Machine Learning in Precision Oncology: Integrating Multimodal Clinical Data for Treatment Selection

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Abstract

Integration of complex molecular, pathological, radiological, and longitudinal clinical data to guide treatment selection is becoming increasingly important for precision oncology. However, the volume and heterogeneity of these data often exceed the capacity of conventional clinical workflows and traditional statistical approaches. Machine learning, particularly deep learning, offers a computational framework for identifying non-linear patterns across high-dimensional datasets and generating clinically relevant predictions. This review summarises current and emerging applications of machine learning in precision oncology, with emphasis on multimodal data integration for biomarker discovery, patient stratification, treatment-response prediction, toxicity monitoring, and molecular tumour board support. Key examples include prediction of microsatellite instability from routine histology, integration of radiology, pathology, and genomic features to predict response to immune checkpoint inhibitors, multi-omic prediction of neoadjuvant chemotherapy response in breast cancer, and radiogenomic approaches for non-invasive assessment of tumour heterogeneity. Despite promising retrospective performance, many models remain investigational and require prospective, multi-centre validation before routine clinical implementation. Established reporting and evaluation frameworks, including TRIPOD+AI, DECIDE-AI, CONSORT-AI, SPIRIT-AI, and CLAIM, provide important guidance for translating machine-learning models from research settings into safe and effective clinical decision support. The central challenge is not whether machine learning can generate accurate predictions, but whether these predictions improve decisions that matter to patients.

Introduction: The Evolving Landscape of Treatment Selection

Cancer remains a major global health challenge, with an estimated 20 million new cases and 9.7 million deaths worldwide in 2022. [1] Its clinical management increasingly depends on integrating molecular, pathological, radiological, and longitudinal clinical data. [2,3] Although this transition has expanded opportunities for individualised treatment, it has also created practical challenges for clinicians who must interpret complex and often discordant information within time-constrained workflows. [4] Traditional statistical models frequently struggle to capture the non-linear interactions inherent in high-dimensional datasets, potentially overlooking critical biological drivers of treatment response. [2]

Machine learning provides a computational framework to identify these intricate patterns within vast data streams. This technology may support more individualised, data-informed treatment selection, provided that models are externally validated and clinically actionable. [2,5,6] For the practising oncologist, the primary value of these tools lies in their potential to refine patient stratification, predict therapeutic efficacy, and potentially detect molecular resistance mechanisms before they become apparent on conventional imaging. [2,6] However, while many

models show high statistical accuracy in retrospective studies, the transition to standard clinical practice requires a critical appraisal of their validation, explainability, and prospective utility. [3,6]

Defining the Technological Framework

Artificial intelligence refers to computational systems designed to mimic human cognitive functions, including learning and problem solving. Within this field, machine learning focuses on algorithms that improve performance by identifying patterns in data through experience. Deep learning utilises multi-layered neural networks to automatically extract complex features from high-dimensional data, such as medical images, without requiring manual human heuristics. [3,5,6] Multimodal learning integrates disparate data modes, including text, imaging, and molecular biology, to produce a unified prediction. [7,8] Most recently, foundation models have emerged as large-scale systems pretrained on massive datasets that can be fine-tuned for multiple downstream tasks. [3,4]

Current Clinical Data Streams

The following data streams form the foundation for multimodal machine-learning approaches in precision oncology:

Genomics and transcriptomics

Next-generation sequencing remains the cornerstone of precision oncology, identifying variants and rearrangements that drive malignancy. While genomics provides the static blueprint, transcriptomics reveals active gene expression programmes, reflecting the functional state of the tumour and its microenvironment. [2,9] These data are essential for identifying actionable mutations, such as *EGFR* in lung cancer or *BRCA* in breast cancer, which guide targeted therapy selection. [10,11]

Digital pathology

Digitised whole-slide images provide high-resolution data on cellular morphology and the spatial organisation of the tumour microenvironment. Deep learning algorithms can extract quantitative features from these images that are often imperceptible to the human eye, such as nuclear morphometry or the spatial distribution of tumour-infiltrating lymphocytes. [3,12]

Radiomics and quantitative imaging

Radiomics involves the high-throughput extraction of quantitative features from standard medical imaging, such as CT, MRI, or PET scans. These features provide a non-invasive means of assessing tumour heterogeneity and can be used to predict molecular characteristics or clinical outcomes. [10,13,14]

Electronic health records (EHRs)

Electronic health records contain vast amounts of structured and unstructured information. Natural language processing can extract outcomes such as progression, toxicity, and treatment discontinuation from unstructured notes, enabling real-world datasets to be used for model development and monitoring. [2,4,5]

Liquid biopsy

Analysis of circulating tumour DNA and exosomes offers a minimally invasive means of longitudinal monitoring. Machine learning models are increasingly employed to track clonal evolution in real time, potentially identifying molecular resistance mechanisms before radiological progression becomes apparent. [2,5,15]

Machine Learning for Biomarker Discovery and Patient Stratification

MSI prediction from routine histology

Prediction of microsatellite instability (MSI) directly from routine histology is a clinically intuitive proof-of-concept application. [11] While MSI status is critical for determining eligibility for immunotherapy, traditional testing is not universal due to cost and tissue requirements. [3,11] Deep learning models have shown strong performance in predicting MSI status across gastrointestinal cancers, potentially serving as a low-cost automated pre-screening tool. [16,17]

Quality assurance and subtyping

In breast cancer, convolutional neural network-based analysis of haematoxylin and eosin images has predicted PD-L1 status with an area under the curve of 0.91. [18] Importantly, these models can identify cases where immunohistochemistry staining may be deficient or subject to misinterpretation. Beyond single markers, machine learning enables fine-grained stratification; for example, multimodal models in glioma have shown that morphological feature importance shifts when conditioning on markers like *IDH1* mutation status. [8,19]

Machine Learning for Predicting Treatment Response

Predicting response to immunotherapy

Responses to immune checkpoint inhibitors are variable, and PD-L1 expression alone is often insufficient for predicting benefit. [4,20] Multimodal models that integrate tumour mutational burden, PD-L1 expression, and radiomic features have outperformed standard biomarkers. [21,22] In non-small cell lung cancer, an attention-based deep learning model integrated clinical, pathological, radiomic, and genomic data to predict objective responses better than any single modality alone. [22,23] For clinicians, such models may eventually help identify patients more likely to derive durable benefit from immune checkpoint blockade, while sparing unlikely responders from toxicity and ineffective treatment. [4]

Predicting chemotherapy efficacy

In breast cancer, the Sammut-ML model integrated clinical, digital pathology, and multi-omic data from pre-treatment biopsies to predict pathological complete response to neoadjuvant chemotherapy. This model achieved an area under the curve of 0.87 in external validation across 75 patients, significantly outperforming baseline clinical predictors and identifying patients who may not benefit from standard chemotherapy. [24]

Imputed transcriptomics

The ENLIGHT-DeepPT framework demonstrates that genome-wide mRNA expression can be imputed directly from haematoxylin and eosin slides. By applying an unsupervised matching algorithm to this imputed transcriptomics, researchers could predict patient response to targeted

therapies without the need for actual RNA sequencing. [25] However, virtual molecular profiling should currently be viewed as investigational and not a substitute for validated molecular testing.

Radiomics and Radiogenomics as Non-Invasive Precision Tools

Radiogenomics bridges the gap between macroscopic imaging and molecular pathways, offering a non-invasive characterisation of the entire tumour volume. While a regional biopsy provides local sampling subject to error, radiomics allows for the assessment of intratumoral heterogeneity throughout the tumour landscape. [10,14,26]

Radiogenomics and habitat radiomics

CT-based radiomic features have been linked to angiogenesis and immune pathways in hepatocellular carcinoma, allowing for non-invasive prediction of systemic therapy response. [6,10] Habitat radiomics further refines this by segmenting tumours into subregions to characterise diverse microenvironments, such as hypoxic versus well-perfused zones. For clinicians, this may provide a future method to assess whether a tumour is heterogeneous enough to justify repeat biopsy or alterations in treatment planning. [14,27]

Toxicity Prediction and Treatment Optimisation

Artificial intelligence is increasingly applied to the domain of treatment safety, dose modification, and the mitigation of adverse events. [4,5]

Managing toxicity and safety

Preliminary models using longitudinal laboratory and clinical data have shown potential to predict chemotherapy-induced cytopenias before clinical onset. [2,5] In radiation oncology, machine learning tools can simulate treatment scenarios to optimise dosages, potentially reducing damage to surrounding healthy tissue and the risk of radiation pneumonitis. [4,5] These models remain largely investigational and require rigorous prospective testing to confirm their clinical utility in improving patient safety. [2,6] The major clinical applications discussed in this review are summarised in Table 1.

Table 1. Representative AI tasks and clinical utilities

Clinical task	Data modalities	Example application	Potential clinical value	Current limitation
MSI prediction	H&E pathology	Predict MSI from routine slides	Trigger confirmatory testing or immunotherapy work-up	Requires external validation and workflow integration
Neoadjuvant response	Clinical + pathology + genomics	Predict pCR in breast cancer (Sammut-ML)	Avoid ineffective chemotherapy; triage for clinical trials	Prospective clinical utility not yet established
Immunotherapy response	Radiology + pathology + genomics	Predict PD-(L)1 blockade response	Better selection for therapy; identifies durable benefit	Biomarker heterogeneity; model calibration

Toxicity prediction	EHR / labs	Predict cytopenias or radiotherapy toxicity	Pre-emptive dose modification; improved patient safety	Needs prospective intervention trials
Trial matching	Genomics + EHR / NLP	Match patients to targeted trials via clinical notes	Improve access to precision trials; reduce time-to-treatment	Data quality and interoperability issues

Clinical Trust: Explainability, Validation, Bias, and Actionability

A major barrier to the clinical adoption of deep learning is its perceived black-box nature, which can erode trust in high-stakes oncology decisions. [3,12] Even a well-calibrated model is clinically useful only if its output is linked to a clear action, such as confirmatory testing, altered surveillance, treatment escalation, de-escalation, or trial referral. [2,3]

Explainable AI (XAI)

Recent efforts have focused on making machine learning decisions comprehensible through techniques such as SHAP and LIME. These methods can provide feature-attribution scores or visual heatmaps indicating which clinical variables, genomic features, or image regions contributed most strongly to a prediction. [2,3,12]

Rigour of validation and addressing population bias

Statistical accuracy alone is insufficient for clinical adoption; models must also demonstrate robust calibration and evidence of clinical utility in prospective trials. Decision-curve analysis can help determine whether using a model improves clinical decisions compared with standard care across relevant risk thresholds. [2,6,28,29] Many AI biomarkers suffer from overfitting, where models learn institution-specific artefacts that do not generalise. [2,17] Furthermore, models trained on narrow institutional or ancestry groups may underperform in populations with different tumour biology, treatment access, imaging protocols, or comorbidity patterns. [2,3,10] To address these challenges, established reporting frameworks such as TRIPOD+AI, DECIDE-AI, CONSORT-AI, SPIRIT-AI, and the CLAIM checklist have been developed to promote transparency and accuracy. [28–32]

Future Direction: Multimodal AI and Molecular Tumour Board Support

The future of precision oncology lies in the transition from narrow, task-specific models to multimodal clinical assistants. [3,4]

Foundation models and virtual assistants

Trained on millions of images and sequences, foundation models can handle multiple tasks simultaneously, such as mutation prediction and subtyping, with minimal fine-tuning. While these may represent an important shift toward more general-purpose artificial intelligence, their routine clinical utility still requires prospective validation. [3,4] Furthermore, multimodal artificial intelligence can serve as a virtual assistant for molecular tumour boards, integrating a patient's entire history and genomic reports to identify therapeutic targets and match patients to clinical

trials. Independent evidence that such systems improve survival, quality of life, trial enrolment, or cost-effectiveness remains essential before widespread adoption. [2,4,6]

Conclusion

Machine learning is moving from a research adjunct toward a potential enabling technology within precision oncology workflows. By integrating complex multimodal data, artificial intelligence may support earlier risk stratification, more informed treatment selection, and proactive monitoring of resistance or toxicity. [2,3,5] However, integration into standard clinical practice requires continued multi-disciplinary collaboration, rigorous prospective validation, and a commitment to algorithmic transparency. Clinicians who understand both the capabilities and limitations of these tools will be better positioned to use them safely and effectively in increasingly data-rich oncology workflows. [2,3,6]

Author Contributions

SGM conceived the review, defined its scope, reviewed and interpreted the literature, drafted the manuscript, critically revised and edited the content, approved the final version.

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Conflicts of interest

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