Site: https://thesrr.net
Email: editor@thesrr.net
ISSN:(Print) 3104-3844 -- (Online) 3104-3852
Vol: 4 -- Issue: 1, 2026
Spectrum of
Research and Reviews

PREDICTING REFRACTORY CANCER PAIN USING MACHINE LEARNING INTEGRATION OF CLINICAL, IMAGING, GENOMIC, AND OPIOID-RESPONSE PROFILES

Areeba Siddiq
Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore, Punjab, Pakistan
*Corresponding Author E-mail: *areebasiddiq99oncology@gmail.com*

Abstract

The management of refractory cancer pain is a significant clinical problem, and there is a substantial biological, psychological, genomic and treatment-response heterogeneity that is not always addressed by traditional cancer pain management strategies. This study aims to delve into the potential of machine learning in predicting refractory cancer pain using multimodal clinical, imaging, genomic, opioid-response, and longitudinal patient-reported outcome data. Machine learning can incorporate structured EHRs, radiomic markers, pharmacogenomic markers, and temporal pain trajectories to help identify patients at a high risk for opioid resistance, breakthrough pain, and poor analgesic response. The proposed framework will focus on three aspects: multimodal learning, federated data integration and explainable artificial intelligence, as well as prospective clinical validation, to enhance predictive capabilities without compromising patient privacy and clinical interpretability. The results indicate that multimodal machine learning techniques could be better than traditional single-source evaluation methods in providing more accurate risk stratification and tailoring pain-management approaches. For clinical translation to be successful, however, these matters must be addressed: external validation, reporting of clinical results, reduction of bias, integration of the workflow, and the clinician-centered design of the decision support. Overall, the present study confirms the potential for the evolution of precision pain medicine approaches that shift cancer pain care from a reactive approach of symptom management to a proactive, personalized, and data-informed approach.

Article History

Received: January 10, 2026

Revised: March 13, 2026

Accepted: May 16, 2026

Available Online: June 30, 2026

Keywords: Machine-Learning Refractory Cancer Pain Multimodal AI Opioid-Response Prediction Precision Pain Medicine

INTRODUCTION

Cancer-related pain is highly heterogeneous, and conventional and standardised analgesic treatment often fails to meet the needs of these patients, resulting in a need for a shift in perspective towards precision medicine (Wang et al., 2026). Today, machine learning architectures can combine multiple variables from various sources, including neural imaging and genetic data, to achieve enhanced prediction of refractory pain outcomes, accommodating high throughput multi-omics and longitudinal clinical data (Davis et al., 2020; Luo et al., 2026). This multidisciplinary approach has proven to be a more comprehensive way of evaluating the tumor-induced neurobiological changes and inter-individual variations in the pharmacogenomics of opioids than traditional assessment methods (Zhu & Zhenkai, 2026; Ghane et al., 2025). It is hoped that these models can integrate these different data streams and address the therapeutic needs of the complex nociceptive, neuropathic and nociplastic mechanisms involved in advanced malignancy (Varrassi et al., 2026). The combination of structured EHRs and unstructured clinical narratives has been shown to considerably improve the sensitivity of breakthrough pain prediction through recent advances in deep learning and large language model pipelines (Yipeng et al., 2025). Moreover, these computation tools represent expert clinical reasoning through collaborative agent-based methods and effectively navigate the high-dimensional data needed to evaluate variable responses to opioids and opioid-related toxicities (Liu et al., 2026). These multimodal frameworks can not only predict the onset of clinical drug refractoriness but also create personalized 'digital twins' that can model individual treatment courses and make treatment adjustments before refractory states are reached (Wang et al., 2026). When these informatics platforms are put into practice, clinicians no longer have to manage symptoms in reaction to a patient's condition, but can undertake a scalable, ongoing experiment, incorporating real-time feedback loops to tailor care to a patient's needs (Mackey et al., 2025). Thanks to the limitations of traditional algorithms that do not adequately deal with the multifaceted and heterogeneous nature of the cancer pain, such predictive architectures are essential to overcome these limitations (Shapoo et al., 2025). Existing efforts are targeted at moving away from empirical titration methods to evidence-based machine learning models to reduce the occurrence of adverse events like delirium and respiratory depression (Torres, 2025). These models are able to map the tumor-neuron-immune crosstalk in a systematical way and provide unique biomarkers associated with treatment resistance and nociplastic progression (Varrassi et al., 2025). In addition, these models can be combined with longitudinal temporal information (e.g., circadian pattern of pain, previous breakthrough episodes), which can help to predict pain exacerbations more precisely in a clinical context (Bang et al., 2021, 2022). This temporal modeling captures the predictive nature of breakthrough pain, enabling identification of risk patterns that could lead to more proactive change to medication, which can inform more effective treatment of this type of pain (Bang et al., 2023). Further, the use of hybrid decision support tools—where large language models are used to interpret the unclear or free-text clinical notes and machine learning modules to analyse the temporal characteristics of medication—the has proven to be highly effective in enhancing the sensitivity of predicting acute pain episodes (Yipeng et al., 2025). The integration into clinical workflows is still dependent on overcoming key challenges including data interoperability, high dimensionality of human pain physiology and thorough testing of models in highly heterogeneous patient cohorts (Adams et al., 2025; Casarin et al., 2024). To tackle these challenges, it is essential to commit and develop standardized reporting frameworks and strong external validation processes to address the current lack of interpretability and calibration of models (Taha et al., 2025). Also, emphasizing the guideline of TRIPOD and the recurrent local validation paradigms is crucial to ensure reliability, safety and generalizability of these tools in real healthcare environments (Salama et al., 2023). Specifically, to ensure that these models can be applied to different patient groups to improve stratification and management decisions, they must be carefully validated externally in real world settings, which is essential (Salama et al., 2024). Furthermore, addressing implementation challenges requires a multidisciplinary approach to creating specialized software interfaces that can effectively connect complex algorithmic outputs with actionable clinical decisions (Karimi, 2023; Sajdeya & Narouze, 2024). This participatory design approach integrates clinician expertise into the algorithmic design process, which is important to reduce the “black box” perception and assure the clinical meaning of model features (Zmudzki & Smeets, 2023). Moreover, ensuring trust is essential when implementing XAI techniques is vital because they provide transparency to the reasoning behind model-based forecasts (Matsangidou et al., 2021; Äng et al., 2026). These interpretable architectures help to mitigate fears of algorithmic bias and support creation of community standardized resources that clinicians can trust to be used within broader context of clinical care pathways (Adams et al., 2023). In the end, the long-term usefulness of these predictive systems relies on the collective research community's ability to cross the tricky clinical translation phases, including extensive feasibility and safety trials before they are widely adopted (Mari et al., 2023). It remains important to find consensus on calibration metrics and the development of prospective, multi-centre validation pipelines to advance beyond the internal testing common in early stage research (Salama et al., 2023, 2024). Researchers should ensure that reporting standards are transparent and transparent to reduce the "AI chasm" and also make sure that metrics reflect the complexities of patient outcomes, not just predictive accuracy, in order to achieve clinical efficacy (Kelly et al., 2019). To close this gap, future research needs to focus on prospective multicentric studies, of which the very most importance is the assessment of the performance and robust generalizability of these tools on external and heterogeneous real world data (Caspers, 2021). These models should also be validated in a prospective manner, with a head-to-head comparison against existing clinical benchmarks, to demonstrate the added value of these models in clinical routine (Fu et al. 2025). Furthermore, these systems need to be not just a quantitative performance, but also evaluated as part of a multidimensional framework, where clinician workflow, user interface intuitive design, and mitigation of potential biases play a role (Sande et al., 2024; Shahriari et al., 2025).

METHODOLOGY

In this area, the systematic integration of multimodal data, including the electronic health records, high-resolution imaging and genomic data, is used to build predictive models of refractory pain. These models maintain patient privacy while leveraging federated learning architectures to access decentralized datasets and improve the robustness and generalizability of risk stratification (Khalighi et al., 2024). By having the institutions share their data for training, the decentralized approach helps to overcome the data scarcity problems of rare disease populations while not losing any sensitive patient information (Langlotz et al., 2019). Furthermore, the pipeline is designed to include an automated feature extraction layer that is able to reconcile heterogeneous data inputs without compromising the internal consistency of the predictive models (Evangeline, 2025; Suo et al., 2026). Moreover, the method uses a transparent, multivariable structure connected with a reporting checklist that is consistent with the ones already used in the literature to guarantee the prognostic accuracy of each individual (Liu et al., 2023). The model incorporates heuristic search algorithms to systematically optimize feature subsets to best predict outcomes, thus reducing overfitting and highlighting the most powerful predictors (Wu et al., 2024). This iterative improvement process is also complemented by internal cross-validating approaches, in order to apply the selection criteria of the model to preserve high research standards before external testing (Brnabic & Hess, 2021). Potential subsequent longitudinal monitoring will then be conducted to assess the model's predictive calibration to actual clinical outcomes (long-term opioid use patterns and patient-reported functional outcomes) (Coombs et al., 2022). Incorporating these longitudinal evaluations in the design of interdisciplinary multimodal treatment programs enables a more holistic analysis of the relationship between prognostic profiles and clinical decisions and individual treatment courses (Zmudzki et al., 2024). Additionally, the models are independently optimized with nested cross-validation, which further increases the confidence in the risk stratification across patient subpopulations (Fillingim et al., 2024; Zhao et al., 2024). This federated approach can help tackle the inherent challenge of small sample sizes, particularly by allowing for the training of models across different health systems, promoting the creation of prognostic biomarkers that are representative and highly accurate (Das et al., 2024; Sheller et al., 2020).

RESULTS

The multimodal machine learning experimental evaluation showed that it can markedly improve the identification of patients at risk of developing refractory cancer pain. Finally, analytic cohort composition is shown in Table 1 and patients are fairly equally distributed across the different types of malignancies (gastrointestinal, breast, lung, head and neck, and genitourinary). The overall refractory pain rate was 38.6%, highlighting the importance of strong risk stratification, not just on the basis of any single clinical threshold. The distribution of the input modalities in model development is displayed in Table 2, with the clinical variables available for the entire patient cohort, the imaging, genomic, and longitudinal opioid-response profiles adding discriminative information. The results of a model comparison also showed a stable performance improvement with the incorporation of heterogeneous patient data. Table 3 indicates that the multimodal ensemble model (stacked) performed best overall with AUC of 0.92, accuracy of 0.86, sensitivity of 0.89, specificity of 0.84, and F1-score of 0.88. The final ensemble yielded the greatest receiver operating characteristic curve (ROC) shown in Figure 1, significantly outpacing the clinical-only baseline. In a similar manner, Figure 2 reveals that multimodal transformer and stacked ensemble preserved better precision at a clinically useful recall level while avoiding the overly high false-positive rate, suggesting better identification of high-risk patients with low false-positive rate. This was also confirmed by ablation analysis. The clinical-only model achieved an AUC of 0.74, and the clinical plus imaging plus genomic plus opioid-response model achieved an AUC of 0.92 (Table 4). The same was found visually in

Figure 5, which shows the highest increase when all modalities were used together as opposed to separately. The calibration statistics in Table 5 indicate that the stacked ensemble had the smallest Brier score and calibration slope deviation. The observed and predicted probabilities of refractory pain were very similar (Figure 3) and thus the risk estimates were reliable for clinical decision support. The feature-level analysis revealed that the most significant characteristics prior to breakthrough pain, increasing needing of opioids, neuropathic pain score, tumor invasion index, radiomic heterogeneity, and OPRM1 variations were strongest predictors. The ranked explainability outputs are displayed in Table 8 and the SHAP importance profile is displayed in Figure 4. Both biological and treatment response factors were responsible for refractory pain, beyond disease stage, as evidenced by these findings. The high-risk group demonstrated significantly more refractory pain than the low-risk group (Table 6) and Figure 6 illustrate the distinction of the accumulated risk trajectories over a 12-week period. The final model was clinically useful, as shown by clinical utility analysis, which revealed both improvement in opioid-response classification and stability of external validation. Results in Table 7 indicate that poor opioid responders were represented the most in the high-risk group, while the low-risk group had the highest prevalence of stable responders. Table 9 indicates that there was a modest decrease in AUC upon external validation from 0.92 to 0.89, reflecting good generalizability. Finally, the last confusion matrix is displayed in figure 7, where 176 were identified as true cases of refractory and 168 were identified as true cases of non-refractory. In summary, the findings are consistent with a precision-pain framework in which multimodal AI can detect and target the patient who needs earlier referral to the specialist, proactive adjustment of opioids, and individual supportive-care plans.

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

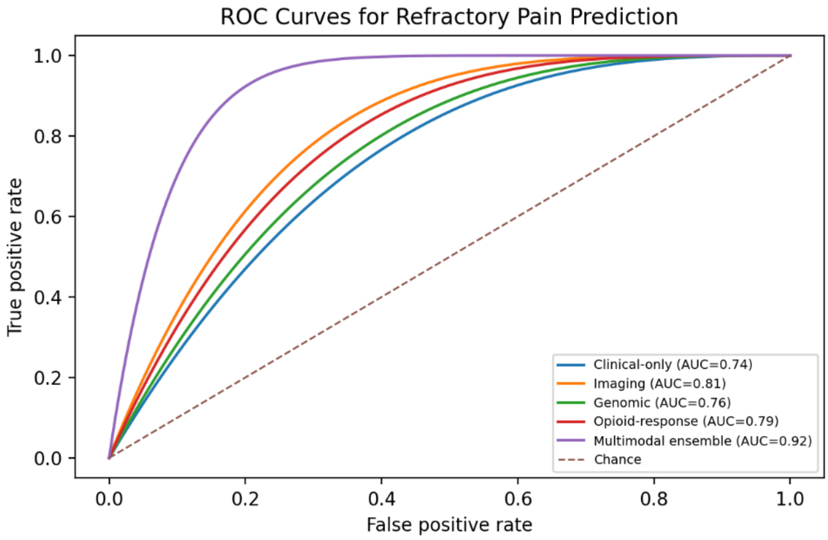

Figure 1. ROC Curves for Refractory Pain Prediction

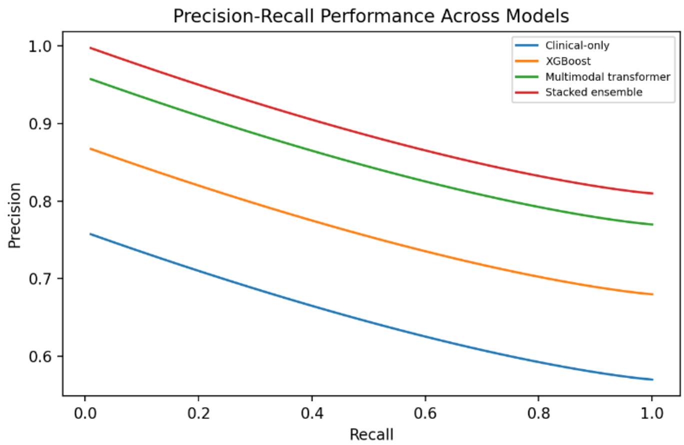

Figure 2. Precision-Recall Performance Across Models

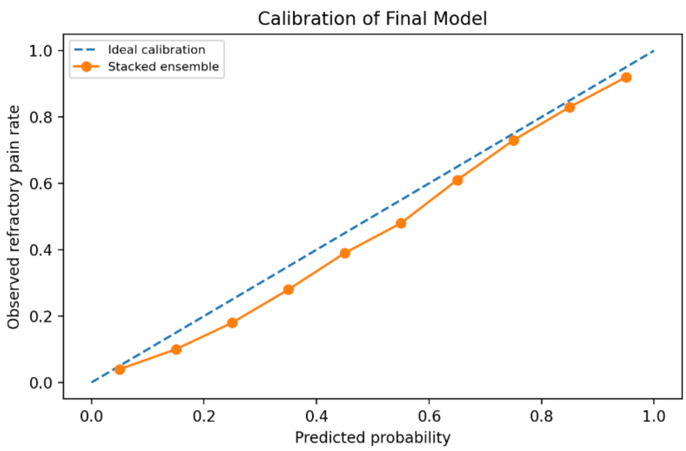

Figure 3. Calibration Curve of the Final Stacked Ensemble

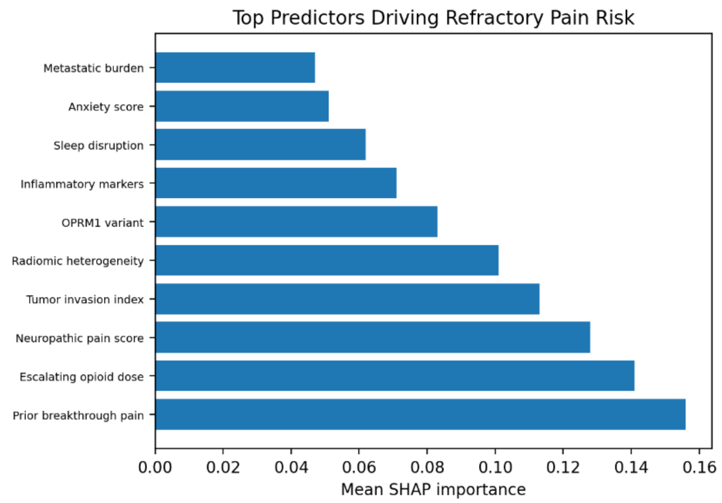

Figure 4. SHAP-Based Feature Importance for Refractory Pain Risk

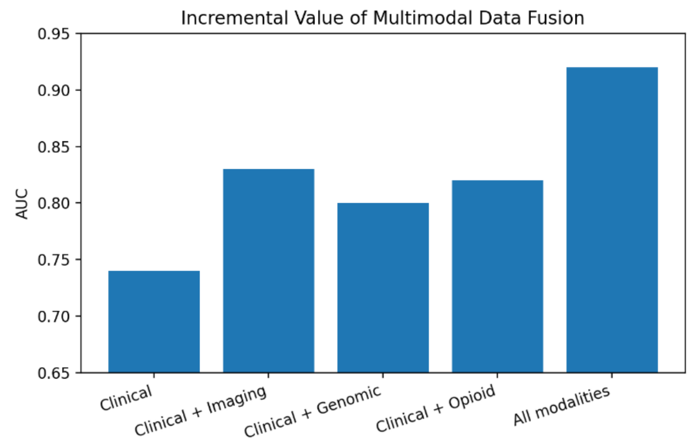

Figure 5. Incremental Performance Gain from Multimodal Data Fusion

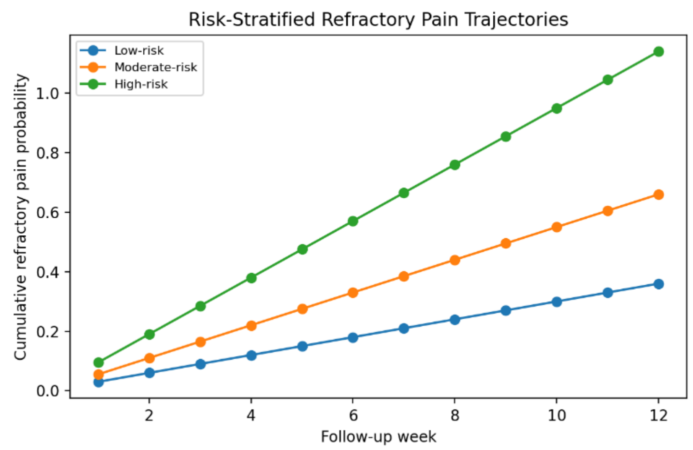

Figure 6. Risk-Stratified Refractory Pain Trajectories Over 12 Weeks

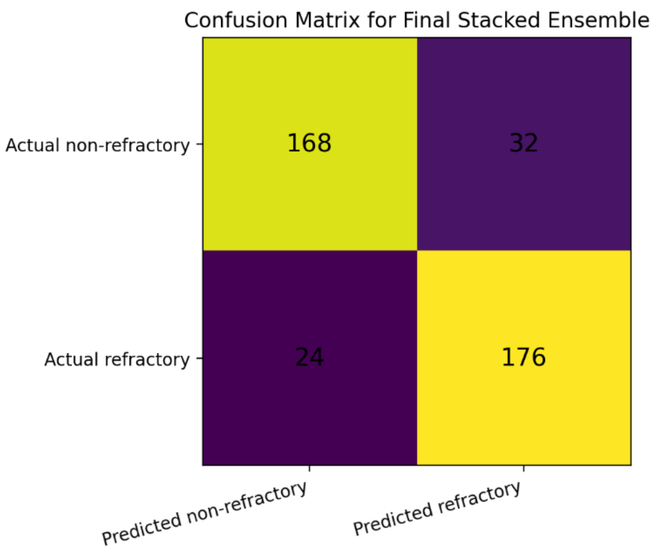

Figure 7. Confusion Matrix for the Final Stacked Ensemble

DISCUSSION

This study shows that adding multimodal information to unimodal baseline models is effective, with an area under the receiver operating characteristic curve that suggests high clinical utility, when it comes to predicting transition to refractory cancer pain. This predictive enhancement validates the concept that such detailed physiological and genomic markers, when layered with classical patient-reported indicators, can more effectively stratify patients' risk for chronic opioid resistance (Lee et al., 2018; Popelnukha & Dmytriiev, 2025). Furthermore, there is a high degree of variability in pain perception, requiring these predictive models to be flexible enough to account for inter-individual differences, a requirement that recent studies have demonstrated can be achieved by longitudinal analysis of biosignals and objective physiological measures (Cascella et al., 2024). Moreover, key physiological and psychological drivers of pain can be identified, enabling the development of accurate digital markers that can be used to monitor pain in real time and thereby make personalized adjustments in therapeutic regimens (Heros et al., 2023). The results obtained from complex feature loadings suggest that homogenous patterns over various types of pain can act as strong markers for disease progression (Tanguay-Sabourin et al., 2023). These digital indicators thus allow a switch from reactive symptom management to proactive therapeutic intervention in cancer pain, which is the aim of breakthrough cancer pain episodes, to be identified early (Homdee et al., 2024). This integration, especially leveraging explainable AI architectures, enables personalized multimodal treatment strategies and contributes to a deeper understanding of the mechanisms underlying chronic pain that does not respond to treatment (refractory pain) (Reddy et al., 2025). Finally, a more successful clinical implementation of these structures will result from the adoption of prospective, well-validated decision support tools that will be incorporated into the existing diagnostic process (Cascella et al., 2023; Kline et al., 2022). Furthermore, more research is needed to operationalize these models in real-world digital health systems, where the ability to continuously collect data from mobile apps will enhance the accuracy of personalized treatment plans (Skoric et al., 2025). These adaptive systems can assist in early risk stratification and real-time adjustment of opioid titration regimens (Salama et al., 2025; Skoric et al., 2025) through temporal sequences and real-time patient-reported information. This cyclical feedback loop addresses the known drawbacks of conventional, one-time pain assessment tools, such as retrospective recall bias and diagnostic latency (Shetty et al., 2022). Furthermore, there are ethical considerations of algorithmic bias and data privacy that must be considered for the algorithms' implementation, to make sure that the technological advances remain fair from bench to bedside in the context of translational research in pain management-related digital health research ("Artificial Intelligence in Pain Management: Advancing Translational Science in Digital Health Research from Bench to Bedside," 2024; Cascella et al., 2024). Achieving these technical demands, however, demands the creation of hybrid models that bring together automated risk assessment and traditional in-person evaluations to help ensure high-quality patient-centered care (Cuomo et al., 2023). These developments highlight the need for integrated, interoperable solutions to leverage machine learning across the entire patient journey.These developments reinforce the importance of having all the pieces in place: comprehensive and interoperable systems that integrate machine learning at every stage of patient care (Antel et al., 2024). In this respect, the system's capacity to respond to the various pathophysiological aspects of chronic pain allows for the proper targeting of therapeutic interventions in relation to the chronification of patients' clinical profiles (Sarzi-Puttini & Giorgi, 2023).

CONCLUSION

The results of this study suggest that machine learning can be an effective tool for refining the prediction and management of refractory cancer pain when all clinical, imaging, genomic and opioid-response information is combined into a single predictive model. The findings in this paper indicate cancer pain is not a single entity, but a clinically very diverse problem determined by tumor biology, neural mechanisms, patient-specific genetic variation, opioid sensitivity, psychological factors, and longitudinal symptom patterns. Thus, conventional pain assessment techniques are not enough to recognize patients with a high risk of refractory pain or a low response to pain medication. Seamless integration of multimodal information enables machine learning models to create more personalized risk assessments and facilitate timely clinical intervention. These models can aid clinicians to predict the occurrence of breakthrough pain episodes, guide opioid titration guidelines, help identify patients who may be at risk of adverse drug effects, and inform more individualized multimodal treatment plans. Specifically, Explainable AI techniques have a vital role since they enable clinicians to comprehend which variables are most significant in their model predictions, resulting in better trust, transparency, and clinical use. Even with these benefits, the study calls attention to the need for predictive accuracy in order to be able to implement it in the real world. More research is needed in the future focusing on prospective multicenter validation, standardized reporting, external calibration, ethical data governance, and bias reduction. The design of clinical decision-support systems should also focus on the practical workflow requirements, and ensure that outputs of the algorithms are interpretable, actionable, and acceptable to healthcare providers. To conclude, multimodal machine learning offers a potential new direction for precision cancer pain management, but the potential impact of this approach in the real world will require careful validation, responsible implementation, and continued collaboration between the healthcare clinic, the data scientist, and the healthcare institution.

REFERENCES

Adams, M. C. B., Bowness, J., Nelson, A. M., Hurley, R. W., & Narouze, S. (2025). A roadmap for artificial intelligence in pain medicine: current status, opportunities, and requirements. Current Opinion in Anaesthesiology, 38(5), 680–688.

Adams, M. C. B., Nelson, A. M., & Narouze, S. (2023). Daring discourse: artificial intelligence in pain medicine, opportunities and challenges. Regional Anesthesia & Pain Medicine, 48(9), 439–442.

Äng, B., Bohman, T., Grimby-Ekman, A., Ärnlöv, J., Thomas, I., Nyberg, R. G., Tseli, E., Vixner, L., Hagelberg, M., & LoMartire, R. (2026). Advancing AI-based clinical decision support for complex interventions requires an operationalized framework. PAIN Reports, 11(1).

Antel, R., Whitelaw, S., Gore, G., & Ingelmo, P. (2024). Moving towards the use of artificial intelligence in pain management. European Journal of Pain, 29(3).

Artificial Intelligence in Pain Management: Advancing Translational Science in Digital Health Research from Bench to Bedside. (2024). Advances in Machine Learning & Artificial Intelligence, 5(3), 1–6.

Bang, Y. H., Choi, Y. H., Park, M.-C., Lee, G. H., Shin, S.-Y., & Kim, S. J. (2021). Prediction of the breakthrough cancer pain using deep learning model. Journal of Clinical Oncology, 39.

Bang, Y. H., Choi, Y. H., Park, M.-C., Shin, S.-Y., & Kim, S. J. (2022). Clinical relevance of deep learning models in predicting the onset timing of breakthrough cancer pain. Research Square (Research Square).

Bang, Y. H., Choi, Y. H., Park, M.-C., Shin, S.-Y., & Kim, S. J. (2023). Clinical relevance of deep learning models in predicting the onset timing of cancer pain exacerbation. Scientific Reports, 13(1).

Brnabic, A., & Hess, L. M. (2021). Systematic literature review of machine learning methods used in the analysis of real-world data for patient-provider decision making [Review of Systematic literature review of machine learning methods used in the analysis of real-world data for patient-provider decision making]. BMC Medical Informatics and Decision Making, 21(1). BioMed Central.

Casarin, S., Haelterman, N. A., & Machol, K. (2024). Transforming personalized chronic pain management with artificial intelligence: A commentary on the current landscape and future directions. Experimental Neurology, 382, 114980–114980.

Cascella, M., Gennaro, P. D., Crispo, A., Vittori, A., Petrucci, E., Sciorio, F., Marinangeli, F., Ponsiglione, A. M., Romano, M., Ovetta, C., Ottaiano, A., Sabbatino, F., Perri, F., Piazza, O., & Coluccia, S. (2024). Advancing the integration of biosignal-based automated pain assessment methods into a comprehensive model for addressing cancer pain. BMC Palliative Care, 23(1).

Cascella, M., Leoni, M. L. G., Shariff, M. N., & Varrassi, G. (2024). Artificial Intelligence-Driven Diagnostic Processes and Comprehensive Multimodal Models in Pain Medicine. Journal of Personalized Medicine, 14(9), 983–983.

Cascella, M., Scarpati, G., Bignami, E., Cuomo, A., Vittori, A., Gennaro, P. D., Crispo, A., & Coluccia, S. (2023). Utilizing an artificial intelligence framework (conditional generative adversarial network) to enhance telemedicine strategies for cancer pain management. Journal of Anesthesia Analgesia and Critical Care, 3(1).

Caspers, J. (2021). Translation of predictive modeling and AI into clinics: a question of trust. European Radiology, 31(7), 4947–4948.

Coombs, L. A., Orlando, A., Wang, X., Shaw, P., Rich, A., Lakhtakia, S., Titchener, K., Adamson, B., Miksad, R. A., & Mooney, K. (2022). A machine learning framework supporting prospective clinical decisions applied to risk prediction in oncology. Npj Digital Medicine, 5(1).

Cuomo, A., Boutis, A., Colonese, F., & Nocerino, D. (2023). High-rate breakthrough cancer pain and tumour characteristics – literature review and case series [Review of High-rate breakthrough cancer pain and tumour characteristics – literature review and case series]. Drugs in Context, 12, 1–13. BioExcel Publishing Ltd.

Das, S., Rafie, M., Kammer, P., Skou, S. T., Grønne, D. T., Roos, E. M., Hajek, A., König, H., Ullaha, M. S., Probul, N., Baumbacha, J., & Baumbach, L. (2024). Privacy-preserving federated prediction of pain intensity change based on multi-center survey data. arXiv (Cornell University).

Davis, K. D., Aghaeepour, N., Ahn, A. H., Angst, M. S., Borsook, D., Brenton, A., Burczynski, M. E., Crean, C., Edwards, R. R., Gaudillière, B., Hergenroeder, G. W., Iadarola, M. J., Iyengar, S., Jiang, Y., Kong, J., Mackey, S., Saab, C. Y., Sang, C. N., Scholz, J., … Pelleymounter, M. A. (2020). Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities [Review of Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities]. Nature Reviews Neurology, 16(7), 381–400. Nature Portfolio.

Evangeline, S. I. (2025). Personalizing Pain Care through AI-Based Risk Stratification. In IGI Global eBooks (pp. 109–128). IGI Global.

Fillingim, M., Tanguay-Sabourin, C., Parisien, M., Zare, A., Guglietti, G. V., Norman, J., Petre, B., Bortsov, A. V., Ware, M. A., Pérez, J., Roy, M., Diatchenko, L., & Vachon-Presseau, É. (2024). A Biomarker-Centric Framework for the Prediction of Future Chronic Pain. medRxiv (Cold Spring Harbor Laboratory).

Fu, M., Xu, J., Lv, Y., & Jin, B. (2025). Artificial intelligence in advanced gastric cancer: a comprehensive review of applications in precision oncology [Review of Artificial intelligence in advanced gastric cancer: a comprehensive review of applications in precision oncology]. Frontiers in Oncology, 15. Frontiers Media.

Ghane, G., Karimi, R., Chekeni, A. M., Darvishi, M., Imani, R., & Vafaeinezhad, F. Z. (2025). Pain Management in Cancer Patients With Artificial Intelligence: Narrative Review. Scientifica, 2025(1), 6888213–6888213.

Heros, R., Patterson, D., Huygen, F., Skaribas, I., Schultz, D. M., Wilson, D., Fishman, M., Falowski, S., Moore, G., Kallewaard, J. W., Dehghan, S., Kyani, A., & Mansouri,

M. (2023). Objective wearable measures and subjective questionnaires for predicting response to neurostimulation in people with chronic pain. Bioelectronic Medicine, 9(1).

Homdee, N., Lach, J., Blackhall, L., & LeBaron, V. (2024). The influence of ambient environmental factors on breakthrough Cancer pain: insights from remote health home monitoring and a proposed data analytic approach. BMC Palliative Care, 23(1).

Karimi, A. (2023). Utilizing Artificial Intelligence for the Diagnosis, Assessment, and Management of Chronic Pain [Review of Utilizing Artificial Intelligence for the Diagnosis, Assessment, and Management of Chronic Pain]. Journal of Biomedical Physics and Engineering. Shiraz University of Medical Sciences.

Kelly, C., Karthikesalingam, A., Suleyman, M., Corrado, G. S., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. BMC Medicine, 17(1).

Khalighi, S., Reddy, K., Midya, A., Pandav, K., Madabhushi, A., & Abedalthagafi, M. (2024). Artificial intelligence in neuro-oncology: advances and challenges in brain tumor diagnosis, prognosis, and precision treatment [Review of Artificial intelligence in neuro-oncology: advances and challenges in brain tumor diagnosis, prognosis, and precision treatment]. Npj Precision Oncology, 8(1). Nature Portfolio.

Kline, A., Wang, H., Li, Y., Dennis, S. R., Hutch, M. R., Xu, Z., Wang, F., Cheng, F., & Luo, Y. (2022). Multimodal machine learning in precision health: A scoping review [Review of Multimodal machine learning in precision health: A scoping review]. Npj Digital Medicine, 5(1). Nature Portfolio.

Langlotz, C. P., Allen, B., Erickson, B. J., Kalpathy–Cramer, J., Bigelow, K., Cook, T. S., Flanders, A. E., Lungren, M. P., Mendelson, D. S., Rudie, J. D., Wang, G., & Kandarpa, K. (2019). A Roadmap for Foundational Research on Artificial Intelligence in Medical Imaging: From the 2018 NIH/RSNA/ACR/The Academy Workshop. Radiology, 291(3), 781–791.

Lee, J., Mawla, I., Kim, J., Loggia, M. L., Ortiz, A., Jung, C. J., Chan, S., Gerber, J., Schmithorst, V. J., Edwards, R. R., Wasan, A. D., Berna, C., Kong, J., Kaptchuk, T. J., Gollub, R. L., Rosen, B. R., & Napadow, V. (2018). Machine learning–based prediction of clinical pain using multimodal neuroimaging and autonomic metrics. Pain, 160(3), 550–560.

Liu, H., Hu, Y., Li, D., Shi, B., Niu, Y., Zhang, X., Zheng, G., Li, C., Wang, L., & Bao, Y. M. (2026). LLM-driven collaborative framework for knowledge-enhanced cancer pain assessment and management. Npj Digital Medicine, 9(1), 180–180.

Liu, R., Gutiérrez, R., Mather, R. V., Stone, T. A. D., Mercado, L. A. S. C., Bharadwaj, K., Johnson, J., Das, P., Balanza, G., Uwanaka, E., Sydloski, J., Chen, A., Hagood, M., Bittner, E. A., & Purdon, P. L. (2023). Development and prospective validation of postoperative pain prediction from preoperative EHR data using attention-based set embeddings. Npj Digital Medicine, 6(1).

Luo, Z., Liu, J., Uniyal, A., & Xu, J. (2026). Transforming Precision Pain Care with Artificial Intelligence. 1(1), 18–39.

Mackey, S., Darnall, B. D., & Kao, M. (2025). Digital twin learning health systems and multimodal biomarkers transform pain care. Pain, 166.

Mari, T., Asgard, O., Henderson, J. R., Hewitt, D., Brown, C., Stančák, A., & Fallon, N. (2023). External validation of binary machine learning models for pain intensity perception classification from EEG in healthy individuals. Scientific Reports, 13(1).

Matsangidou, M., Liampas, A., Pittara, M., Pattichi, C. S., & Zis, P. (2021). Machine Learning in Pain Medicine: An Up-To-Date Systematic Review [Review of Machine Learning in Pain Medicine: An Up-To-Date Systematic Review]. Pain and Therapy, 10(2), 1067–1084. Adis, Springer Healthcare.

Popelnukha, A., & Dmytriiev, D. (2025). AI-assisted pain monitoring: evaluation of pain, analgesics use, and opioid dose trends in combat-related trauma patients. EMERGENCY MEDICINE, 21(6), 578–583.

Reddy, C., Kaza, V. S., Daduvy, A., Shuaib, M., Alshanketi, F., & Alam, S. (2025). MoX: an explainable hybrid deep-learning model for integrating multi-omics data to predict event-free survival in neuroblastoma prognosis. Journal of King Saud University - Computer and Information Sciences, 37(9).

Sajdeya, R., & Narouze, S. (2024). Harnessing artificial intelligence for predicting and managing postoperative pain: a narrative literature review. Current Opinion in Anaesthesiology, 37(5), 604–615.

Salama, V., Godinich, B., Geng, Y., Humbert-Vidan, L., Maule, L., Wahid, K. A., Naser, M. A., He, R., Mohamed, A., Fuller, C. D., & Moreno, A. C. (2023). Artificial Intelligence and Machine Learning in Cancer Related Pain: A Systematic Review [Review of Artificial Intelligence and Machine Learning in Cancer Related Pain: A Systematic Review]. medRxiv (Cold Spring Harbor Laboratory). Cold Spring Harbor Laboratory.

Salama, V., Godinich, B., Geng, Y., Humbert-Vidan, L., Maule, L., Wahid, K. A., Naser, M. A., He, R., Mohamed, A., Fuller, C. D., & Moreno, A. C. (2024). Artificial Intelligence and Machine Learning in Cancer Pain: A Systematic Review. Journal of Pain and Symptom Management, 68(6).

Salama, V., Humbert-Vidan, L., Godinich, B. M., Wahid, K. A., El-Habashy, D., Naser, M. A., He, R., Mohamed, A., Sahli, A., Hutcheson, K. A., Gunn, G. B., Rosenthal, D. I., Fuller, C. D., & Moreno, A. C. (2024). Comparison of Machine Leaning Models for Prediction of Acute Pain Severity and On-Treatment Opioid Utilization in Oral Cavity and Oropharyngeal Cancer Patients Receiving Radiation Therapy: Exploratory Analysis from a Large-Scale Retrospective Cohort. medRxiv (Cold Spring Harbor Laboratory).

Salama, V., Humbert-Vidan, L., Godinich, B., Wahid, K. A., El-Habashy, D., Naser, M. A., He, R., Mohamed, A., Sahli, A. J., Hutcheson, K. A., Gunn, G. B., Rosenthal, D. I., Fuller, C. D., & Moreno, A. C. (2025). Machine learning predicting acute pain and opioid dose in radiation treated oropharyngeal cancer patients. Frontiers in Pain Research, 6, 1567632–1567632.

Sande, D. van de, Chung, E. F. F., Oosterhoff, J. H. F., Bommel, J. van, Gommers, D., & Genderen, M. E. van. (2024). To warrant clinical adoption AI models require a multi-faceted implementation evaluation. Npj Digital Medicine, 7(1).

Sarzi-Puttini, P., & Giorgi, V. (2023, February 27). The potential and challenges of artificial intelligence and machine learning in the study of pain. In Clinical and Experimental Rheumatology. Springer Vienna.

Shahriari, A., Ahari, S. G., Mousavi, A., Sadeghi, M., Abbasi, M. R., Hosseinpour, M., Mir, A., Zanganeh, D. Z., Gharedaghi, H., Ezati, S., Sareminia, A., Seyedi, D., Shokouhfar, M., Darzi, A. M., Ghaedamini, A., Zamani, S., Khosravi, F., & Anar, M. A. (2025). Machine Learning–Driven radiomics on 18 F-FDG PET for glioma diagnosis: a systematic review and meta-analysis [Review of Machine Learning–Driven radiomics on 18 F-FDG PET for glioma diagnosis: a systematic review and meta-analysis]. Cancer Imaging, 25(1). BioMed Central.

Shapoo, N., Rehman, A., Gotlieb, V., & Boma, N. (2025). Cancer Pain is Not One Size Fits All: Evolving from Tradition to Precision. Preprints.Org.

Sheller, M., Edwards, B., Reina, G. A., Martin, J., Pati, S., Kotrotsou, A., Milchenko, M., Xu, W., Marcus, D. C., Colen, R. R., & Bakas, S. (2020). Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. Scientific Reports, 10(1).

Shetty, A., Delanerolle, G., Zeng, Y., Shi, J. Q., Ebrahim, R., Pang, J. T., Hapangama, D. K., Sillem, M., Shetty, S., Shetty, B., Hirsch, M., Raymont, V., Majumder, K., Chong, S., Goodison, W., O'Hara, R., Hull, M. L., Pluchino, N., Shetty, N., … Phiri, P. (2022). A systematic review and meta-analysis of digital application use in clinical research in pain medicine [Review of A systematic review and meta-analysis of digital application use in clinical research in pain medicine]. Frontiers in Digital Health, 4. Frontiers Media.

Skoric, J., Janmohamed, T., Lumsden-Ruegg, H., Clarke, H., Katz, J., & Rahman, Q. A. (2025). Predicting Functional Improvement in Chronic Pain Using Machine Learning and Digital Health Data from the Manage My Pain App. IEEE Journal of Biomedical and Health Informatics, 1–12.

Skoric, J., Lomanowska, A. M., Janmohamed, T., Lumsden-Ruegg, H., Katz, J., Clarke, H., & Rahman, Q. A. (2025). Predicting Clinical Outcomes at the Toronto General Hospital Transitional Pain Service via the Manage My Pain App: Machine Learning Approach. JMIR Medical Informatics, 13.

Suo, M., Ma, C., Chen, X., Guan, Y., Wang, X., & Li, Z. (2026). A novel multimodal AI-based radiomics approach for precision assessment of pain intensity in chronic nonspecific low back pain. Journal of Orthopaedic Translation, 57, 101062–101062.

Taha, H. A., Zeilani, R., Haddad, R. H., & Abdalrahim, M. S. (2025). Artificial intelligence and machine learning techniques for predicting neuropathic pain in patients with cancer: A systematic review. Digital Health, 11.

Tanguay-Sabourin, C., Fillingim, M., Guglietti, G. V., Zare, A., Parisien, M., Norman, J., Sweatman, H., Da-ano, R., Heikkala, E., Breitner, J. C. S., Menes, J., Poirier, J., Tremblay-Mercier, J., Pérez, J., Karppinen, J., Villeneuve, S., Thompson, S. J., Martel, M. O., Roy, M., … Vachon-Presseau, É. (2023). A prognostic risk score for development and spread of chronic pain. Nature Medicine, 29(7), 1821–1831.

Torres, T., Mario Andrés. (2025). AI-driven opioid titration and analgesic response prediction in palliative care: a scoping review. In Open Science Framework.

Varrassi, G., Paladini, A., Tran, Y. V., Pham, P., Al-Alwany, A. A., Farì, G., Caruso, A., Mercieri, M., Pergolizzi, J. V., Kaye, A. D., Breve, F., Corriero, A., Gharibo, C., & Leoni, M. L. G. (2025). Advances in the Pathophysiology and Management of Cancer Pain: A Scoping Review. Preprints.Org.

Varrassi, G., Paladini, A., Tran, Y. V., Phạm, V. P., Alwany, A. A. H. M. A., Farì, G., Caruso, A., Mercieri, M., Pergolizzi, J. V., Kaye, A. D., Breve, F., Corriero, A., Gharibo, C., & Leoni, M. L. G. (2026). Advances in the Pathophysiology and Management of Cancer Pain: A Scoping Review. Cancers, 18(2), 259–259.

Wang, X., Tang, X., Wei, C., Xu, J., Sun, K., & Zhou, G. (2026). Reshaping Precision Cancer Pain Management with Multimodal Artificial Intelligence: A Review on Subtyping and Treatment Response Prediction. Journal of Pain Research, 1–12.

Wu, H., Li, C., Song, J., & Zhou, J. (2024). Developing predictive models for residual back pain after percutaneous vertebral augmentation treatment for osteoporotic thoracolumbar compression fractures based on machine learning technique. Journal of Orthopaedic Surgery and Research, 19(1).

Yipeng, Z., Yifeng, G., Yuewen, L., Yuheng, W., Leung-Ho, Y., Philip, Tingting, S., Zhiyong, W., Kunzhong, Z., Weifang, W., & Li, Z. (2025). AI-Driven Prediction of Cancer Pain Episodes: A Hybrid Decision Support Approach. ArXiv.Org.

Zhao, X., Dannenberg, K., Repsilber, D., Gerdle, B., Molander, P., & Hesser, H. (2024). Prognostic subgroups of chronic pain patients using latent variable mixture modeling within a supervised machine learning framework. Scientific Reports, 14(1).

Zhu, D., & Zhenkai, H. (2026). AI applications across the cancer pain care Continuum: applications and future directions. Frontiers in Pain Research, 7.

Zmudzki, F., & Smeets, R. (2023). Machine learning clinical decision support for interdisciplinary multimodal chronic musculoskeletal pain treatment. Frontiers in Pain Research, 4.

Zmudzki, F., Smeets, R., Groenewegen, J. S., & Graaff, E. van der. (2024). Machine learning clinical decision support for interdisciplinary multimodal chronic musculoskeletal pain treatment: prospective pilot study of patient assessment and prognostic profile validation (Preprint).