
Beyond Single Biomarkers: Multimodal Machine Learning for Precision Medicine Across Clinical Specialties

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Abstract

Precision medicine has traditionally relied on individual biomarkers to guide diagnosis, risk stratification, and treatment selection. However, most clinical phenotypes arise from complex interactions between molecular, imaging, physiological, behavioural, and environmental factors that cannot be captured by a single data source. Multimodal machine learning offers a framework for integrating heterogeneous data streams, including electronic health records, medical imaging, genomics, clinical text, biosignals, and wearable-device outputs, to generate more comprehensive patient-level predictions. This review examines the role of multimodal machine learning in advancing precision medicine across oncology, cardiology, neurology, critical care, rare disease, and cardiometabolic medicine. Common data-fusion strategies, including early, intermediate, and late fusion, are summarised. In addition, emerging approaches such as transformer-based architectures and graph neural networks are highlighted. Clinically relevant applications include treatment-response prediction, risk stratification, early detection of deterioration, diagnostic prioritisation, and remote monitoring. Despite encouraging performance in retrospective studies, translation into routine care remains limited by challenges in external validation, calibration, interpretability, bias, data quality, privacy, and workflow integration. Clinicians should therefore evaluate multimodal AI tools not only by discrimination metrics such as area under the curve, but also by clinical utility, generalisability, uncertainty, fairness, and actionability. Established frameworks, including TRIPOD+AI, DECIDE-AI, CONSORT-AI, SPIRIT-AI, and CLAIM, can support more transparent reporting and evaluation. Ultimately, multimodal machine learning should be viewed not as autonomous decision-making, but as a potential clinical decision-support approach whose value depends on whether it improves decisions that matter to patients.

Introduction: The Evolution of Precision Medicine

Precision medicine aims to deliver the correct intervention to the correct patient at the ideal time. Historically, this approach has often focused on single, powerful biomarkers, such as a specific genetic mutation in oncology or a laboratory threshold in metabolic disease.^{1,2} However, human health is determined by a complex interplay of genomic, environmental, and lifestyle factors that are rarely captured by a single data source. Relying on a solitary modality provides a fragmented view of the patient, potentially missing the nuanced interactions that drive disease progression.^{3,4} For example, while medical imaging can identify the physical presence of a tumour, it cannot always reveal the underlying molecular characteristics that determine therapeutic sensitivity.⁴ Clinical decision-making is inherently multimodal. Physicians do not assess patients based on isolated data points; they integrate physical findings, medical history, laboratory tests, and imaging to form a diagnostic or prognostic conclusion. A survey indicated that more than 85 per

cent of radiologists consider clinical context vital for the accurate interpretation of radiological examinations.³ Traditional machine learning models have often been restricted to single modalities, limiting their ability to replicate the comprehensive nature of expert clinical judgment.^{3,5} Multimodal machine learning addresses this gap by synthesising heterogeneous data streams into a unified analytical framework, aiming to capitalise on the complementary information provided by different sources. This transition from single-modality tools to integrative systems represents an important evolution in the pursuit of personalised healthcare.^{1,2}

Defining Multimodal AI in Clinical Practice

In a clinical context, multimodal AI refers to computational models capable of simultaneously processing and integrating two or more distinct types of data modalities.^{3,6} These may include structured data from electronic health records (EHRs), unstructured text from clinical notes, visual data from medical imaging, high-frequency waveforms from bedside monitors, and multi-omics data such as genomics and proteomics. By combining these disparate sources, multimodal AI can uncover complex, non-linear relationships that are invisible when data is analysed in isolation.^{3,4,7}

For clinicians, the practical implication is that these models may support more context-rich and patient-specific decision-making. Research suggests that multimodal approaches often outperform unimodal baselines.^{3,8} A scoping review of precision health applications found a mean relative improvement in predictive accuracy or area under the curve (AUC) of approximately 6.4 per cent when data fusion was employed.³ In critical care settings, similar integrative approaches achieved an average 4.4 per cent relative improvement in AUC for diagnosis and prognosis tasks.⁸

Clinical Applications and Decision Support

The potential utility of multimodal AI is increasingly evidenced across various high-stakes medical specialties.

Oncology

In cancer care, multimodal AI facilitates enhanced tumour characterisation and personalised treatment selection.^{4,9} The fusion of histopathology images with genomic data allows for more accurate prediction of breast cancer molecular subtypes.⁴ Furthermore, models integrating liquid biopsy data, such as circulating tumour DNA (ctDNA), with clinical and mutation data enable earlier cancer detection.^{4,10} For clinicians, the practical implication is the ability to predict which patients will respond to specific immunotherapies by analysing tumour microenvironment immune signatures alongside radiological and clinical information.^{4,11} Multimodal real-world data has also been used to decode pan-cancer treatment outcomes, revealing complex mutation-treatment interactions.⁹ Moreover, radiogenomics links quantitative imaging phenotypes with molecular and genomic tumour features, enabling non-invasive tumour characterisation and potentially supporting prognosis, treatment-response prediction, and precision oncology decision-making.¹²

Cardiology

Cardiovascular medicine relies heavily on synthesising clinical, imaging, and laboratory data for risk stratification. Multimodal deep learning models have been developed to detect pulmonary embolism (PE) by combining volumetric CT scans with large-scale EHR data, significantly outperforming single-modality vision or clinical models.^{3,13} In interventional cardiology, a trimodal framework integrating coronary angiography videos, procedural text reports, and structured clinical features demonstrated superior performance in predicting five-year all-cause

mortality after percutaneous coronary intervention (PCI).¹⁴ For clinicians, the practical implication is more precise risk assessment, allowing for the targeted escalation of care for high-risk patients or the de-escalation of monitoring for low-risk individuals.^{14,15}

Neurology and Psychiatry

Multimodal AI is particularly valuable for neurodegenerative conditions where symptom progression is insidious. Models that synthesise structural MRI, functional MRI, and PET scans with cognitive assessments and genomic data can identify preclinical indicators of decline.^{6,16} For example, one transformer-based framework achieved a benchmark AUC of 0.993 for the diagnosis of Alzheimer's disease by learning from imaging, clinical, and genetic information.⁶ It should be emphasised that this extremely high performance was achieved in a retrospective benchmark study, and generalisability to real-world populations remains a critical area for validation. In psychiatry, models integrating MRI with neurocognitive measures are being explored for earlier diagnosis and trajectory monitoring in bipolar disorder.¹⁷

Critical Care

The intensive care unit (ICU) produces enormous volumes of high-resolution data. Multimodal AI models are being developed for the earlier diagnosis of sepsis and the prediction of clinical deterioration by identifying subtle changes in physiological parameters across multiple waveforms and EHR variables.^{8,18} For clinicians, the practical implication is the potential provision of alerts that may identify deterioration before overt clinical signs are recognised. These systems combine historical clinical information with real-time input to provide dynamic risk forecasts that can support earlier intervention.^{8,18,19}

Wearables and Remote Monitoring

The integration of multimodal AI with wearable technologies may support a shift toward more proactive health surveillance. Smartwatches can now passively detect atrial fibrillation (AF) by combining photoplethysmography and accelerometer data with deep learning algorithms.^{20,21} For clinicians, the practical implication is the ability to continuously monitor high-risk patients outside the hospital, enabling earlier detection of arrhythmias.²⁰ In diabetes care, the fusion of continuous glucose monitor (CGM) data with behavioural and nutritional information provides real-time glycaemic feedback and personalised lifestyle recommendations. Such integrated wearable ecosystems may support a gradual shift from episodic care toward continuous risk monitoring.^{21,22}

Rare Diseases and Cardiometabolic Care

For rare genetic disorders, AI models trained on large genomic databases can assist in diagnostic prioritisation by recognising complex phenotypic and genotypic correlations. Facial recognition technology can further assist by analysing craniofacial phenotypes from patient images to prioritise pathogenic variants in whole-genome sequencing.¹⁰ In diabetes care, the integration of real-time monitoring data with clinical medical records allows for the identification of clinically significant sub-phenotypes.^{22,23} For clinicians, the practical implication is the ability to shorten the diagnostic odyssey for rare diseases and provide more granular risk stratification for metabolic complications.^{10,23}

Table 1. Representative multimodal AI applications across clinical specialties.

Specialty	Modalities integrated	Clinical task	Potential value	Key limitation
Oncology	Pathology + genomics + imaging	Treatment response prediction	Better therapy selection	Prospective utility unclear
Cardiology	CT + EHR / angiography + reports	PE detection / PCI mortality	Improved risk stratification	Workflow and external validation
Neurology	MRI + PET + cognition + genomics	Alzheimer's prediction	Earlier diagnosis	Generalisability and overfitting
Critical care	Waveforms + labs + notes	Sepsis or deterioration prediction	Earlier intervention	Alert fatigue and local dependence
Rare disease	Genomics + facial phenotype	Diagnostic prioritisation	Shorter diagnostic odyssey	Bias and data scarcity
Diabetes	Retinal images + EHR + wearables	Complication prediction	Personalised prevention	Data standardisation and flow

Examples derived from published multimodal AI studies and reviews. ^{4,6,8,10,14,23}

How Multimodal Models Combine Disparate Data

The integration of data is achieved through various technical architectures known as data fusion strategies. ^{3,6}

Early Fusion (Data-Level Fusion)

In early fusion, different data sources are combined into a single feature vector before the machine learning model is trained. This approach is typically less computationally complex and can capture correlations between features from different modalities at the outset. However, it requires precise data alignment and can be difficult when modalities have vastly different time scales. ^{3,6}

Intermediate Fusion (Joint Fusion)

Intermediate fusion integrates multimodal information within the latent feature space of deep learning architectures. Separate encoders are typically used for each modality to learn feature representations, which are then fused at intermediate layers. This is currently a predominant strategy in critical care research, as it can automatically uncover complementary intermodal relationships, though it often suffers from a lack of clinical explainability. ^{3,6,8}

Late Fusion (Decision-Level Fusion)

Late fusion involves building separate models for each modality and integrating their final outputs, such as prediction scores, at the last stage. This strategy is modular and robust to missing data; if one modality is unavailable, the system can still operate using the remaining components. However, it may miss important synergies between modalities during the initial feature-learning phase. ^{3,6}

Advanced Frameworks: Transformers and Graph Neural Networks

Emerging approaches are moving toward transformer-based models and graph neural networks (GNNs). Transformers employ self-attention mechanisms to weigh the importance of different parts of the input data, such as specific terms in a clinical note or regions in a medical image.^{4,5,24} Large language models (LLMs) may support clinical text integration and reasoning tasks, although robust prospective validation in clinical workflows remains limited.⁵ GNNs are designed to capture non-linear dependencies in data structured as graphs, explicitly modelling complex relationships between nodes such as anatomical structures and genetic markers.^{24,25}

Clinical Decision Support vs. Autonomous Decision-Making

It is critical to distinguish between AI as a clinical decision support system (CDSS) and as an autonomous agent. Most current medical AI applications are designed to support, rather than replace, clinician judgment. CDSS tools turn large datasets into actionable advice, such as alerts for patient deterioration, which are then delivered to clinicians for validation.^{18,26,27} The ultimate responsibility for a diagnostic or therapeutic decision remains with the physician. Human judgment is considered indispensable because AI models may be less able to navigate unique individual patient contexts or nuances. Accordingly, most current systems are best viewed as decision-support tools rather than autonomous decision-makers.^{27,28} Clinicians must be aware of the "AI chasm", which is the gap between an algorithm's mathematical performance in *in silico* studies and its actual utility in improving patient outcomes.^{3,29}

Model Interpretability, Calibration, and Clinical Utility

The "black box" nature of deep learning is a significant barrier to clinical adoption. If a clinician cannot understand the reasoning behind an AI-driven diagnosis, they may be reluctant to trust the tool.^{3,26,30} Explainable AI (XAI) techniques aim to address this:

- **SHAP (SHapley Additive exPlanations):** Quantifies the marginal contribution of each input feature to a specific prediction, helping identify key driving factors.^{4,9}
- **Grad-CAM:** Generates saliency heatmaps that highlight specific regions in a medical image that most influenced the model's decision.^{4,9}
- **Attention Weights:** In transformer models, these highlight which parts of the input data the model focused on.^{4,24}

Beyond high AUC or accuracy, clinicians should look for evidence of calibration and clinical utility. Calibration refers to the agreement between a model's predicted probabilities and the actual observed outcomes. A well-calibrated model ensures that a "10 per cent risk" alert actually corresponds to a 1 in 10 chance of the event occurring.^{29,31} Clinical utility should be assessed via decision-curve analysis or net clinical benefit, which evaluates whether using the model leads to better patient outcomes compared to standard care. A model is clinically useful only when its output is linked to a predefined action, such as treatment escalation, diagnostic testing, monitoring intensity, or referral.²⁹

Barriers to Implementation: Bias, Privacy, and Workflow

The clinical deployment of multimodal AI faces several structural hurdles:

- **Algorithmic Bias:** If training datasets lack diversity, algorithms may produce discriminatory outcomes for underrepresented populations.^{3,30}

- **Data Quality and Missing Data:** Real-world medical data is often messy and incomplete. While some models use imputation techniques like generative adversarial networks (GANs), clinicians must be wary of "misleading evidence" from poor data quality. ^{4,7,32}
- **Privacy and Security:** The integration of diverse datasets increases the risk of re-identification. Federated learning is an emerging solution that allows AI models to be trained across decentralised data sources without raw data leaving its original institution. ^{28,30,32}
- **Workflow Integration:** AI must integrate seamlessly into clinical workflows without creating alert fatigue or increasing documentation burdens. ^{5,19}

Reporting Standards and Validation

To ensure transparency and reproducibility, multimodal AI studies should adhere to established reporting guidelines. Adherence to these standards allows clinicians to critically appraise the rigour and generalisability of a model.

- **TRIPOD+AI:** Updated guidance for reporting clinical prediction models using machine learning. ³¹
- **DECIDE-AI:** For the early-stage clinical evaluation of decision-support systems in live settings. ²⁷
- **CONSORT-AI / SPIRIT-AI:** For clinical trial protocols and reports involving AI interventions. ^{33,34}
- **CLAIM:** A specific checklist for AI applications in medical imaging. ³⁵

Checklist for Clinicians: Evaluating Multimodal AI Tools

Before using a multimodal AI tool for patient-level decisions, clinicians should consider:

1. **Intended Use:** Is the tool regulatory-cleared for this specific population and purpose? ^{27,28}
2. **Reporting Standards:** Was the study reported according to TRIPOD+AI, CLAIM, or DECIDE-AI? ^{27,31,35}
3. **Generalisability:** Was the model externally validated on data from a different institution? ^{29,31}
4. **Calibration:** Does the model report its calibration, or just its AUC/accuracy? ³¹
5. **Net Clinical Benefit:** Is there evidence of a net clinical benefit via decision-curve analysis? ³¹
6. **Bias Assessment:** Was the model evaluated for fairness across sex, age, and racial subgroups? ^{30,31}
7. **Interpretability:** Does the system provide explanations (e.g. SHAP, Grad-CAM) that align with clinical knowledge? ^{4,9}
8. **Actionability:** Are the model outputs clearly linked to a predefined clinical intervention or care pathway? ^{27,29}

Conclusion

Multimodal machine learning may represent an important evolution in precision medicine, moving beyond fragmented biomarkers toward a more holistic digital representation of the patient. By integrating clinical, imaging, genomic, and wearable data, these tools offer the potential for earlier disease detection and more precise risk stratification. However, the transition from experimental success to everyday clinical practice requires clinicians to be informed partners who demand rigorous validation, transparency, and seamless workflow integration. Ensuring that multimodal AI is evidence-based and clinically grounded will be essential for its successful adoption as a trustworthy partner in patient care. ^{4,8,27,31}

Author Contributions

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

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Conflicts of interest

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