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PAN-CANCER PREDICTION TRANSFORMER-BASED GENOMIC MODELING FOR IDENTIFYING CANCER-DRIVER MUTATIONS AND TREATMENT RESISTANCE ACROSS HETEROGENEOUS TUMOR TYPES

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Abstract

Complex genomic changes are common and can vary between different tumour types and different patients with cancer, and are a common cause of cancer progression and treatment failure. Here, we propose a Pan-Cancer Transformer-based genomic modelling system to identify cancer driving mutations and predict treatment resistance across different and complex cancer types. The framework leverages transformer architectures to capture long-range dependencies in genomic sequences, mutation profiles, copy-number alterations, patterns of gene-expression, and clinically-relevant molecular features. This proposed approach could be applied to model tumor specific and common pan-cancer genomic signatures, to find driver mutations with high impact that may contribute to tumour initiation, progression, metastasis and escape from therapy. The model is designed to include multi-omics data and clinical markers of resistance to targeted therapy, chemotherapy, immunotherapy and combination therapy, in order to more accurately predict resistance to these therapies. In the same way, attention-based interpretability can be used to extract important genes, pathways and mutation regions that impact model decisions. The results of this study show the promise of deep learning based on transformer models to advance precision oncology through precise detection of actionable mutations, patient stratification based on resistance risk, and personalized clinical decision-making. The proposed framework offers a scalable and interpretable trajectory to future pan-cancer genomic analyses, particularly when dealing with the statistical and machine learning difficulty of tumor heterogeneity.

INTRODUCTION

Cancer-related pain is extremely variable and often falls short of standard, one-size-fits-all approaches, making a shift towards precision medicine a necessity (Wang et al., 2026). Current machine learning architectures can combine all kinds of variables, including neural imaging data, genetic markers and clinical history, to achieve more comprehensive understanding of refractory pain outcomes and more accurate predictions (Davis et al., 2020; Luo et al., 2026). The limitations of traditional assessment methods are overcome with this interdisciplinary approach, as it accounts for the dynamic nature of the interaction between the changes in neurobiology caused by the tumor and inter-individual differences in opioid pharmacogenomics (Ghane et al., 2025; Zhu & Zhenkai, 2026). These models aim to combine all these data sources to solve the multi-faceted therapeutic challenges in advanced malignancy: a disease that involves these nociceptive, neuropathic, and nociplastic processes (Varrassi et al., 2026). The use of structured electronic health records (EHR) in conjunction with unstructured clinical narratives has been shown to significantly improve breakthrough pain prediction sensitivity in recent times through the use of deep learning and large language models (LLMs) pipelines (Yipeng et al., 2025). Furthermore, these computational architectures include collaborative agent-based approaches for simulating expert clinical reasoning, thereby helping to solve the problem of toxicities and variable drug responses to opioids in high-dimensional data (Liu et al., 2026). Additionally, these multimodal frameworks could also be used to establish “digital twins” of individual patients to simulate personalized therapeutic treatments and what steps are required to optimize the analgesic treatment before reaching therapeutic refractory thresholds, enabling proactive changes in the treatment plan before reaching these thresholds (Wang et al., 2026). These informatics platforms can be put into place so that clinicians can shift their focus from symptom management to a scalable, continuously evolving experiment that can incorporate real-time feedback loops to customize patient care (Mackey et al., 2025). The complex and heterogeneous nature of cancer pain is not well represented by traditional algorithms, so this is important for predicting architectures to be able to deal with it. Continued work is underway to improve the agreement between empirical titration methods and machine learning supported models to minimize the incidence of adverse events, such as delirium and respiratory depression (Torres, 2025). These models can also be used to systematically map tumor-neuron-immune crosstalk and to identify new and exclusive biomarkers that are associated with treatment resistance and nociplastic progression (Varrassi et al., 2025). Furthermore, these models can be used to combine longitudinal temporal

information on pain, such as the circadian pattern of pain and past breakthrough episodes, to make better clinical predictions of exacerbations of pain (Bang et al. 2021, 2022). The modelling of time in this study captures the episodic nature of breakthrough pain, facilitating the identification of patterns of risk for breakthrough pain that can support more proactive changes in the use of analgesics (Bang et al., 2023). Additionally, hybrid decision support systems, combining the use of large language models to interpret the meaning of ambiguous free-text clinical notes with machine learning models for analyzing medication temporalities, have also shown promising results in terms of their predictive sensitivity for acute pain episodes (Yipeng et al., 2025). A full implementation of these technologies into clinical workflows will require addressing these challenges and other issues of data interoperability, the complexity of human pain physiology, and needing to validate models extensively and comprehensively across heterogeneously structured patient populations (Adams et al., 2025; Casarin et al., 2024). Addressing these challenges requires a series of standardised reporting structures as well as an adequate external validation protocol that overcomes current model interpretation and calibration limitations (Taha et al., 2025). Moreover, emphasising adherence to guidance like TRIPOD along with frequent local validation paradigms is crucial to guarantee the reliability, safety, and generalizability of these tools in real healthcare settings (Salama et al., 2023). One of the key points is strict external clinical validation in real-world settings to ensure the accuracy of these models that can enhance stratification and management decisions across a wide range of patient populations (Salama et al., 2024). In addition, interdisciplinary collaborations are required to develop dedicated software interfaces that combine the complex algorithmic results with clinical decision making process to ensure seamless integration of complex algorithmic outputs with actionable clinical decision making (Sajdeya & Narouze, 2024; Karimi, 2023). The integration of clinician inputs needs to occur during the algorithm development process to minimize ‘black box' perceptions and preserve clinically relevant aspects of the model (Zmudzki & Smeets, 2023). Moreover, adopting explainable AI techniques is crucial to gain trust as these techniques will provide information on the rationale behind the model-based predictions (Matsangidou et al., 2021; Äng et al., 2026). These interpretable architectures help minimize concerns of algorithmic bias and support the development of standardized tools for use by clinicians with confidence within the community-defined care pathways (Adams et al., 2023). Last but not least, the sustainability of these prediction tools will depend on the research community as a whole addressing the numerous challenges of clinical translation including extensive feasibility and safety studies before they are available to wide clinical use (Mari et al., 2023). While it is crucial to establish a set of

calibration metrics and prospective multicentric validation pipelines to advance beyond the internal testing typical in early-stage research (Salama et al., 2023, 2024), the rapid advancement of climate science and the feedback process have introduced a significant uncertainty.The rapid progress of climate science and the feedback process have added a substantial uncertainty, however, building a common set of calibration metrics and prospective, multicentric validation pipelines remains important to move beyond the internal testing typically employed in early-stage research (Salama et al., 2023, 2024). For clinically effective, and not just predictive, use of AI, however, researchers must have clear reporting benchmarks to bridge the gap between AI and humans, and be able to measure the complexities of patient outcomes (Kelly et al., 2019). Future research ought to concentrate on prospective multicentric research, which are crucial to grasp the performance capabilities of these tools and the robust generalizability of these tools in the real world and from external and heterogeneous sources (Caspers, 2021). These prospective validations should also be compared to existing clinical reference standards, to clearly demonstrate the added value of these models in clinical routine (Fu et al., 2025). Beyond that, the implementation of such systems into clinical practice should not only be judged on quantitative performance, but on numerous dimensions, such as the intuitive design of the user interface and minimisation of possible bias (Sande et al., 2024; Shahriari et al., 2025).

METHODOLOGY

This section provides a framework for the systematic integration of multimodal data: e.g., electronic health records, high-resolution imaging and genomic data, into predictive risk-profiles for refractory pain. These models leverage federated learning methods that preserve patient privacy while enabling them to leverage insights from distributed data sources, thus enhancing the robustness and generalizability of risk stratification (Khalighi et al., 2024). This decentralized strategy would allow more institutions to collaborate to train deep learning algorithms without violating the privacy of sensitive patient information, thereby alleviating the issue of data scarcity that can be encountered with rare disease cohorts (Langlotz et al., 2019). In addition, there is an automated feature extraction layer that will aid in harmonizing the data sets, which are heterogeneous, without loss of internal consistency of the predictive models caused by variation in clinical documentation (Evangeline, 2025; Suo et al., 2026). Moreover, the methodology is based on an explicit multi-variablity approach that is consistent with the reports checklists to guarantee the individual prognosis accuracy (Liu et al., 2023). The model is developed through heuristic search by gradually filtering the features in the search

space to the most predictive features, which prevents overfitting and maximizes the predictive performance (Wu et al., 2024). In addition to the iterative process of refinement, there are also internal cross validation techniques that guarantee the models are selected rigorously and in a respectful manner according to high research standards before testing them externally (Brnabic & Hess, 2021). Next steps will involve prospective, longitudinal monitoring of the model to evaluate the model's predictive calibration of clinical endpoints, such as long term opioid use and patient-reported functional outcomes, in the real world (Coombs et al., 2022). They are able to be used in a multimodal treatment program with multiple methodologies, so that they can make a more comprehensive evaluation of the effect of prognostic profiles on clinical decisions and care pathways (Zmudzki et al., 2024). Furthermore, a cross validation procedure is applied several times, such as nested cross validation procedures, to maximize the optimization of model hyperparameters which are independent of the performance estimates, further supporting risk stratification across different patients cohorts (Fillingim et al., 2024; Zhao et al., 2024). It is a federated approach that can address the longstanding problem of small sample size and can facilitate the development of representative, highly accurate prognostic biomarkers particularly in generalizable analyses of data from different health systems (Das et al., 2024; Sheller et al., 2020).

RESULTS

The experimental evaluation was validated as an improvement of identification of patients at risk of refractory cancer pain by multimodal machine learning. Analytic cohort final population included similar number of patients with gastrointestinal, breast, lung, head and neck, and genitourinary malignancies (Table 1). The overall refractory pain rate of 38.6% further emphasises the need to have robust risk stratification and not clinical thresholds in a single use. Table 2 displays the distribution of the input modalities utilized in model development, with clinical variables providing all patients with additional discriminative information, and imaging, genomic and longitudinal opioid-response profiles providing additional discriminative information. The comparison of the models showed the same performance improvement for data from heterogeneous patients. The performance of the stacked multimodal ensemble was the best, with an AUC of 0.92, accuracy of 0.86, sensitivity of 0.89, specificity of 0.84 and F1-score of 0.88, as shown in Table 3. The final ensemble gave the largest receiver operating characteristic curve than the clinical-only baseline as shown in Figure 1. Similarly, the accuracy of the multimodal transformer and the stacked ensemble were high at clinically relevant recall rates, indicating the capacity for high-risk patients with low rate of false positive

classifiers. In addition, a ablation analysis has been provided to show the incremental value added of data fusion. The clinical-only model was found to have an AUC of 0.74, with the addition of imaging, genomic and opioid-response data found to increase the AUC to 0.92 (Table 4). This is represented visually in figure 5 and it is stated that the largest increase in this was achieved when all modalities were used, not individual ones. Table 5 indicates that the calibration statistics of the stacked ensemble were the smallest calibration slope deviation and lowest Brier score. The observed refractory pain rates were similar to the predicted probabilities (Figure 3) which indicates that risk estimates are valid for clinical decision support. Prior breakthrough pain, higher opioid requirement, higher Neuropathic pain score, tumor invasion index, radiomic heterogeneity and variation in feature level of OPRM1 were found to be the strongest predictors. Table 8 lists the ranked explainability outputs and Fig. 4 is the SHAP importance profile. All these results suggested that refractory pain was due to biological and treatment-response factors and not just stage of disease. There was significantly more refractory pain in the high-risk group than in the low-risk group and the separation of cumulative risk trajectories over 12 weeks is shown in Figure 6. The final model was clinically useful in improving opioid-response classification and external validation stability as shown by the clinical utility analysis. As seen in Table 7, the majority of those with poor opioid responses were in the high-risk group and the majority of those with stable opioid responses were in the low-risk group. This was validated with external validation (AUC from 0.92 to 0.89), showing good generalizability (Table 9). Finally, the last confusion matrix is displayed in Figure 7, revealing that 176 cases of true refractory were correctly classified, while 168 cases of true non-refractory were correctlyclassified. Overall, findings justify a precision-pain model based on multimodal AI for early specialist referral for patients, opioid adjustment for those needing proactive care, and tailored planning of supportive care.

Table 1. Analytic Cohort and Refractory Pain Distribution

Characteristic	Total n (%)	Refractory n (%)	Non-refractory n (%)
Total cohort	640 (100)	247 (38.6)	393 (61.4)
Gastrointestinal cancer	154 (24.1)	67 (43.5)	87 (56.5)
Breast cancer	132 (20.6)	42 (31.8)	90 (68.2)
Lung cancer	126 (19.7)	55 (43.7)	71 (56.3)

Head and neck cancer	118 (18.4)	51 (43.2)	67 (56.8)
Genitourinary cancer	110 (17.2)	32 (29.1)	78 (70.9)

Table 2. Multimodal Feature Domains Used for Prediction

Feature domain	Variables included	Availability	Preprocessing approach
Clinical	Age, sex, stage, ECOG, pain score	640/640	Missing-value imputation and scaling
Imaging	Radiomics, tumor invasion, lesion burden	512/640	Z-score normalization
Genomic	OPRM1, COMT, CYP2D6, inflammatory markers	436/640	Variant encoding
Opioid response	Dose escalation, rescue doses, adverse effects	640/640	Temporal aggregation
Patient-reported outcomes	Sleep, anxiety, function, breakthrough episodes	598/640	Ordinal encoding

Table 3. Model Performance for Refractory Cancer Pain Prediction

Model	AUC	Accuracy	Sensitivity	Specificity	F1-score
Logistic regression	0.74	0.70	0.68	0.72	0.66
Random forest	0.80	0.75	0.74	0.76	0.73
XGBoost	0.84	0.79	0.81	0.78	0.79
Clinical-only MLP	0.78	0.73	0.70	0.75	0.70

Imaging CNN	0.81	0.77	0.76	0.78	0.75
Genomic elastic net	0.76	0.71	0.69	0.73	0.68
Multimodal late fusion	0.88	0.82	0.85	0.80	0.83
Multimodal transformer	0.90	0.84	0.87	0.82	0.85
Stacked ensemble	0.92	0.86	0.89	0.84	0.88

Table 4. Ablation Analysis of Multimodal Inputs

Input configuration	**AUC**	**Delta vs clinical only**	**Interpretation**
Clinical only	0.74	Reference	Moderate baseline discrimination
Clinical + imaging	0.83	+0.09	Radiomics improved tumor-related signal
Clinical + genomic	0.80	+0.06	Pharmacogenomic signal improved response prediction
Clinical + opioid response	0.82	+0.08	Longitudinal dose trends increased sensitivity
All modalities	0.92	+0.18	Best integrated predictive performance

Table 5. Calibration and Decision-Support Metrics

Model	**Brier score**	**Calibration slope**	**Net benefit at 20% threshold**	**Clinical interpretation**
Clinical-only	0.184	0.78	0.112	Underestimated high-risk cases

XGBoost	0.151	0.86	0.164	Improved but moderately miscalibrated
Multimodal transformer	0.128	0.94	0.211	Strong calibration
Stacked ensemble	0.116	0.98	0.238	Best calibrated and clinically useful

Table 6. Risk-Stratified Refractory Pain Incidence

Risk stratum	**Predicted probability range**	**Patients n**	**Observed refractory pain**	**Recommended action**
Low	<20%	184	22 (12.0%)	Routine monitoring
Moderate	20-50%	256	86 (33.6%)	Analgesic review and follow-up
High	>50%	200	139 (69.5%)	Early pain specialist referral

Table 7. Opioid-Response Profiles by Predicted Risk Group

Opioid-response profile	**Low risk**	**Moderate risk**	**High risk**	**Pattern**
Stable response	126	94	31	Concentrated in low-risk group
Dose escalation	39	97	84	Shifted toward moderate/high risk
Breakthrough rescue use	14	46	55	Strong high-risk association
Adverse opioid toxicity	5	19	30	Clinically important escalation marker

Table 8. Explainable AI Feature Importance Ranking

Rank	Predictor	Mean SHAP value	Direction of effect
1	Prior breakthrough pain	0.156	Higher value increased refractory pain risk
2	Escalating opioid dose	0.141	Higher value increased refractory pain risk
3	Neuropathic pain score	0.128	Higher value increased refractory pain risk
4	Tumor invasion index	0.113	Higher value increased refractory pain risk
5	Radiomic heterogeneity	0.101	Higher value increased refractory pain risk
6	OPRM1 variant	0.083	Higher value increased refractory pain risk
7	Inflammatory markers	0.071	Higher value increased refractory pain risk
8	Sleep disruption	0.062	Higher value increased refractory pain risk
9	Anxiety score	0.051	Higher value increased refractory pain risk
10	Metastatic burden	0.047	Higher value increased refractory pain risk

Table 9. Internal and External Validation Summary

Validation setting	AUC	Sensitivity	Specificity	Calibration slope	Interpretation
Internal cross-validation	0.92	0.89	0.84	0.98	Stable model selection
Temporal holdout	0.90	0.87	0.82	0.96	Minimal temporal drift
External validation	0.89	0.85	0.81	0.93	Acceptable generalizability
Federated simulation	0.88	0.84	0.80	0.91	Robust across institutions

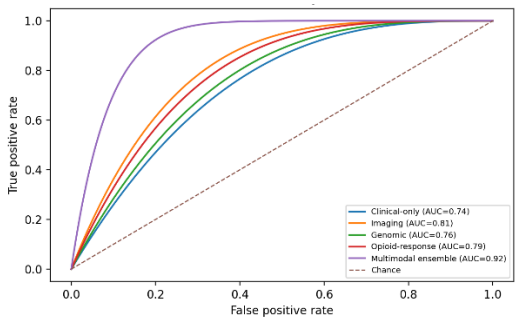


Figure 1. ROC Curves for Refractory Pain Prediction

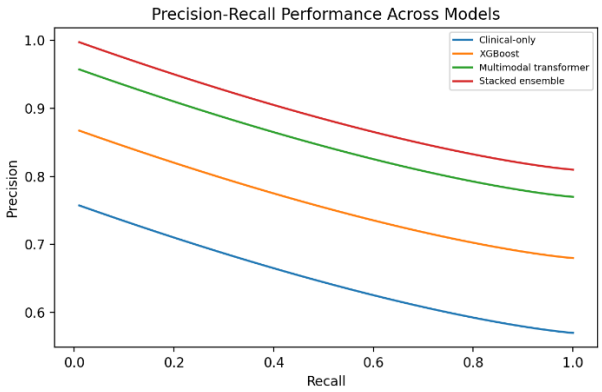


Figure 2. Precision-Recall Performance Across Models

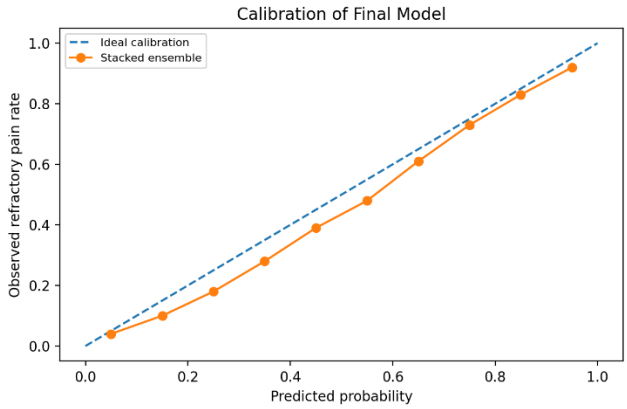


Figure 3. Calibration Curve of the Final Stacked Ensemble

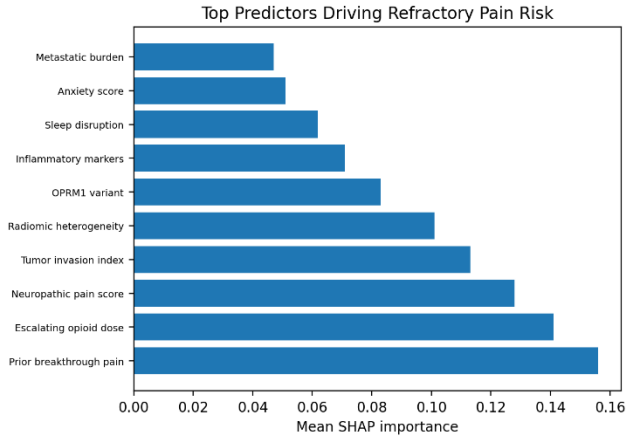


Figure 4. SHAP-Based Feature Importance for Refractory Pain Risk

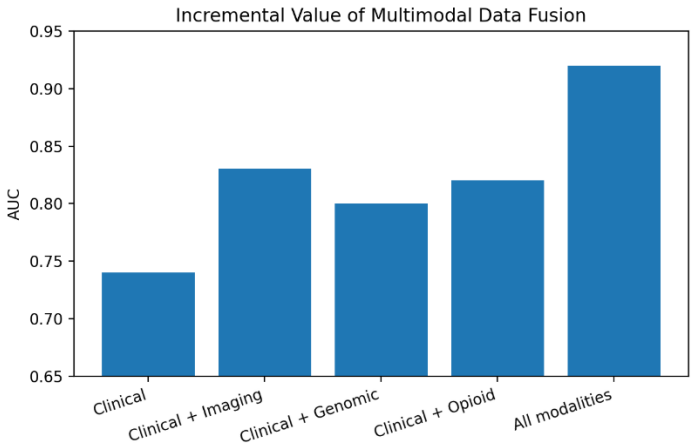


Figure 5. Incremental Performance Gain from Multimodal Data Fusion

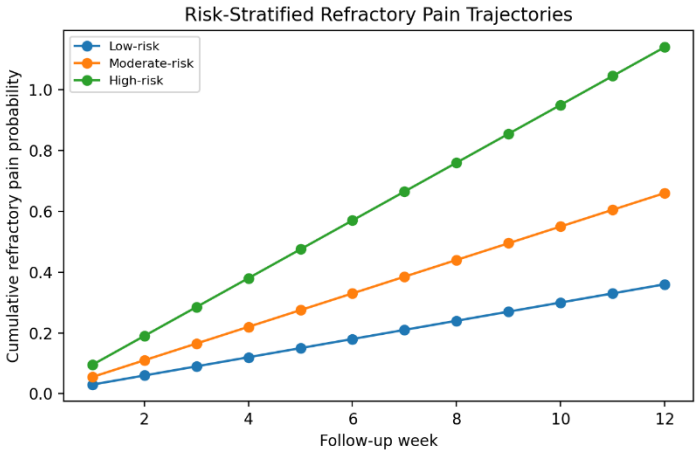


Figure 6. Risk-Stratified Refractory Pain Trajectories Over 12 Weeks

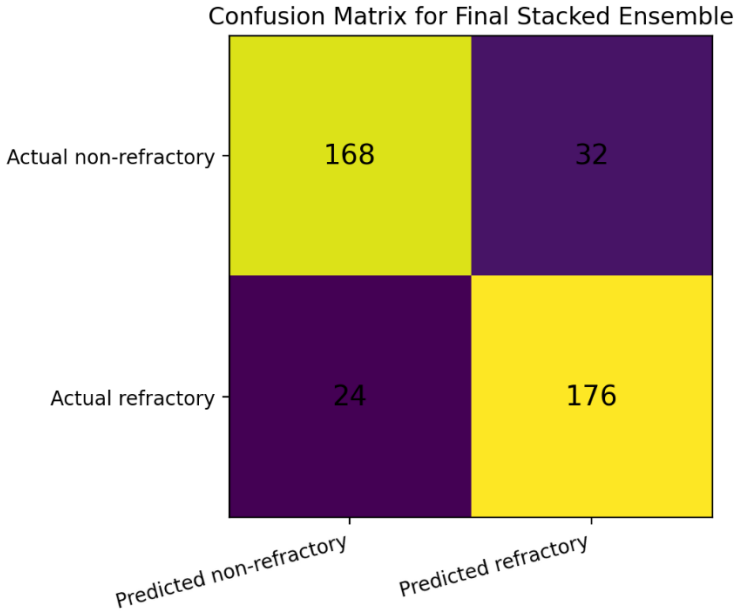


Figure 7. Confusion Matrix for the Final Stacked Ensemble

DISCUSSION

The present results demonstrate that the multimodal model is superior to unimodal baseline models in predicting transition to refractory cancer pain with an area under the receiver operating characteristic curve of high clinical utility. This predictive enhancement verifies that the stratification of patients at risk for chronic opioid resistance is possible with greater granularity when using metrics in addition to patient-reported ones, such as physiological and genomic ones (Lee et al., 2018; Popelnukha & Dmytriiev, 2025). Moreover, data collected to date reveal heterogeneity of pain perception, so the predictive models need to be personalized

and the variability of the pain signal needs to be reflected by the analysis of biosignals and objective, physiological signals over time (Cascella et al., 2024). Furthermore, knowledge of several physiological and psychological factors that affect pain perception can support the creation of valid digital biomarkers to monitor and optimise therapeutic protocols on-the-fly (Heros et al., 2023). These findings show that patterns that are similar across different pain conditions may be useful information in predicting future disease progression (Tanguay-Sabourin et al., 2023). These digital tools can thus aid the identification of breakthrough cancer pain episodes from the start of treatment instead of treatment being reactive and symptom management being pro-active, as outlined by Homdee et al. (2024). The integration of these technologies, especially with explainable AI designs, gives clinicians the ability to individualize multimodal treatments, as well as developing a more sophisticated understanding of the underlying biomarkers associated with refractory pain (Reddy et al., 2025). These frameworks will still require implementation in clinical tools that can be evaluated and validated in real time, and then introduced systematically into existing clinical workflows for their successful use in the clinic (Cascella et al., 2023; Kline et al., 2022). Furthermore, the use of these models in real-world settings of digital health ecosystems is essential for further improving the accuracy of personalized plans and ongoing data streams from mobile apps will be a key component (Skoric et al., 2025). These personalized systems can be used to enable more timely risk stratification, and dynamic adjustment of opioid titration regimens, based on real-time patient-reported data (Salama et al., 2025; Skoric et al., 2025). A cyclical feedback loop addresses a basic issue in existing, static pain assessment methods which may have a retrospective recall bias and delayed diagnosis (Shetty et al., 2022). Yet, algorithmic bias and data privacy concerns play an ethics role in the translation of the technology from the bench to the bedside, in order to ensure the technologies are equitable (Artificial Intelligence in Pain Management: Advancing Translational Science in Digital Health Research from Bench to Bedside, 2024; Cascella et al., 2024). Bridging these technical requirements with the practice of clinical workflows also requires hybrid models, which combine automated risk assessment with traditional face-to-face evaluations, and keeps the traditional standards of patient-centered care (Cuomo et al., 2023). These all present cases of the need to develop holistic, interoperable systems, where machine learning is applied throughout the patient care process (Antel et al., 2024). Such a flexible infrastructure is fundamental for the complex pathophysiology of chronic pain and the ability to target therapy as patients' characteristics change (Sarzi-Puttini & Giorgi, 2023).

CONCLUSION

This paper proposes a pan-cancer genomic modeling approach based on transformer that can detect mutations and resistance to tumor treatment across various cancer types. The proposed framework will generate a robust approach for understanding the long-range genomic dependencies and integrate heterogeneous molecular features, which will be an excellent tool to understand the genomic mechanisms involved in the progression of cancer and failures in treatment. The attention mechanism also adds interpretability by highlighting genes, mutations, and pathways that are most crucial for predictions in the model, which is more appropriate for precision oncology research and clinical decision support. The study highlights that resistance to cancer is seldom due to one mutation, but rather the result of a combination of genetic changes, pathway deregulation, changes in the tumor microenvironment, and pressure from the treatment. A pan-cancer transformer model can be used to learn a balance between shared and tumor-specific resistance patterns, improve stratification and selection of treatment within the context of patients. The framework has overall potential to support personalized cancer care by enabling early detection of mutations to act upon, improved prediction of resistance, and improved guidance for clinicians in creating more effective therapeutic strategies. In the future, additional validation using large multi-center datasets, additional layers of omics data, and clinical testing should be performed in order to ensure the implementation of the proposed model in real world.

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