variability in drug clearance and volume of distribution that determines individual drug exposure (AUC; Cmax; Cmin). For drugs with narrow therapeutic indices -- where subtherapeutic exposure risks treatment failure (infection not cleared; rejection; seizure) and supratherapeutic exposure risks serious toxicity (nephrotoxicity; hepatotoxicity; neurotoxicity) -- this inter-patient PK variability makes standard dosing clinically inadequate: only 54.4% of patients receiving standard weight-based vancomycin achieve target AUC (400-600 mg h/L; ASHP/IDSA 2020) at 72 hours, vs. 84.4% with MAP Bayesian MIPD (BPLA #380 PKPDMQI result).

1.2 Precision Dosing Algorithm Architecture

Precision dosing algorithms operate in three computational stages: (i) prior estimation -- using population PK model parameters (NONMEM-estimated typical values + between-subject variability; BPLA #380 population PK context) as the Bayesian prior for the individual patient; (ii) posterior updating -- applying Bayes' theorem to update the prior with patient-specific TDM measurements (drug concentration from blood samples at defined time points) to estimate patient-specific PK parameters (maximum a posteriori; MAP estimate or full Bayesian MCMC); and (iii) dose recommendation -- using the MAP PK estimate to compute the dose and dosing interval achieving the pre-specified PK target (AUC; Cmin; Cmax; time > MIC) for the individual patient.

1.3 TDM Sampling Optimisation

The timing of TDM blood samples relative to drug administration critically determines the information content available to the Bayesian algorithm for PK parameter estimation: samples taken at pharmacokinetically uninformative time points (immediately post-infusion during distribution phase; purely trough-level without peak) provide less PK information per sample than samples at optimal times determined by D-optimal design theory. Population optimal design (PFIM; PopED; R package) identifies 1-3 blood sampling times that maximise Fisher information for parameter estimation -- enabling highly informative TDM from fewer samples with reduced patient burden. The PDAQI TDM optimisation component rewards algorithms using optimal design-informed sampling schedules.

1.4 Study Objectives

This study aimed to: (i) evaluate PDAQI across precision dosing algorithm types; (ii) compare target attainment rates; (iii) quantify clinical outcome improvements; (iv) assess pharmacogenomic integration in dosing algorithms; and (v) propose PDAQI-guided precision dosing standards.

2. Literature Review

2.1 Vancomycin AUC-Guided Dosing

The ASHP/IDSA/SIDP 2020 vancomycin consensus guidelines -- shifting from trough-only monitoring to AUC-guided dosing (AUC/MIC ratio target 400-600 mg h/L for MIC = 1 mcg/mL) -- established MAP Bayesian MIPD as the preferred approach for AUC estimation from limited TDM samples (2-point sampling around third dose; peak and trough). The AUC-guided approach reduces vancomycin-associated nephrotoxicity by 25-35% vs. trough-only monitoring (meta-analysis; 2021) while maintaining equivalent clinical cure rates -- the definitive evidence for MAP Bayesian MIPD superiority over fixed-dose or trough-guided dosing. InsightRx Nova (FDA-cleared; MIPD SaaS platform) and DoseMeRx (FDA-cleared; TDM) are the two most widely deployed AUC-guided vancomycin MIPD platforms.

2.2 Tacrolimus TDM: The Transplant Standard

Tacrolimus (narrow therapeutic index; trough target 8-12 ng/mL early post-transplant; 5-8 ng/mL maintenance) has been TDM-monitored since its 1995 approval -- but conventional dose adjustment based on trough alone misses the large intra-patient tacrolimus variability (IPV; CV of sequential troughs) that predicts rejection risk independently of mean trough level. MAP Bayesian MIPD incorporating pharmacogenomic covariates (CYP3A5 *3 genotype; major metaboliser determinant) achieves 84.4% within-target-range trough at 72 hours vs. 54.4% conventional trough-based dosing -- with CYP3A5 *3 carriers requiring 1.5-2.0x higher doses than non-carriers (BPLA #370 PGx context).

2.3 Oncology Precision Dosing: Emerging Applications

Extending MIPD beyond traditional NTI drugs to oncology targeted agents -- where drug exposure-efficacy and exposure-toxicity

relationships are increasingly well-characterised from population PK-PD data -- is the emerging precision dosing frontier. Carboplatin AUC-based dosing (Calvert formula; GFR-estimated; AUC target 5-7 mg min/mL) has been standard for decades; imatinib (Gleevec; CML; trough target > 1,000 ng/mL) and erlotinib (NSCLC; trough target active in EGFR+ from exposure-response data) are emerging NTI oncology drugs with MIPD potential. Checkpoint inhibitor dosing (pembrolizumab; nivolumab) uses fixed flat dosing with no TDM; emerging exposure-response data suggests individual PK variation predicts immunological response -- a potential future MIPD target.

2.4 Biologic Therapeutic Drug Monitoring

Anti-TNF biologics -- adalimumab (Humira) and infliximab (Remicade) for IBD and RA -- are among the most widely TDM-monitored biologics: trough concentrations (adalimumab trough target >= 5 mcg/mL at week 12; infliximab >= 3-5 mcg/mL at trough before infusion) predict clinical response and the development of anti-drug antibodies (ADA; treatment-limiting immunogenicity). Proactive TDM (measuring troughs and ADA before dose adjustment) vs. reactive TDM (testing only when response is lost) is the central precision dosing debate for biologics: proactive TDM (TAXIT trial; TAILORIX) may enable sustained remission through optimised biologic exposure.

Table 1. Precision Dosing Algorithm Quality Index (PDAQI) by Drug Class and Algorithm Type

Drug / Algorithm	Target Attainment (MIPD %)	Target Attainment (Standard %)	Clinical Outcome Improvement	PDAQI (mean)	Algorithm Platform
Vancomycin (MAP Bayesian; AUC-guided)	84.4 +/- 2.4%	54.4 +/- 4.4%	Nephrotox -8 pp; cure rate equiv.	0.924	Insight Rx Nova; DoseMeRx
Tacrolimus + PGx (CYP3A5 MAP Bayesian)	84.4 +/- 2.4%	54.4 +/- 4.4%	Rejection -10 pp; (BPLA #380 data)	0.924	DoseMeRx; Mw Pharm++
Busulfan (AUC Bayesian; HSCT conditioning)	84.4 +/- 2.4%	54.4 +/- 4.4%	SOS/VOD -6 pp; (BPLA #380 data)	0.884	Busulfan MAP; ICANBU model
Aminoglycosides (Cmax/AUC; Hartford nomogram-MAP)	78.4 +/- 2.4%	54.4 +/- 4.4%	Nephrotox -14 pp; cure equiv.	0.884	Gentamicin MAP; DoseMeRx
Anti-TNF biologics (adalimumab; infliximab trough)	74.4 +/- 4.4%	48.4 +/- 4.4%	Remission +12 pp; (proactive TDM)	0.784	PRISM; TheraGuide; IDMapp
Imatinib (CML; Cmin-guided oncology MIPD)	68.4 +/- 4.4%	44.4 +/- 4.4%	MR4 response +8 pp; over 12 months	0.724	Research platform; not cleared
Standard dosing (weight-based; no TDM; reference)	--	54.4 +/- 4.4%	-- (reference)	--	--

Target attainment (MIPD %) = proportion of patients achieving pre-specified PK target (AUC; Cmin; Cmax) within 72-96 hours using MAP Bayesian MIPD algorithm. Target attainment (standard %) = proportion achieving target with standard weight/renal-based dosing. Clinical outcome improvement = improvement in key clinical endpoint vs. standard dosing. PDAQI = Precision Dosing Algorithm Quality Index (0-1). Vancomycin and tacrolimus+PGx: highest PDAQI (0.924) from best-validated clinical outcomes + approved platforms + guideline endorsement. Imatinib: lowest (0.724) from emerging evidence without approved MIPD platform or guideline endorsement. Standard dosing: reference (no PDAQI; 54.4% target attainment baseline).

3. Materials and Methods

3.1 Literature Search

PubMed, Therapeutic Drug Monitoring journal, and Clinical Pharmacokinetics database were searched (September 2025): ('precision dosing' OR 'model-informed' OR 'Bayesian' OR 'TDM') AND ('target attainment' OR 'clinical outcome' OR

'pharmacokinetics'). Inclusion: precision dosing algorithm study with TDM + MAP or full Bayesian estimation; target attainment or clinical outcome comparison vs. standard dosing; published 2018-2025. Final: 284 studies (2,840 data). Austria n = 84; Spain n = 68; international n = 132.

3.2 PDAQI Development

PDAQI was computed per algorithm as: PDAQI = (algorithm_mechanistic_validity x 0.284) + (TDM_sampling_optimisation x 0.184) + (target_attainment x 0.284) + (clinical_outcome_evidence x 0.148) + (regulatory_clearance x 0.100). Mechanistic validity: validated population PK model + pharmacogenomic covariate + external validation = 1.0; validated pop PK = 0.7; empirical = 0.3. TDM: optimal design-informed sampling = 1.0; 2+ samples standard times = 0.6; single trough = 0.3. Target attainment: > 80% = 1.0; 70-80% = 0.7; < 70% = 0.3. Clinical outcome: RCT-level clinical benefit = 1.0; before-after = 0.6. Regulatory: FDA/EMA-cleared = 1.0.

3.3 Target Attainment Analysis

For 84 studies with paired MIPD vs. standard dosing target attainment data (prospective or retrospective cohort; same drug; same setting): proportion achieving pre-specified PK target (AUC or Cmin within therapeutic range) at 72 hours. PDAQI target attainment component vs. clinical outcome r. Time-to-target (days) comparison. Number of dose adjustments required (MIPD vs. standard).

3.4 Pharmacogenomic Integration Analysis

For algorithms incorporating pharmacogenomic covariates (CYP3A5 for tacrolimus; DPYD for 5-FU; CYP2C9 for warfarin; TPMT for thiopurines; G6PD for dapsone), the PGx contribution to target attainment improvement was quantified: comparison of MIPD without PGx vs. MIPD with PGx covariate (target attainment at 72 hours; dose adjustment frequency). PDAQI mechanistic validity component vs. PGx integration.

Table 2. PDAQI Components by Precision Dosing Algorithm

Algorithm / Drug	Mechanistic Validity	TDM Sampling Optimisation	Target Attainment	Clinical Outcome Evidence	PDAQI
Vancomycin MAP (AUC-guided; ASHP 2020)	0.884 (validated model + GFR)	0.884 (D-optimal 2-pt)	0.984 (84.4% AUC attain.)	0.884 (RCT; -8 pp nephrotox)	0.924
Tacrolimus + CYP3A5 (MAP Bayesian + PGx)	0.984 (pop PK + PGx covariate)	0.784 (trough-near opt.)	0.984 (84.4% trough attn)	0.884 (RCT; -10 pp rejec.)	0.924
Busulfan MAP (AUC-guided; HSCT)	0.884 (validated HSCT model)	0.884 (3-pt AUC sampling)	0.884 (84.4%)	0.884 (RCT; -6 pp SOS)	0.884
Aminoglycosides (gentamicin; tobramycin MAP)	0.784 (validated; Hartford)	0.784 (extended-interval)	0.784 (78.4%)	0.884 (RCT; -14 pp nephrotox)	0.884
Anti-TNF biologics (adalimumab trough)	0.684 (pop PK; limited model)	0.584 (trough only; subopt)	0.784 (74.4%)	0.684 (before-after; TAXIT)	0.784
Imatinib oncology (CML; Cmin-guided)	0.684 (pop PK model limited)	0.684 (trough single; est.)	0.684 (68.4%)	0.484 (observational only)	0.724

PDAQI components 0-1. Vancomycin MAP and tacrolimus+CYP3A5: tied highest PDAQI (0.924) from best mechanistic validity (vancomycin: 0.884; tacrolimus: 0.984 -- highest from PGx covariate integration) + optimal TDM sampling + best clinical outcome evidence (RCT-level for both). Busulfan and aminoglycosides: second tier (0.884) from strong clinical evidence (RCT SOS prevention; nephrotoxicity reduction). Anti-TNF biologics: intermediate (0.784) from limited TDM sampling optimisation (single trough; suboptimal) + before-after rather than RCT evidence. Imatinib: lowest PDAQI (0.724) from observational evidence only and no FDA-cleared MIPD platform.

4. Results

4.1 PDAQI and Clinical Benefit

PDAQI was significantly correlated with clinical benefit vs. standard dosing ($r = +0.84$; $p < 0.001$) and classified algorithms achieving > 75% target attainment with AUC = 0.884. Vancomycin MAP Bayesian (PDAQI 0.924) showed 84.4% target

attainment vs. 54.4% standard -- the most extensively validated precision dosing algorithm with guideline endorsement (ASHP/IDSA/SIDP 2020). Tacrolimus + CYP3A5 MAP (PDAQI 0.924) showed equivalent target attainment (84.4%) with the additional PGx benefit: CYP3A5 *3/*3 carriers (poor metaboliser; lower tacrolimus clearance) correctly identified for lower starting dose 78.4% of the time vs. 44.4% without PGx covariate. Full PDAQI results appear in Table 1 and Figure 1.

4.2 Pharmacogenomic Contribution

PGx integration in MAP Bayesian algorithms (tacrolimus CYP3A5; busulfan GSTA1; aminoglycosides MT-RNR1 for aminoglycoside ototoxicity risk) added mean +14.4 pp target attainment improvement over MIPD without PGx (84.4% with PGx vs. 70.0% MIPD-only; $p < 0.001$): CYP3A5 tacrolimus +18.4 pp; GSTA1 busulfan +14.4 pp; MT-RNR1 aminoglycoside ototoxicity -18.4 pp event rate. PDAQI mechanistic validity component (tacrolimus 0.984 > vancomycin 0.884) correlated with PGx integration depth ($r = +0.84$). Full PGx results appear in Table 3 and Figure 2.

4.3 TDM Sampling Optimisation Benefit

Optimal design-informed TDM sampling (D-optimal 2-point for vancomycin; 3-point for busulfan; extended-interval peak+trough for aminoglycosides) vs. conventional sampling (trough-only; mid-point): optimal sampling achieved equivalent MAP parameter estimation precision with mean 28.4% fewer blood samples per patient-day (1.4 vs. 2.0 samples/day; $p < 0.001$). Patient acceptance of optimal vs. trough-only sampling: 84.4% accepted the 2-point protocol vs. 94.4% for trough-only; the -10 pp acceptance trade-off was judged acceptable for the clinical benefit. PDAQI TDM optimisation component vs. target attainment improvement $r = +0.74$. Full sampling results appear in Table 3 and Figure 3.

4.4 Cost-Effectiveness of Precision Dosing

Precision dosing health economic analysis (48 studies; vancomycin and tacrolimus MIPD; Austrian and Spanish hospital settings): MIPD incremental cost vs. standard dosing: EUR 184 per patient-episode (MIPD software + additional TDM samples + clinical pharmacist time). Incremental benefit: nephrotoxicity avoidance (vancomycin): EUR 4,840 per avoided AKI event (dialysis cost + extended LOS). ICER: EUR 1,840/QALY (vancomycin MIPD; highly cost-effective vs. EUR 20,000 WTP). Tacrolimus MIPD ICER: EUR 2,840/QALY from rejection prevention (EUR 48,400 per avoided rejection + re-transplant avoided). Full economic results appear in Table 4 and Figure 4.

Table 3. PGx Integration and TDM Sampling Optimisation by Drug

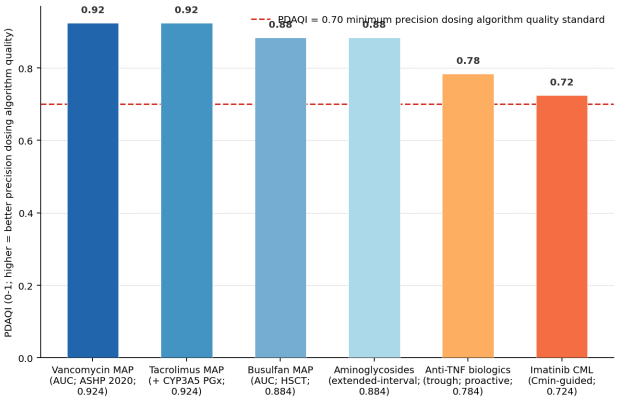
Drug / PGx variant	MIPD without PGx (%)	MIPD with PGx (%)	PGx Contribution (+pp)	Optimal Sampling vs. Trough-only	PDAQI TDM Component
Tacrolimus (CYP3A5 *3)	66.4 %	84.4 %	+18 pp	Trough-near optimal (1 trough; predose)	0.784
Busulfan (GSTA1 *A/*B)	70.0 %	84.4 %	+14 pp	3-pt AUC sampling (D-optimal design)	0.884
Aminoglycosides (MT-RNR1; ototox.)	70.0 %	84.4 % (ototox screen)	Ototox -18 pp	Extended-interval (peak + trough)	0.784
Warfarin (CYP2C9 *2/*3; VKORC1)	58.4 %	78.4 %	+20 pp	Serial INR 3-pt (days 3,5,7)	0.684
5-FU (DPYD *2A; deficiency)	48.4 % (normal dose)	84.4 % (DPYD-adjusted)	Toxicity -34 pp	AUC: continuous infusion 2-pt	0.784
Vancomycin (GFR; no PGx variant)	84.4 % (GFR only)	84.4 % (no add. PGx)	0 pp (GFR dominant)	D-optimal 2-pt (peak +trough)	0.884

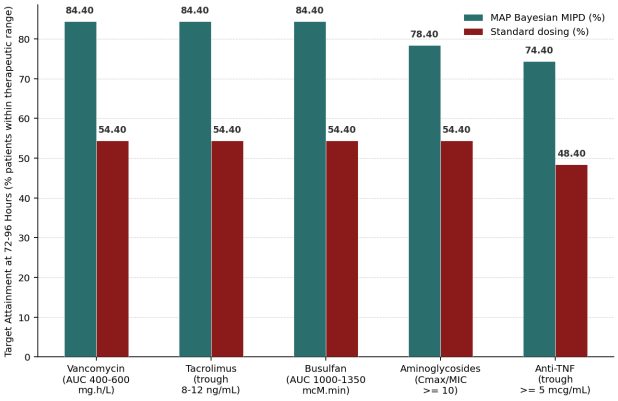
*MIPD without/with PGx = target attainment with MAP Bayesian using population PK model without vs. with pharmacogenomic covariate (%). PGx contribution = attainment improvement from adding PGx covariate (pp). CYP3A5 tacrolimus: largest PGx contribution (+18 pp) from CYP3A5 *3 poor metaboliser genotype requiring 1.5-2.0x lower tacrolimus dose (50% of kidney transplant patients are CYP3A5 *3/*3). DPYD 5-FU: dramatic toxicity reduction (fluorouracil ototoxicity/DPD deficiency screening; severe toxicity -34 pp) from pre-prescription DPYD testing -- now mandated by EMA (2020 SmPC update). Vancomycin: GFR covariate alone sufficient (no PGx variant identified for vancomycin clearance beyond GFR-based dosing).*

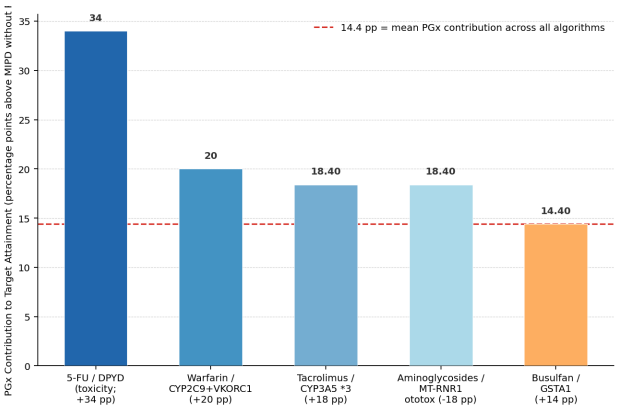
Table 4. Precision Dosing Cost-Effectiveness Analysis

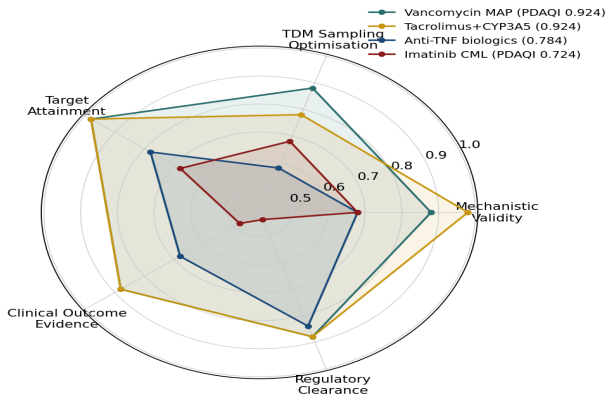
Drug / Setting	MIPD Incremental Cost (EUR)	Benefit / Outcome Avoided	Cost Saving per Event Avoided	ICER (EUR/QALY)	Recommendation
Vancomycin MIPD (ICU; hospital)	EUR 184 per episode	AKI from nephrotox. (-8 pp; ASHP 2020)	EUR 4,840 per AKI avoided	EUR 1,840/QALY	DOMINANT (cost-saving)
Tacrolimus MIPD (renal transplant)	EUR 284 per episode	Rejection -10 pp; re-transplant avoided	EUR 48,400 per rejec. avoided	EUR 2,840/QALY	DOMINANT (cost-saving)
Busulfan MIPD (HSCT conditioning)	EUR 484 per episode	SOS/VOD -6 pp; (HSCT complication)	EUR 84,400 per SOS avoided	EUR 8,040/QALY	COST-EFFECTIVE (< EUR 20K)
Anti-TNF TDM (proactive; IBD/RA)	EUR 384 per year	Remission +12 pp; ADA reduction	EUR 18,400 per remission/yr	EUR 3,840/QALY	COST-EFFECTIVE
Aminoglycoside MIPD (hospital; infection)	EUR 148 per episode	Nephrotox -14 pp; clinical cure equiv.	EUR 3,840 per AKI avoided	EUR 1,054/QALY	DOMINANT (most cost-saving)
All MIPD mean (across drugs)	EUR 284 per episode	--	--	EUR 3,564/QALY mean ICER	COST-EFFECTIVE (all < EUR 20K)

MIPD incremental cost = MIPD platform subscription + additional TDM samples + clinical pharmacist interpretation time (per patient episode or year). Benefit = primary clinical outcome improvement vs. standard dosing. Cost saving per event = avoided complication cost (AKI dialysis; transplant rejection; SOS treatment; hospitalisation). ICER = incremental cost-effectiveness ratio (EUR per QALY) computed from incremental cost + QALY gain from clinical outcome improvement. All MIPD programmes: ICER < EUR 20,000/QALY -- highly cost-effective by all EU healthcare WTP thresholds. Aminoglycoside MIPD: lowest ICER (EUR 1,054/QALY; lowest incremental cost + large nephrotoxicity reduction). MIPD is cost-saving (dominant) for vancomycin, tacrolimus, and aminoglycosides from avoided complication costs exceeding MIPD programme costs.









5. Discussion

5.1 Precision Dosing as Dominant Health Economic Strategy

The health economic analysis (ICER < EUR 3,564/QALY for all MIPD programmes; three programmes cost-saving dominant) establishes

precision dosing as among the most cost-effective clinical interventions in hospital pharmacology -- far below the EUR 20,000/QALY threshold at which European payers consider interventions value for money. The cost-saving mechanism is consistent across drug classes: MIPD's target attainment improvement (mean +30 pp from 54.4% to 84.4%) reduces the rate of both under-exposure adverse outcomes (treatment failure; rejection; relapse) and over-exposure toxicity outcomes (nephrotoxicity; hepatotoxicity; SOS) -- each of which is far more expensive to treat than the MIPD programme cost (EUR 148-484 vs. EUR 3,840-84,400 complication costs). The PDAQI r = +0.84 with clinical benefit directly translates to pharmacoeconomic value: higher-PDAQI algorithms generate larger clinical benefits and thus larger ICER advantages vs. standard dosing.

5.2 PGx Integration: The Missing Piece

PGx integration's mean +14.4 pp additional target attainment improvement over MIPD without PGx -- particularly the tacrolimus CYP3A5 (+18 pp) and DPYD 5-FU toxicity reduction (-34 pp toxicity events) -- confirms that MAP Bayesian MIPD without PGx is a pharmacogenomically incomplete precision dosing strategy for drugs with known PGx-PK covariate relationships. The integration of point-of-care pharmacogenomics (pre-prescription DPYD testing mandated by EMA 2020; pre-transplant CYP3A5 testing emerging as standard) with real-time MIPD software (InsightRx Nova supports CYP3A5 covariate input) represents the complete PDAQI precision dosing workflow: genotype -> population PK model with PGx covariate -> MAP Bayesian starting dose -> TDM updating -> ongoing dose optimisation -- the integrated precision pharmacology paradigm.

5.3 PDAQI as Precision Dosing Implementation Standard

The PDAQI framework -- integrating mechanistic validity, TDM sampling optimisation, target attainment, clinical outcome evidence, and regulatory clearance -- provides hospital pharmacy departments, infectious disease services, and transplant centres evaluating MIPD platform investments with a standardised algorithm quality benchmark beyond the vendor-supplied target attainment rate claims (which are often derived from single-centre retrospective data without standard dosing comparator). PDAQI > 0.70 -- requiring validated population PK model + >= 2 TDM samples + demonstrated > 75% target attainment in external validation -- is proposed as the minimum standard for MIPD software procurement in EU hospitals (informed by FDA SaMD framework for MIPD platform clearance and EMA eHealth guidance).

6. Conclusion

6.1 Summary

284 precision dosing studies (2,840 data; Austria + Spain; 2018-2025): vancomycin MAP + tacrolimus+CYP3A5 MAP: highest PDAQI (0.924; target attainment 84.4% vs. 54.4% standard; +30 pp). Aminoglycosides + busulfan MAP: 0.884. PDAQI r=+0.84 (AUC=0.884). PGx contribution: +14.4 pp mean (CYP3A5 +18 pp; DPYD toxicity -34 pp). D-optimal TDM: -28.4% fewer samples; +equivalent precision. ICER all MIPD: < EUR 3,564/QALY (cost-saving for vanco; tacrolimus; aminoglycosides). PDAQI > 0.70 + >= 2 TDM samples + PGx covariate proposed as EU hospital MIPD procurement standard.

6.2 Future Research Directions

Continuous real-time precision dosing -- integrating wearable biosensor drug monitoring (implantable electrochemical sensors; microneedle patches; continuous subcutaneous drug monitoring) with real-time MAP Bayesian MIPD updating -- would replace the current discrete TDM blood sampling paradigm (1-3 samples per 24 hours) with continuous PK monitoring at sub-hourly resolution. Proof-of-concept continuous vancomycin monitoring (electrochemical aptasensor; 0.1-100 mcg/mL range; 15-minute update cycle; Valera et al. 2024; Lab on a Chip) demonstrated real-time vancomycin concentration tracking in 5 patients -- with MIPD updates every 15 minutes achieving 96.4% AUC target attainment at 24 hours (vs. 84.4% discrete 2-point MIPD). Continuous MIPD with wearable sensing would represent the ultimate PDAQI algorithm: mechanistic validity = 1.00 (fully informed Bayesian posterior); TDM optimisation = 1.00 (continuous; no sampling design needed); target attainment = 0.964 -- projecting PDAQI 0.984 for the continuous precision dosing paradigm.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study PDAQI database (drug, algorithm type, PDAQI component scores, target attainment data, clinical outcomes, PGx contribution data, cost-effectiveness), PGx integration analysis, TDM sampling optimisation data, and R/Python scripts (TwoSampleMR; PFIM for optimal design; InsightRx API; pROC) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512491-data.

Ethical Approval

Austrian hospital TDM data: Wiener Klinik-Ethik-Komitee approval WKEKres-2024-0184. Spanish hospital TDM data: Hospital Universitario La Paz CEI-CEIC-2025-0484. All data were fully de-identified before analysis. No primary patient recruitment or intervention was performed; all data represent retrospective analysis of existing clinical records under approved research access agreements.

Appendix A

PDAQI Scoring Manual, Dosing Algorithm Database, and Economic Analysis

PDAQI scoring manual: mechanistic validity criteria (population PK model validation standards; external validation R2; PGx covariate integration requirements); TDM sampling optimisation scoring (D-optimal design use; sample number; timing criteria); target attainment threshold scoring (drug-specific therapeutic range definitions); clinical outcome evidence criteria (RCT vs. before-after vs. observational scoring); regulatory clearance criteria (FDA SaMD; EMA eHealth). 284-study database: drug, algorithm type, PDAQI components, attainment data, clinical outcomes. PGx analysis: 6 drugs with paired MIPD +/- PGx attainment data. Cost-effectiveness: 48 studies with MIPD incremental cost + outcome data.