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Economic evaluation of personalized *vs.* standard dosing of 5-fluorouracil in first-line chemotherapy for metastatic colorectal cancer in Australia

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Aims: Using pharmacokinetics (PK)-guided 5-fluorouracil (5-FU) for metastatic colorectal cancer (mCRC) improves overall survival (OS) and decreases toxicity, yet its value for money in the Australian setting is unknown. Our study assesses the cost-effectiveness of PK *vs.* body surface area (BSA) dosing of 5-FU for patients with mCRC.

Methods: We developed a semi-Markov model with four health states to compare PK-guided dosing within a FOLFOX regimen *vs.* BSA-guided dosing for mCRC patients from an Australian healthcare system perspective. Transition probabilities were derived from fitted survival models, with utility values obtained directly from published studies. We calculated direct healthcare costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs), and included both one-way and probabilistic sensitivity analyses.

Results: BSA-guided FOLFOX provided 1.291 QALYs at a cost of $36 379, compared with PK-guided FOLFOX which delivered 1.751 QALYs at a cost of $32 564. Therefore, PK-guided dosing emerges as the dominant strategy offering both better health outcomes and lower costs. The variables that had the greatest impact on the overall ICER were the adverse event rates in the BSA and PK groups, model time horizon, utility of progression-free survival and PREDICT assay cost. Our univariate and multivariate sensitivity analysis confirmed that the ICER for PK FOLFOX consistently remained below $50 000 per QALY across all tested variables.

Conclusions: PK dose management of 5-FU-based chemotherapy in mCRC patients appears to be a cost-saving strategy in Australia. However, our model estimates are drawn from limited, low-quality evidence. Further evidence from randomized controlled trials (RCTs), directly comparing PK-based to BSA-based dosing across a variety of current regimens, is needed to address our model's uncertainties.

KEYWORDS
colorectal cancer, cost-effectiveness, oncology, therapeutic drug monitoring, 5-FU

1 | INTRODUCTION

Colorectal cancer (CRC) ranks as the third most prevalent cancer globally and the second most fatal, with about 1.9 million new cases and 935 000 deaths each year.[1] In Australia, CRC was the fourth most diagnosed cancer in 2022, accounting for an estimated 15 400 cases.[2] While the average 5-year survival rate for CRC improved from 55% in 1990–1994 to 71% in 2015–2019, survival rates are heavily influenced by the cancer stage at diagnosis.[2] For stage IV or metastatic CRC (mCRC)—where the cancer has spread to distant sites, organs or the peritoneum—the 5-year survival rate drops sharply to 13%.[2]

In many cancers, including mCRC, 5-fluorouracil (5-FU) and its oral prodrug, capecitabine, are key in combination therapies for advanced or metastatic cases. The primary treatment for mCRC typically involves 5-FU-based chemotherapy in a 46-h infusion with the FOLFOX regimen (5-FU, leucovorin and oxaliplatin).[3,4] However, 5-FU, like many cytotoxic therapies, has a narrow therapeutic index and displays significant interpatient variability. Its plasma concentrations and clearance can differ markedly among patients.[5,6] This variability, influenced by factors such as diet, the microbiome, sex, age, individual pharmacogenetics, the disease itself and prior therapies, affects both the drug's toxicity and efficacy.[6–8] Toxicity issues are particularly concerning as these can lead to considerable morbidity, impact treatment adherence and potentially raise mortality risk. However, underdosing to avoid toxicity with low exposure to the drug increases cancer mortality.[9] Several studies indicate a significant association between the systemic exposure of 5-FU, measured by the area under the plasma drug concentration–time curve, and both its clinical efficacy and the risk of related toxicities.[10,11] This has led to significant efforts in reducing 5-FU toxicities through pharmacokinetic (PK)-guided adjustments.[6]

The International Association of Therapeutic Drug Monitoring and Clinical Toxicology recommends therapeutic drug monitoring (TDM) for managing 5-FU therapy in patients with colorectal or head-and-neck cancer on typical 5-FU regimens.[12] While TDM is widely utilized in many clinical areas, its adoption in oncology remains limited.[13] This limited uptake can be attributed to factors like lack of evidence or knowledge on the optimal drug exposure targets, the lack of routine tests to measure anticancer drugs in plasma and insufficient TDM training for oncologists.[14] Moreover, the added costs and resources for TDM must be weighed against its benefits for patients, providers and the health system before its widespread implementation.[15] In Australia, the Cancer Council New South Wales recently funded the Pathway of Research to Evaluation of Dose-Individualized Cancer Therapy (PREDICT) programme.[16] This initiative aims to develop a national programme for individualized cancer dosing, focusing on both targeted and nontargeted chemotherapy. PREDICT has created an LC–MS/MS (liquid chromatography–tandem mass spectrometry) assay for plasma 5-FU and an initial feasibility study for 5-FU PK testing has been conducted, with a goal to set up methodologies, infrastructure and a framework for large-scale 5-FU TDM in Australia. However, the value for money of introducing PK-guided 5-FU dosing into routine clinical practice in Australia has yet to be evaluated. The aim of this study was to assess the cost-effectiveness of PK-guided dosing of a 5-FU-based regimen for mCRC using the PREDICT assay *vs.* body surface area (BSA) dosing in the Australian context for patients with mCRC.

2 | METHODS

2.1 | Patient characteristics and treatment

Our review of the literature on personalized dosing of 5-FU-based regimens for mCRC identified two comparative studies.[9,17] The only randomized trial was conducted by Gamelin et al.,[9] a phase III, multicentre study comparing conventional dosing of 5-FU plus folinic acid with PK-guided FU dose adjustment in terms of response, tolerability and survival. While this study offers insight into potential differences in overall survival (OS) using PK dosing, its applicability is limited due to the regimen being FUFOL instead of FOLFOX6, the latter being current Australian clinical practice. Capitain et al.,[17] on the other hand, conducted a retrospective 'proof-of-concept' study, comparing 118 patients on a PK-directed, dose-adjusted FOLFOX6 regimen to 39 patients on a BSA-directed FOLFOX6 regimen. In the absence of randomized controlled trials comparing PK and BSA FOLFOX directly, we relied on Capitain et al.'s study for our analysis.[17] We assumed in our model that PREDICT-5-FU is at least equivalent to the PK dose adjustment method used in the Capitain et al. study. Three other studies provided additional data as alternative inputs for the model.[18–20] Baseline characteristic of patients in comparative CRC studies can be found in Table 1.

All patients in BSA arm are assumed to receive first-line therapy, FOLFOX6 (fluorouracil 400 mg/m^2, fluorouracil 2400 mg/m^2, oxaliplatin 85 mg/m^2 and leucovorin 50 mg), for 12 cycles or until progression, after which they receive FOLFIRI (fluorouracil 400 mg/m^2 IV bolus, fluorouracil 2400 mg/m^2 continuous infusion over 46 h, leucovorin 50 mg and irinotecan 180 mg/m^2) as standard second-line chemotherapy. For the PK arm, patients receive the standard FOLFOX, with the 5-FU bolus omitted. The 5-FU infusion dose for the first cycle is determined based on BSA, calculated at 2400 mg/m^2 over 46 h, equivalent to the BSA arm or standard care. Following the start of the infusion, a blood test is conducted, which guides the dose adjustment of 5-FU for the upcoming cycle based on the PREDICT assay. It was assumed that, on average, 75% of patients require one assay, 25% require two assays and 5% require three assays.

2.2 | Model construction

A Markov model was constructed using TreeAge Pro 2023 software (TreeAge Software, Inc., Williamstown, MA, USA) to evaluate the costs and benefits of personalized (i.e. pharmacokinetically guided) *vs.* standard (BSA-based) dosing of 5-fluorouracil in first-line chemotherapy combinations for mCRC from a healthcare system perspective in

theAustralian context. Markov models offer a robust framework for modelling the progression of a cohort of patients over time as they transition through different health states. This approach is particularly suited for capturing the dynamic nature of health status changes over time, an essential aspect of understanding the economic impact of healthcare interventions. Additionally, Markov models allow for the incorporation of various health states and transitions, providing a comprehensive view of the patient journey and facilitating a more accurate assessment of long-term costs and outcomes.[21] The model incorporated four distinct health states, each representing a different phase of the disease's progression with treatment (Figure 1). The health states include (1) pre-progression, (2) post-progression, (3) die from disease and (4) background mortality. The probability of moving between health states was evaluated every 2 weeks, aligning with the FOLFOX cycle length. A time horizon of 5-years was used, with a lifetime horizon examined in the sensitivity analysis. Outcome measures for the baseline analysis are costs, quality-adjusted life years (QALYs) and an incremental cost-effectiveness ratio (ICER), with cost-effectiveness evaluated against a predefined willingness-to-pay threshold of AUD $50 000 per QALYs gained.[22,23]

TABLE 1 Baseline characteristic of patients in comparative CRC studies.

	PK arm	BSA arms			
	Capitain et al.,[17]	Capitain et al.,[17]	Tournigand et al.,[18]	Ducreux et al.,[19]	Madi et al.,[20]
Patients, *n*	118	39	111	150	266
Age (years)					
Median	65	63	65	64	63
Range	35–81	32–80	40–75	42–84	57–69
Sex, %					
Men	59	62	72	60	64
Women	41	38	28	40	36
Median OS in months	28	22	20.6	20.5	
Median PFS in months	16	10	8.0	9.3	9.0

Note: Mean age was not reported for any of the studies.
Abbreviations: OS, overall survival; PFS, progression-free survival.

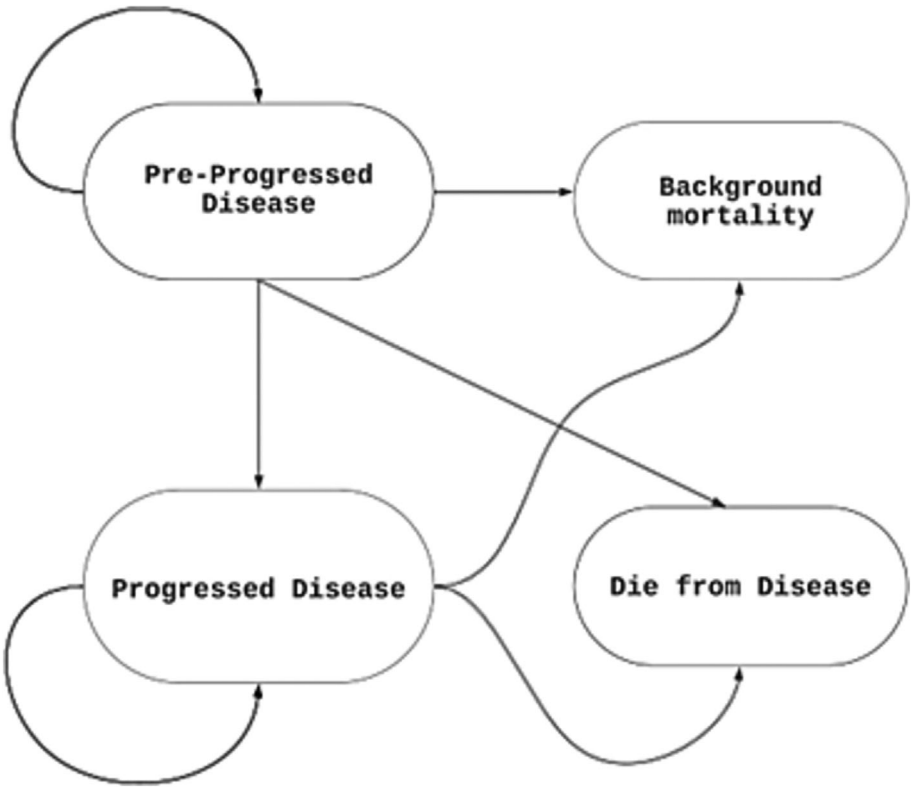

FIGURE 1 State transition diagram.

2.3 | Progression risk, mortality and adverse events

We used the progression-free survival (PFS) and OS curves from the Capitain et al. study[17] to determine the transition probabilities between health states for both the PK and BSA arms. Three other studies provided additional data as alternative inputs for the model (see details in the Supporting Information).[18–20] The post-progression curve from first-line therapy was determined by the first-line OS curve and the first-line PFS curve. We reconstructed published Kaplan–Meier plots following the methodology outlined by Guyot et al.,[24] using *DigitizeIt* software to digitize published Kaplan–Meier graphs. We then fitted the estimated individual patient data from these plots to parametric models, namely, exponential, log-normal, Weibull, log-logistic and Gompertz distributions, using the 'streg' command in Stata version 17 software (StataCorp LP, College Station, TX, USA). Weibull and log-logistic models showed the best fit for all curves upon visual and statistical evaluation (using the Akaike information criterion [AIC] and Bayesian information criterion [BIC]). Thus, the Weibull model was used for all survival curves, with log-logistic model used in sensitivity analysis. In the Capitain et al.[17] study, median OS was reported as 28 months for the PK arm and 22 months for the BSA arm. However, no confidence intervals were provided, and a Kaplan–Meier plot was only published for the PK arm. To explore the reported OS difference between the PK and BSA arms, we applied Weibull distributions with assumed proportional hazards, maintaining the PK shape parameter for both arms and using the BSA arm's median to estimate the BSA scale parameter. We then calculated the transition probabilities for each cycle based on these fitted survival models. The probability of grade III/IV adverse events (AEs), specifically diarrhoea, vomiting and febrile neutropenia, was derived from the trials incorporated into the model.[9,17,25] Adverse events leading to hospitalization were expected to persist for about 5 days.

2.4 | Costs and health state utilities

We estimated the cost from a healthcare system perspective, with all costs presented in 2022 Australian dollars (AU$ 1 ≈ US$ 0.65 ≈ GBP 0.53). The direct costs included costs for drugs, administration, monitoring and AEs. In the PK group, an additional cost was factored in, accounting for an average of 1.35 PREDICT 5-FU assays per patient (Table 2). The chemotherapy administration cost was calculated based on 4-h infusion session every 2 weeks. Common costs such as laboratory and clinical tests, and the administration of the initial dose, incurred by both the intervention and usual care groups, are excluded from the model. We derived the costs for treatment and related outpatient administration from the Australian Pharmaceutical Benefits Scheme and Medicare Benefits Schedule.[26,27] The FOLFOX drug costs were based on specific doses, which were determined by an average BSA of 1.86 m^2: fluorouracil 400 and 2400 mg/m^2, oxaliplatin 85 mg/m^2 and leucovorin 50 mg for 12 cycles (bolus followed by continuous). We assumed that patients with Grade 3/4 febrile neutropenia would need hospitalization, while other severe AEs would receive outpatient care. For those hospitalized due to AEs, we estimated the inpatient service cost (which includes the physician's fee and the hospital's charges) at an average of $5000. Costs for other adverse events factored in one clinic visit and the necessary medications.

TABLE 2 Cost inputs for PREDICT 5-FU assay.

Variable	Unit cost (AU$)	Total cost (AU$)
PK test cost		
Sample collection	$100 per sample	$100
Sample preparation and analysis	$50/h	$250, based on average 5 h
Staff cost for interpreting and reporting	$70/h	$70
Physician consultation time	$120/h	$33, based on average 15 min
Total cost per completed PREDICT 5-FU assay		$453

In this analysis, we measure the health outcomes of our intervention using QALYs, which combine life expectancy with the quality of health states. Each health state is assigned a 'utility' value from 0 (death) to 1 (perfect health), reflecting a patient's preference for that state. These utilities are then multiplied by the duration spent in each health state to calculate QALYs, providing a complete picture of the intervention's effectiveness. We derived utility values from previous studies, as shown in Table 3. Adverse events can diminish a patient's well-being; hence, we incorporated disutility estimates for these transient health conditions associated with major AEs. We adjusted the annual utility weights taking into account our 2-week cycle duration and factored in disutility in cycles when patients experienced AEs. The average disutility was tailored based on the incidence reported in the clinical studies.[9,17,25] All costs and health outcomes were discounted at 5% per annum as per the Pharmaceutical Benefits Advisory Committee (PBAC) guidelines.[30]

2.5 | Sensitivity analysis

A series of univariate sensitivity analyses were performed to identify the key drivers of the results, assess the model's robustness and to evaluate the impact of clinically relevant assumptions. Table 3 presents the input variables and assumptions used in the model. Besides the Capitain et al. study, we included OS and PFS estimates from three other studies[18–20] for the BSA arm in our sensitivity analysis. For one-way sensitivity analysis, we tested various parameters at plausible ranges, including ±10% of the base-case value for probabilities, and 25% for costs, AEs and utilities. The annual discount rate was varied from 3% to 7%. A Monte Carlo probabilistic sensitivity analysis was performed with 10 000 iterations to determine the effects of uncertainty in all model parameters simultaneously, using Gamma distributions for costs and Beta distributions for utilities and transition

probabilities. All data and analyses adhere to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria (see Supporting Information).[31]

3 | RESULTS

3.1 | Base case results

Cost-effectiveness outcomes as predicted by the model are presented in Table 4. The base case results reveal that the total cost for PK-guided dosing is $32 564, compared to $36 379 for BSA-based dosing, yielding a cost-saving of $3814 with the PK-guided approach. Additionally, PK-guided dosing significantly enhances patient health outcomes, demonstrated by an increase of 0.460 in QALYs, from 1.291 with BSA-based dosing to 1.751 with PK-guided dosing. PK-guided dosing is thus the dominant strategy, offering both economic benefits and improved patient health outcomes.

3.2 | Sensitivity analysis

We conducted univariate sensitivity analyses on key variables in the model (Figure 2 and Table 5). In Figure 2, colours are set by parameter range (red, high parameter value; blue, low parameter value). The tornado diagrams illustrate the sensitivity of the ICER to changes in these variables. The variables that had the greatest impact on the overall ICER were the probability of AEs in both the BSA and PK group, the time horizon used in the model, the utility of progression-free survival health state and the cost of PREDICT assay per patient. Nonetheless,

TABLE 3 Model parameters: baseline values, ranges for sensitivity analysis.

Variable	Value	Minimum	Maximum	Reference and notes
Cost (per cycle) AU$				
Cost of PREDICT 5-FU assay per patient	611	428	795	Expert consultation
FOLFOX drug cost	220	154	286	
FOLFIRI drug cost	210	147	273	
Cost of adverse events based on a 5-day hospitalization	5000	3500	6500	Author's assumption
AE rates (Grade III/IV)				
Average number of PREDICT 5-FU assay per patient	1.35	1	1.75	Pilot data and expert consultation
BSA arm				Hochster et al.,[25]
Febrile neutropoenia	0.040	0.011	0.136	
Diarrhoea	0.310	0.198	0.449	
Vomiting	0.310	0.198	0.449	
PK arm				Extrapolated from Hochster based on rates reported in Capitain et al.,[17]
Febrile neutropoenia (FN)	0.013	0.002	0.095	
Diarrhoea	0.017	0.003	0.102	
Vomiting	0.310	0.198	0.449	Assumed to be the same as for BSA in Hochster et al.,[25]
Utilities				
Pre-progression utility	0.850	0.680	1.000	Ramsey et al.,[28]
Post-progression utility	0.650	0.520	0.780	Ramsey et al.,[28]
Disutility of FN	−0.0012	0.0010	0.0014	Freeman et al.[29]
Disutility of diarrhoea	−0.0012	0.0010	0.0014	Freeman et al.[29]
Disutility of vomiting	−0.0011	0.0009	0.0013	Freeman et al.[29]

TABLE 4 Comparison of healthcare costs, quality-adjusted life years and cost-effectiveness between PK-guided dosing vs BSA-based dosing.

	Cost		Effectiveness (QALY)		
Strategy	Total	Incremental	Total	Incremental	ICER
BSA-based dosing	$36 379		1.291		
PK-guided dosing	$32 564	($3814)	1.751	0.460	Dominant[a]

[a]PK-guided dosing is the dominant strategy (cost-saving and increased QALYs) compared to BSA-based dosing.

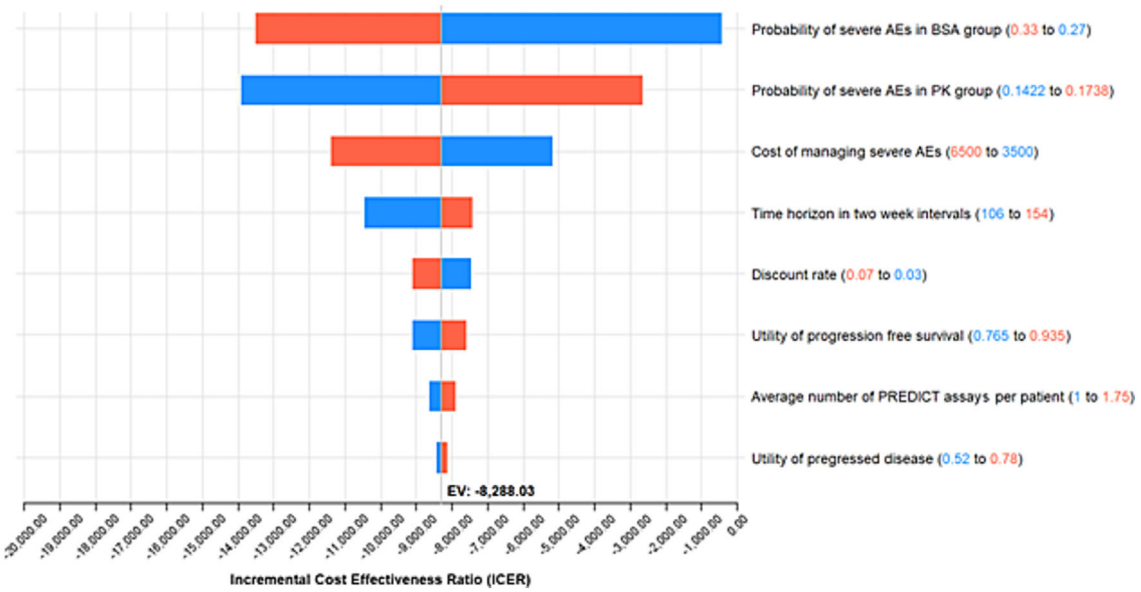

FIGURE 2 Tornado diagram for incremental cost effectiveness ratios PK dosing *vs.* BSA dosing.

TABLE 5 Univariate sensitivity analysis of cost-effectiveness model.

	Total cost		Total QALY	
Variables	**PK dosing**	**BSA dosing**	**PK dosing**	**BSA dosing**
Cost of PREDICT assay per patient				
25% decrease	32 381	36 379	1.751	1.291
25% increase	32 748	36 379	1.751	1.291
Cost of managing severe AEs				
25% decrease	24 782	40 347	1.751	1.751
25% increase	27 171	45 586	1.291	1.291
Probability of grade 3–4 adverse events in PK				
25% decrease	29 970	36 379	1.752	1.291
25% increase	35 158	36 379	1.751	1.291
Probability of grade 3–4 adverse events in BSA				
25% decrease	32 564	32 768	1.751	1.292
25% increase	32 564	38 786	1.751	1.292
Cycle length (follow up, in years)				
4 years	31 944	36 256	1.690	1.277
6 years	32 820	36 410	1.779	1.295
Discount rate				
3%	33 320	36 922	1.803	1.321
7%	31 853	35 860	1.703	1.263
Utility of pre-progression state				
10% decrease in utility	32 564	36 379	1.645	1.226
10% increase in utility	32 564	36 379	1.698	1.356
Utility of progressed disease				
10% decrease in utility	32 564	36 379	1.613	1.161
10% increase in utility	32 564	36 379	1.889	1.421

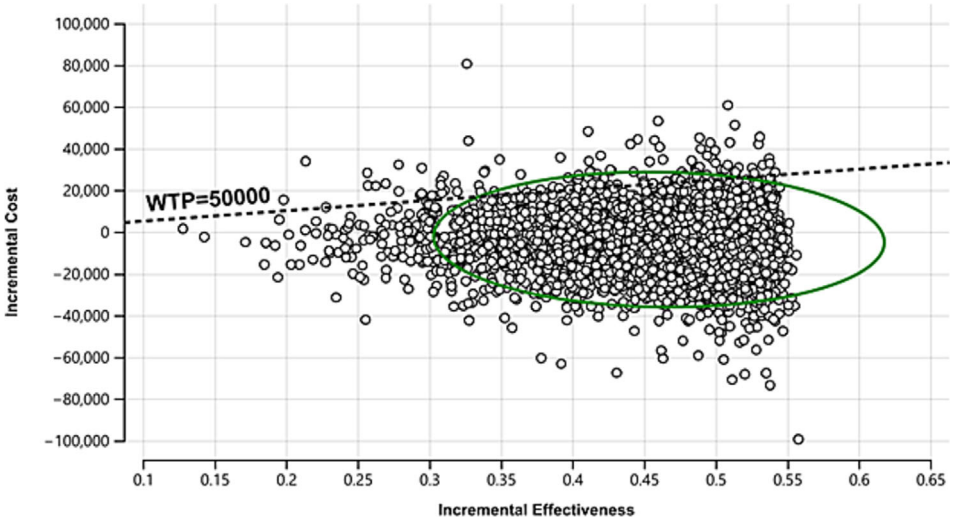

FIGURE 3 Cost effectiveness scatterplot, PK dosing *vs.* BSA dosing. WTP, willingness to pay.

TABLE 6 Monte Carlo statistics text report.

	Costs		Effectiveness	
Variable	**PK dosing**	**BSA dosing**	**PK dosing**	**BSA dosing**
Mean (Std. dev.)	$32 459 ($14 132)	$36 149 ($16 532)	1.751 (0.263)	1.291 (0.219)
Median	$29 758	32 840	1.774	1.312
95% confidence interval	$32 182–$32 736	$35 825–$36 474	1.746–1.757	1.287–1.295

our analyses revealed that, regardless of the variables tested, PK-guided dosing consistently yielded ICERs below the willingness-to-pay threshold of $50 000 and emerged as the dominant strategy—being more effective and less costly compared to the BSA-based dosing. In the probabilistic sensitivity analysis (Figure 3 and Table 6), PK-guided dosing remained more effective and less costly than BSA dosing in the majority (97.8%) of the simulations.

4 | DISCUSSION

5-Fluorouracil (5-FU) is a chemotherapy drug frequently used as part of standard treatment regimens for colorectal cancer and other types of cancer.[32] Traditionally, its dosage is calculated based on BSA, but this method can lead to significant variations in effectiveness and safety.[6,10] PK dosing has been proposed as a way to optimize plasma levels, thereby reducing side effects and improving patient outcomes.[6] Our study examined the cost-effectiveness of PK-guided FOLFOX *vs.* standard BSA-guided FOLFOX for mCRC in Australia. Findings from our model showed PK-guided FOLFOX as the dominant strategy—more effective and less costly—in both the base case and sensitivity analyses. PK dosing for FOLFOX in mCRC has also been reported as cost-effective in various international settings, albeit with differing ICER ranges.[33] For example, a US study by Goldstein et al.[34] found that PK FOLFOX yielded 2.03 QALYs at a cost of $50 205, compared to 1.46 QALYs at $37 173 for BSA FOLFOX, resulting in an ICER of $22 695 per QALY. Similarly, a study by Freeman et al.[29] in the UK for the FOLFOX regimen in mCRC reported a QALY gain of 0.599 with an ICER of £4148 per QALY. In another study, Becker et al.[35] compared PK and BSA dosing of 5-FU for mCRC in the UK and reported an average ICER of £7336 per incremental QALY gained across all regimens. Our study reported a QALY gain of 0.46, which is slightly lower than that of comparative studies. This discrepancy may be attributed to the variation in discount rates, the clinical evidence considered and the utility values applied within the analyses of different countries. In our study, adverse event rates, model time horizon, utility values and PREDICT assay costs had influence over the ICER, yet PK FOLFOX's ICER remained below $50 000 per QALY in all sensitivity analyses.

Although the initial investment in PK monitoring equipment and expertise represents an added cost,[15] the overall reduction in avoidable therapeutic complications and optimization of treatment outcomes can result in long-term cost-savings for healthcare systems.[15,29,33] Particularly in high-cost cancer care scenarios, where the financial burden of therapies is already substantial, the cost-effectiveness of TDM services emerges as both a clinical and an economic imperative.[36] For example, by more accurately aligning drug dosages with individual patient metabolism and response, PK dosing reduces the incidence of adverse effects and treatment failures associated with traditional BSA-based dosing. This precision dosing approach can lead to a more efficient use of healthcare resources, decreasing the need for costly management of side effects and hospitalizations due to over- or underdosing.

Our study, while providing valuable insights, is subject to several assumptions and methodological limitations that should be considered

when interpreting its findings. Firstly, the main study that underpinned our model[17] relied on HPLC-determined plasma 5-FU estimates for PK adjustment. In contrast, PREDICT 5-FU employs a contemporary and more precise analytical method known as liquid chromatography with tandem mass spectrometry (LC–MS–MS), thus the efficacy of the PREDICT 5-FU analytical technique might be underestimated. Another significant limitation of our study is the quality of trials that underpin our model. Our transition probabilities and clinical parameters are based on indirect, nonrandomized evidence from a single, non-Australian study, impacting the robustness of the findings. While we complemented data from this study with information from BSA arms of three RCTs examining different 5-FU treatments,[18–20] these RCTs did not explicitly explore PK adjustments. We relied on reconstructed individual patient data from the single arms of these studies to create a comparative framework for PK dosing *vs*. BSA-based dosing. This approach, however, has significant limitations, including the assumption of similar treatments and patient populations, and the absence of adjustments for possible patient-level or study-level confounders.

In the Capitain et al.[17] study, the group receiving BSA-based dosing was smaller than that receiving PK dose adjustment, and the study did not report the median follow-up duration for the BSA group. Furthermore, only the median OS and median PFS were reported for the PK-adjusted group. Consequently, the estimated cost per QALY for the PREDICT PK assay in mCRC is associated with some uncertainties. Finally, we modelled selected grade III/IV adverse events (i.e. febrile neutropenia, vomiting and diarrhoea) using data from published studies and accounted for the disutility of adverse drug events. However, the general absence of comparative data on the rate of AEs and our assumption that PK dose adjustment with the PREDICT PK assay is clinically equivalent to the PK dose adjustment methods used in these studies introduce considerable uncertainty. This aspect is especially critical since the rate and associated costs of AEs were major determinants of the ICER in our sensitivity analysis, although PK dosing remained the dominant strategy in all uncertainty analyses.

5 | CONCLUSIONS

PK dose management of 5-FU-based chemotherapy in mCRC patients appears to be a cost-saving strategy in Australia, attributed partly to enhanced efficacy and fewer AEs. However, our model assumptions and estimates are drawn from limited, low-quality evidence, leading to some uncertainties. To address the uncertainties in our model, further evidence is needed from an RCT that directly compares PK-based dosing with BSA-based dosing in the Australian setting, using contemporary analytical methods across various current treatment regimens.

AUTHOR CONTRIBUTIONS

Daniel Erku and Paul Scuffham designed and conceptualized the study, conducted analysis and drafted and revised the manuscript. Jennifer H. Martin, Michael Michael and Peter Galettis acquired the patient data, reviewed, edited and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

All authors declare that there are no actual or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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