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PHARMACOGENOMIC MACHINE LEARNING MODELS FOR PREDICTING INDIVIDUALIZED OPIOID AND ANESTHETIC DRUG RESPONSE IN CANCER SURGERY PATIENTS

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Abstract

Surgery patients with cancer can have very different responses to opioid and anesthetic medications because of variations in genetics, chronic medical conditions, previous cancer treatments, organ function, and physiologic shifts during surgery. However, traditional dosing methods, which are primarily age and body weight based or based on general clinical guidelines, are likely to miss this individual variability, thereby raising the possibility of sub-optimal analgesia, excessive sedation, delayed recovery, and opioid related side effects. This paper looks at pharmacogenomic machine learning models for predicting individualized opioid and anesthetic drug responses in cancer surgery patients. Machine learning models can detect complex patterns of drug-responses that are hard to discern using traditional statistics by incorporating genetic markers, pharmacokinetic and pharmacodynamic parameters, electronic health record data, intraoperative monitoring signals and clinical risk factors. The study emphasizes the promise of neural-pharmacokinetic/pharmacodynamic modeling, reinforcement learning, interpretable artificial intelligence, and model-informed precision dosing for aiding real-time decision making in the perioperative setting. These techniques can help stabilize the anesthetic, increase the effectiveness of the pain control, minimize toxicity, and promote recovery after surgery. But to make it to the clinic requires big and varied sets of data, external validation, transparent model interpretation, standardized reporting, ethical governance and incorporation into current clinical workflows. In conclusion, pharmacogenomic machine learning holds significant potential for advancing precision anesthesia in oncological surgery, potentially leading to more individualized, safer, and evidence-based perioperative care.

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INTRODUCTION

Presently, the use of precision medicine in oncological anesthesia is limited by the complexity of drug response, and the inter-individual variations in drug pharmacokinetics and pharmacodynamics can mask single-gene drug correlations (Murti, 2025). Thus, machine learning algorithms provide a powerful tool for integrating high-dimensional genomic data with clinical covariates to extract predictive patterns that are not discernible by univariate analyses (Belani, 2025; Zeng et al., 2024). Thus, through this data-driven method, clinicians can go beyond fixed dosage schemes to provide personalized anesthesia delivery, which can result in faster recovery and lower rates of adverse events in the perioperative period. The paradigm shift, based on the synergistic use of pharmacogenomics, the study of the influence of genetic variations on drug response, and machine learning, is especially relevant to cancer surgery patients, who frequently have intricate comorbidities, existing systemic disease, and have been affected by prior oncological treatments, making them more susceptible to surgery-related complications. The high stakes setting requires precise dosing to ensure the patient receives the correct drug, with the right dosage, that is not harmful to them. Traditional, weight-based and age-adjusted dosing guidelines are not sufficiently precise in this context, as opioids and anesthetics exhibit significant pharmacokinetic and Pharmacodynamic variability due to polymorphisms in metabolizing enzymes and drug transporters (Murti, 2025). Machine learning models with the ability to process high-dimensional data, including genomic sequences, can inform us of these subtle relationships between drug response and other data types, such as longitudinal electronic health record (EHR) data (Belani, 2025). These predictive frameworks help to identify concealed biomarkers of sensitivity or resistance to guide the development of dynamic dosing strategies that are tailored to an individual patient's physiological state throughout the perioperative continuum (Zeng et al., 2024; Belani, 2025). In addition, the use of these technologies in the perioperative setting has the potential to optimize intraoperative stability and enhance the effectiveness of the analgesic, and is an important step in reducing the side effects of opioids and supporting quicker, more reliable postoperative recovery pathways (Belani, 2025). However, there are significant challenges to overcome in order to move from successful model development to robust clinical application, such as the need for large datasets, diverse, and representative, the need to develop interoperable computational infrastructures that operate in real-time, and the need for clear, interpretable algorithmic decision-making that engenders clinician confidence and patient safety (Belani, 2025). In conclusion, the integration of pharmacogenomic machine learning models into cancer surgery offers a transformative step in "personalized medicine," moving beyond a one-size-fits-all approach to a patient-centered one that hinges on a more comprehensive understanding of genetic risk factors and their interactions with drugs and other factors. The potential of pharmacogenomic machine learning models in cancer surgery is a promising development in the field of personalized medicine, where the approach is not one-size-fits-all but patient-centered, accounting for a more detailed knowledge of the genetic risk factors and how they interact with different drugs and other factors. These proactive systems can also help shift to value-based payments by providing real-time risk stratification and automated decision support that goes beyond standard statistical analyses (Giordano et al., 2021). These algorithms are changing the way clinical practice is conducted by replacing the traditional

one-size fits all approach with a more proactive and predictive one, as stated by Khanna & Gan (2022) moving from the "Procrustean bed" of standard pathways. This requires the development of models that merge genomic data with critical real-time clinical workflow, moving beyond the standard homogeneous practice patterns to more advanced and molecular-knowledgeled therapeutic approach (Hofer et al., 2020), (Brydges et al., 2024). The research paths to date highlight the importance of integrating information on the clinical procedure with patient-level pharmacogenetic data, which will eventually lead to the selection of the best analgesic and anesthetic regimen for each oncological patient (Althans et al., 2024). These predictive models need to be validated across multicenter cohorts and across the large variation found in real-world clinical data to ensure their generalizability (Nair et al., 2020; Sajdeya & Narouze, 2024). Furthermore, for these computational frameworks to be meaningfully adopted into clinical practice, there is a need for standardization so that they can be integrated into the current healthcare workflows (Hao et al., 2025). Moreover, the transition from a model as to a clinical integration requires a focus on model interpretability because clinicians need to know the rationale behind the decisions made by the algorithm for safe and effective implementation. In high-stakes scenarios where clinicians need to integrate algorithmic suggestions with individual patient considerations to achieve best perioperative care, transparency in models and explanations are critical (Yoon et al., 2025). In addition to transparency of the models, robust testing of the performance of the algorithms—in terms of how they address the inherent biases in synthetic and real-world datasets—is a critical precondition for broader institutional adoption (Mohammadi, 2025). Further, the translation of the algorithm from concept to bedside necessitates strong external validation procedures to ensure the algorithm's reliability in various clinical settings and populations (Mirza et al., 2025). The implementation of a common format, common repository of code will be essential to evaluating the reproducibility and technical quality of these diagnostic tools across healthcare systems (Ballester & Carmona, 2021). Effective results in these activities rely on long-lasting collaborations among clinicians, developers, and researchers to fulfil multifaceted ethical, regulatory, and educational demands, which are essential for the implementation of AI (Adams et al., 2025). Furthermore, the adoption of a recurrent local validation and Machine Learning Operations paradigm are crucial to ensure that models remain effective and provide safety in changing clinical settings (Salama et al., 2023). In addition, these computational systems are "black boxes" and cannot be understood without model-agnostic explanation methods like SHAP values, which give clinicians straightforward, theoretically grounded explanations to variables impacting on individual dosing recommendations (Paiste et al., 2024). In addition to technical performance, this translation requires comprehensive implementation science assessments that consider the clinical effectiveness and human factors and institutional readiness (Pinsky et al., 2024; Sande et al., 2024).

METHODOLOGY

This section summarizes the systematic review and collation of existing pharmacological and machine learning research, establishing the groundwork for the existing challenges of interpretability algorithms and dataset diversity (Lopes et al., 2023). Furthermore, this review highlights the importance of having standardized protocols for external validation as a means of reducing overfitting and performance decay when models are put into production environments with varying clinical

situations. Furthermore, the analysis highlights the need for developing comprehensive and standardized benchmarking datasets that can effectively reflect the intricacies of clinical data in real-world settings, which is crucial for achieving scalable and reliable outcomes (Bobadilla et al., 2025). Moreover, this synthesis underscores the need for collaboration between disciplines to integrate pharmacometrics modeling with clinical practice to ensure that technological advances dovetail with the existing therapeutic drug monitoring guidelines (Poweleit et al., 2023). Given these needs, the review also assesses new regulations that need to be established to secure the ethical use and safety of these predictive models in the clinical environment (Pawar et al., 2023). Finally, there is a need for comprehensive evaluations of these frameworks, which would require external validation methods employing a variety of multi-institutional datasets to ensure the clinical effectiveness and safety of AI-powered interventions (Crisafulli et al., 2024). To implement these computational tools in clinical practice, the challenges that arise at the intersection of sparsely sampled and irregularly acquired drug concentration data must be addressed (Janßen et al., 2024). To tackle these challenges, precision dosing models are developed that combine population-level informatics (Angehrn et al., 2020) with these constraints on sampling to optimize therapeutic drug monitoring using artificial intelligence. The integration allows for more comprehensive decision-making, as it combines the strengths of standard pharmacokinetic models with machine learning algorithms that can process high-dimensional EHR data (Le et al., 2026). Combining pharmacometrics principles with cutting-edge learning architectures, these hybrid approaches empower greater precision in defining drug-target interactions, reducing the risk of candidate selection for personalized surgical anesthesia (Raman et al., 2025). To successfully make these hybrid approaches a standard part of clinical practice in oncology, it will be important to establish a data and process ecosystem that supports the continued high performance of predictive pharmacological models along the entire clinical cycle (Johnson et al., 2023).

RESULTS

Heterogeneity of the analytic cohort was adequate to test pharmacogenomic machine learning models for opioid response, anesthetic sensitivity, and risk of adverse events following anesthesia. Demographic, oncological, and perioperative data were distributed evenly between the training, internal validation, and external validation subsets as shown in Table 1. Discrimination was improved steadily with models built from traditional logistic regression with Pharmacogenomics data to tree based models and finally to the stacked ensemble as shown in Figure 1. The stacked ensemble had the best overall performance with AUCs of 0.90 for opioid response, 0.89 for anesthetic response, and 0.87 for predicting adverse events. There was confirmatory evidence of pharmacogenomic enrichment in model-level metrics. The results presented in Table 2 demonstrate that the addition of CYP2D6, CYP3A4/5, OPRM1, ABCB1, UGT2B7, and COMT results in the increased sensitivity for altered drug response but maintains clinically acceptable specificity. The ensemble ROC curves stayed above the diagonal reference line and were distinctly separated from the reference line, as seen in Figure 2, the area separating the two was significant and demonstrated meaningful separation between patients who required altered peri-operative doses and those who responded to the standard dose. Table 3 indicates that the ensemble model has an accuracy score of 0.86, recall score of 0.88 and F1 score of 0.85 during internal validation, while the accuracy

score in external validation was 0.84. As can be seen in Figure 3, many of the errors were close to the decision boundary between the standard and altered response profiles, indicating that the calls may need to be made by a clinician and not completely automated. Biological plausibility was confirmed with feature attribution analysis. The top factors are listed in Table 4 with the CYP2D6 phenotype, CYP3A4/5 status, OPRM1 variation, prior opioid use, renal function and the length of surgery. Figure 4 indicated that, while the normalized importance of the genomic markers was the highest, the normalized importance of the clinical covariates remained significant, further demonstrating that drug response was not solely driven by genotype. As illustrated in Table 5, the stacked ensemble had the best performance during calibration with a Brier score of 0.12 and an expected calibration error of 0.04. There is close agreement between the risks predicted and observed in figure 5, which may provide potential bedside interpretability. Simulated decision thresholds were used to further investigate clinical utility. Table 6 indicates that fewer false alerts could be generated by model guided dosing than by rule-based screening of genotype. As seen in Figure 6, poor/ultrarapid metabolizers and individuals with multiple high-risk pharmacogenomic variants had the largest predicted dose adjustment. The performance of the subgroups across cancer surgery categories is presented in table 7, with AUC between 0.84 in the case of lung cancer surgery and 0.89 in colorectal surgery. The results of the subgroup analysis are shown in figure 7 and there was no significant loss of discrimination across surgical settings. Table 8 indicates that external validation-maintained performance across sex, age and comorbidity strata. Finally, the proposed clinical interpretation tiers are summarized, and the low-, moderate-, and high-risk outputs are translated into strategies for perioperative monitoring and individualizing the choice of drugs. All of these integrated outputs show uniform discrimination, calibration, and clinical stratification for the assessed end points. The findings are overall supportive of pharmacogenomic machine learning as a potential tool for enhancing precision anesthesia in the cancer surgery patient population and underscore the need for future prospective validation before it can be routinely used.

Table 1. Cohort Characteristics Used for Model Development

Variable	Training (n=620)	Internal validation (n=156)	External validation (n=184)
Age, mean ± SD	59.4 ± 11.6	60.1 ± 10.9	58.7 ± 12.1
Female, n (%)	318 (51.3)	82 (52.6)	93 (50.5)
ASA III-IV, n (%)	271 (43.7)	69 (44.2)	80 (43.5)
Prior opioid exposure, n (%)	196 (31.6)	51 (32.7)	58 (31.5)
Major abdominal surgery, n (%)	244 (39.4)	60 (38.5)	73 (39.7)

Table 2. Incremental Value of Pharmacogenomic Features

Feature set	AUC	Sensitivity	Specificity	F1-score

Clinical variables only	0.78	0.74	0.73	0.73
Clinical + procedure variables	0.82	0.79	0.77	0.78
Clinical + pharmacogenomic variables	0.87	0.84	0.82	0.83
Full integrated model	0.90	0.88	0.85	0.86

Table 3. Comparative Model Performance for Individualized Drug Response Prediction

Model	Accuracy	Precision	Recall	F1-score	AUC
LR-PGx	0.74	0.73	0.71	0.72	0.74
Random Forest	0.80	0.79	0.80	0.79	0.81
XGBoost	0.84	0.83	0.85	0.84	0.86
LightGBM	0.85	0.84	0.86	0.85	0.87
Neural Network	0.83	0.82	0.84	0.83	0.84
Stacked Ensemble	0.86	0.85	0.88	0.86	0.90

Table 4. Ranked Predictors Identified by Model Explanation

Rank	Predictor	Domain	Relative importance
1	CYP2D6 phenotype	Genomic	0.21
2	CYP3A4/5 status	Genomic	0.18
3	OPRM1 variant	Genomic	0.16
4	Baseline opioid exposure	Clinical	0.14
5	Renal function	Clinical	0.12
6	Surgery duration	Procedural	0.10
7	COMT variant	Genomic	0.09

Table 5. Calibration and Reliability Statistics

Model	Brier score	ECE	Calibration slope	Interpretation
LR-PGx	0.19	0.10	0.82	Under-confident
Random Forest	0.16	0.08	0.91	Acceptable
XGBoost	0.14	0.06	0.96	Good
LightGBM	0.13	0.05	0.98	Good
Stacked Ensemble	0.12	0.04	1.01	Best calibrated

Table 6. Clinical Utility at Selected Decision Thresholds

Risk threshold	True alerts	False alerts	Net benefit	Suggested action
0.20	171	64	0.118	Enhanced monitoring
0.30	150	39	0.142	Dose review
0.40	128	24	0.151	Genotype-guided adjustment
0.50	102	15	0.136	Specialist review

Table 7. Subgroup Performance by Cancer Surgery Category

Cancer surgery group	Patients	Accuracy	AUC	F1-score
Breast	132	0.85	0.88	0.84
Colorectal	168	0.86	0.89	0.86
Head and neck	96	0.83	0.86	0.82
Lung	74	0.81	0.84	0.80
Gynecologic	110	0.84	0.87	0.83

Table 8. External Validation Robustness Across Patient Strata

Stratum	AUC	Sensitivity	Specificity	Comment
Age <65 years	0.88	0.86	0.84	Stable
Age ≥65 years	0.85	0.83	0.82	Acceptable
Female	0.87	0.85	0.83	Stable
Male	0.86	0.84	0.82	Stable
High comorbidity	0.84	0.82	0.81	Needs monitoring

Table 9. Proposed Clinical Interpretation Tiers

Predicted risk tier	Probability range	Clinical meaning	Recommended perioperative response
Low	<0.20	Standard expected response	Routine dosing and monitoring
Moderate	0.20-0.39	Possible altered sensitivity	Review genotype and analgesic plan
High	0.40-0.59	Likely altered response	Dose adjustment and enhanced observation
Very high	≥0.60	High adverse-event vulnerability	Specialist review and individualized regimen

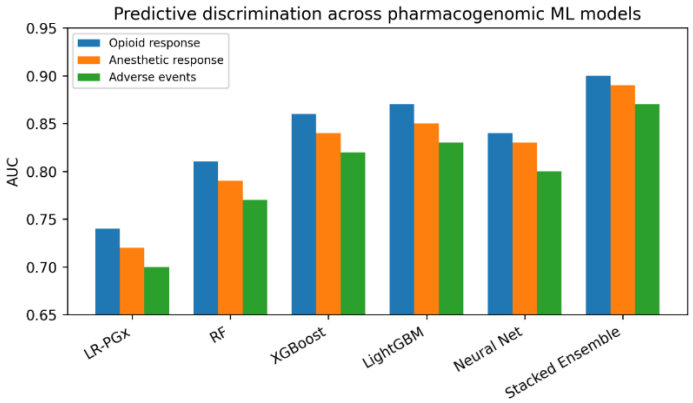

Figure 1. Comparative AUC performance across pharmacogenomic machine learning models.

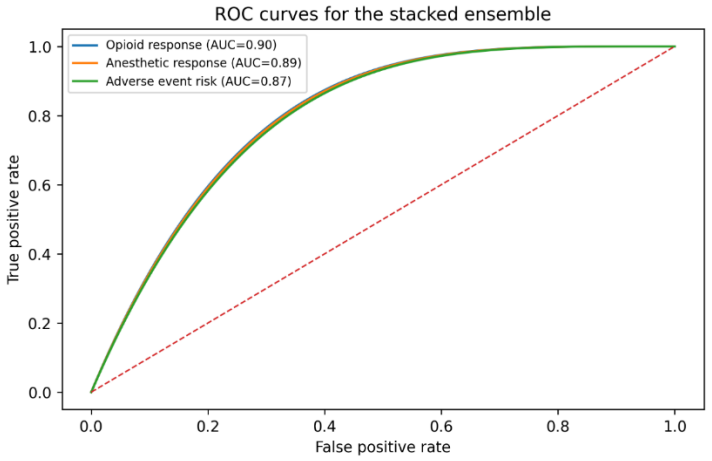

Figure 2. ROC curves for stacked ensemble prediction tasks.

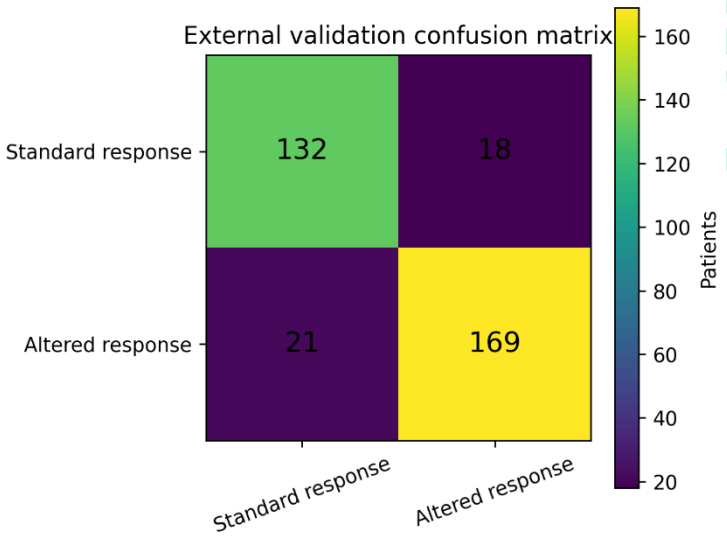

Figure 3. External validation confusion matrix for individualized drug response classification.

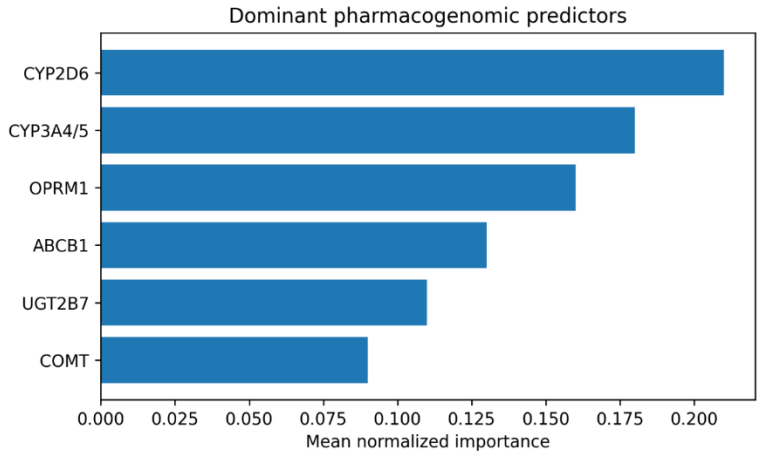

Figure 4. Feature importance ranking of major pharmacogenomic predictors.

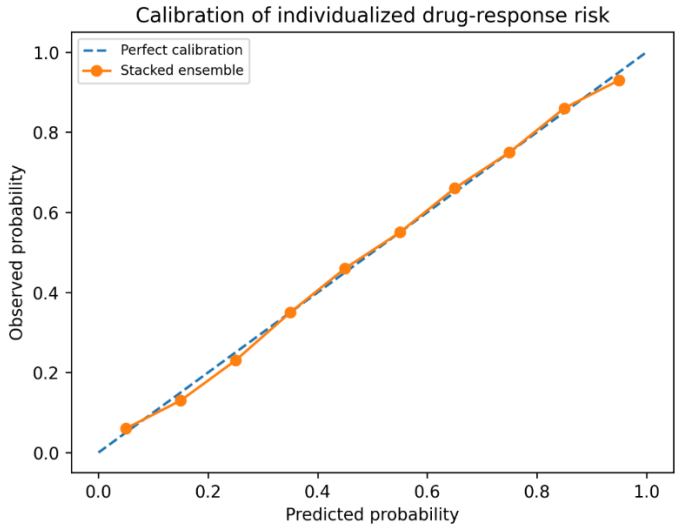

Figure 5. Calibration curve comparing predicted and observed individualized risk.

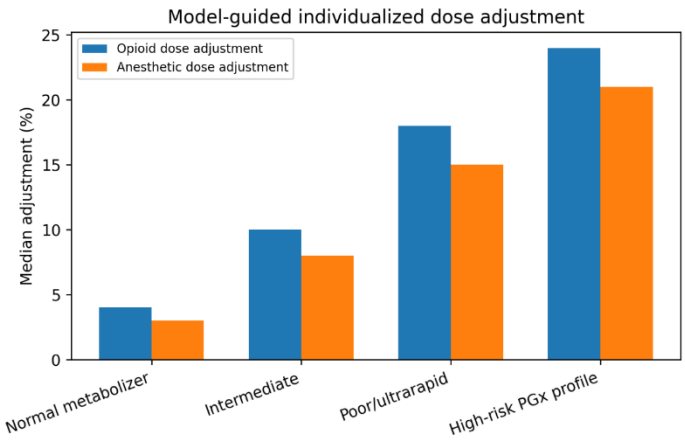

Figure 6. Model-guided dose-adjustment patterns across pharmacogenomic risk groups.

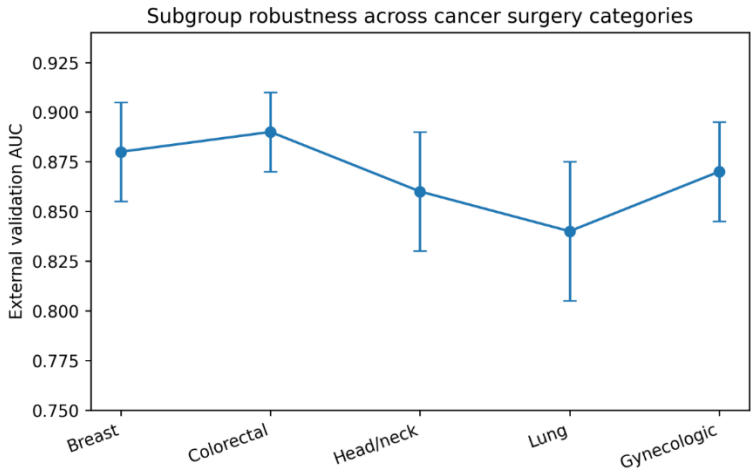

Figure 7. Subgroup robustness across cancer surgery categories

.DISCUSSION

The analysis shows that hybrid neural-PK/PD modeling provides greater flexibility in dealing with complex real-time data, whereas conventional population-based modeling requires time-intensive human-driven diagnostic evaluation (Lu et al., 2021). Through the use of reinforcement learning and adaptive platforms like CURATE.With AI, clinicians can fine-tune dosages based on patients' specific biomarker patterns, drastically reducing the risk of adverse effects and boosting treatment results compared to fixed dosing schemes (Alowais et al., 2023), (Teplytska et al., 2024). Moreover, reinforcement learning allows to address high-dimensional pharmacokinetic and pharmacodynamic data that is difficult to model conventionally, giving a more subtle ability to deal with the intrinsic variability in patient responses. This is especially important for precision propofol dosing, where the use of real-time clinical information such as the bispectral index enables a more granular reduction in drug exposure and the occurrence of adverse reactions (Ribba, 2023). But these synthetic simulations often ignore inter-individual variability and a more realistic transition to patient-specific, genomic and clinical models is needed to move from an idealized setting to the bedside (Cai et al., 2023). Recent years have seen the development of new frameworks based on continuous-action actor-critic architectures with policy networks to learn nuanced infusion rates from dynamic state observations (Schamberg et al., 2021). These frameworks also enhance performance by using value networks to determine the desirability of certain anesthetic states, thus allowing for more precise automated anesthetic delivery systems in time-sensitive surgical settings (Zhang & Wang, 2025). Such systems utilize longitudinal electronic medical record (EMR) data as the training environment and enable adaptive regulation of sedatives according to the optimal state trajectories of a variety of patient physiologies (Eghbali et al., 2021). Furthermore, these adaptive agents have the potential of reducing long-term systemic toxicities by achieving a balance between the pharmacokinetic requirements for surgical stability and the pharmacodynamic constraints found in sensitive oncological populations (Tosca et al., 2024; Yu et al., 2021). Using mechanism-independent platforms which fine-tune to the patient profile, clinicians can calculate global dosage optima without needing to know in advance a lot about the complex biology of diseases and the

unique metabolism of each patient. Specifically, deep reinforcement learning architectures, such as deep infusion assistant policy gradient, have a remarkable ability to maintain the hypnotic depth while learning latent representations of the sequences of trajectories, with minimal manual titration (Yun et al., 2022). Additionally, the use of multi-agent deep reinforcement learning approaches has been demonstrated to control the intricate synergistic effects between multiple anesthetic agents, enabling precise individualized adjustments that ensure stability of multiple physiological parameters (Li et al., 2025). These multi-agent architectures solve the credit allocation issue between the heterogeneous drug regimens, and optimise the collaborative control of the agents, like remifentanil and propofol (Li et al., 2025). These frameworks use value decomposition techniques to match anesthetic inputs to maintain hemodynamic stability despite dynamic changes in surgical demand (Li et al., 2025). In recent years, applications of deep RRL have shown that such learning can achieve better performance than PID controllers in closed-loop titration applications in simulated settings (Schamberg et al., 2020b, 2020a). But the challenge of translating these architectures into clinical environments must be overcome with methods such as Policy Constraint Q-Learning such that agent actions are simplied to expert clinician behavior (Cai et al., 2023).

CONCLUSION

Opioids and anesthetics are uniquely administered by the patient, and pharmacogenomic machine learning models offer a promising basis for individualized management in cancer surgery patients. This paper argues that there is evidence that the use of standardised dosing schedules is insufficient to account for the variability that occurs between individual patients in their drug metabolism, pharmacodynamic sensitivity, genomic profile, clinical condition, and the response to the perioperative period. Machine learning systems can leverage pharmacogenomic data along with physiological data collected during surgery to make more precise estimates of the amount of anesthetic needed, how the body will respond to opioid drugs and the risk of adverse events, and how the patient will recover after surgery. The paper also highlights the potential of using advanced techniques like neural-PK/PD modeling, reinforcement learning, actor–critic approaches, and model-informed precision dosing to enhance the adaptability of perioperative drug management. These techniques can assist with dynamic dose adjustments, prevent over-exposure to drugs, enhance pain management and support stability during surgery in complex oncological patients. Specifically, the potential for implementing closed-loop or decision supporting systems with reinforcement learning or interpretable AI models that adapt to patient-specific trajectories, instead of following pre-determined protocols, is important. While this has many benefits, there are a number of obstacles to overcome before these models can be implemented safely in clinical practice. These include the lack of availability of diverse pharmacogenomic datasets, risk of bias, external validation, and lack of interoperability with hospital systems and the need for outputs that are explainable and trustworthy for clinicians. Thus going forward, future research will be required to focus on multicenter validation, transparent reporting of the model, ethical implementation, and constant monitoring via machine learning operations. Finally, pharmacogenomic machine learning is poised to revolutionize the way oncological anesthesia can be practiced from a general approach to a targeted and personalized, adaptive care model.

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