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Review

AI-Enhanced Patient-Derived Cancer Organoids: Integrating Machine Learning for Precision Oncology

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Abstract

Cancer remains a leading cause of mortality worldwide. Patient-derived organoids (PDOs) are three-dimensional (3D) cultures that recapitulate tumor histology, genetics, and cellular heterogeneity, providing physiologically relevant preclinical models. Integrating PDOs with artificial intelligence (AI) and machine learning (ML) enables scalable analysis of high-dimensional datasets, including imaging, transcriptomics, proteomics, and pharmacological readouts. These approaches support prediction of drug sensitivity, biomarker discovery, and patient stratification. Recent advances—such as deep learning (DL), transfer learning, federated learning, and self-supervised learning—enhance phenotypic profiling, cross-institutional model training, and translational prediction. In this review, we summarize the current state of AI-driven PDO research, highlighting methodological approaches, preclinical and clinical applications, challenges, and emerging trends. We also propose strategies for standardization, validation, and multi-modal integration to accelerate patient-specific therapeutic strategies.

Keywords: patient-derived organoids (PDOs); precision oncology; artificial intelligence (AI); machine learning (ML); deep learning; high-content imaging; drug screening; biomarker discovery; personalized medicine; multi-omics integration

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1. Introduction

Cancer incidence is projected to surpass 35 million cases by 2050, highlighting the urgent need for patient-specific preclinical models such as PDOs, which can recapitulate individual tumor biology and predict therapeutic responses [1–3]. This rise is driven by aging populations, environmental exposures, lifestyle factors, and unequal access to preventive care. Developing patient-specific therapies requires preclinical models that preserve the histological architecture, genetic landscape, and functional responses of the original tumor. PDOs derived from breast, pancreatic, and colorectal cancers have demonstrated superior predictive accuracy for chemotherapeutic response compared with conventional 2D cultures [4–6].

Patient-derived organoids (PDOs) are physiologically relevant 3D models that preserve the histological architecture, genetic landscape, cellular heterogeneity, and functional characteristics of the source tumor [7–10]. PDOs are typically generated by dissociating tumor tissue into clusters or single cells, embedding them in extracellular matrices, and allowing self-organization into structures resembling the original tumor. They can be expanded, cryopreserved, and derived from minimal patient material, including fine-

needle biopsies or circulating tumor cells, making them highly adaptable for translational research [11,12].

PDOs preserve native cell–cell and cell–matrix interactions, maintain inter-patient heterogeneity, and reflect human-specific tumor biology. For instance, pancreatic PDOs accurately recapitulated patient-specific gemcitabine responses with an R^2 of 0.71 between and clinical outcomes [5]. These characteristics make PDOs particularly suitable for high-throughput drug screening, co-culture studies with stromal or immune cells, and mechanistic investigations of tumor heterogeneity [9,13–19].

The integration of PDOs with AI and ML enables scalable analysis of complex, multimodal datasets, including imaging, transcriptomics, proteomics, and pharmacological readouts. Supervised learning predicts phenotypic or therapeutic outcomes, while unsupervised methods reveal latent patterns, such as morphological phenotypes or molecular subtypes [20–26]. Deep learning architectures, including convolutional and recurrent neural networks, allow for hierarchical feature extraction from complex datasets such as high-content imaging and time-lapse studies [27–29]. Advanced strategies—transfer learning, self-supervised learning, and federated learning—enhance predictive capability, generalization, and cross-institutional collaboration while preserving patient privacy [30–33]. Interestingly, although federated learning has made substantial progress in cancer research—for instance, in proteomic cancer subtyping with the ProCanFDL framework (n = 6265 samples across 29 cohorts) achieving performance comparable to centralized models [34]—its application to patient-derived organoids (PDOs) remains limited.

Integrating PDOs with AI/ML allows for scalable analysis of multi-modal datasets, enabling prediction of drug responses, biomarker discovery, and patient stratification (Figure 1). Transformer-based frameworks like PharmaFormer integrated multi-omics PDO datasets to predict therapy response with a PR-AUC of 0.81 and calibration error < 0.05, illustrating cross-domain predictive capacity [35].

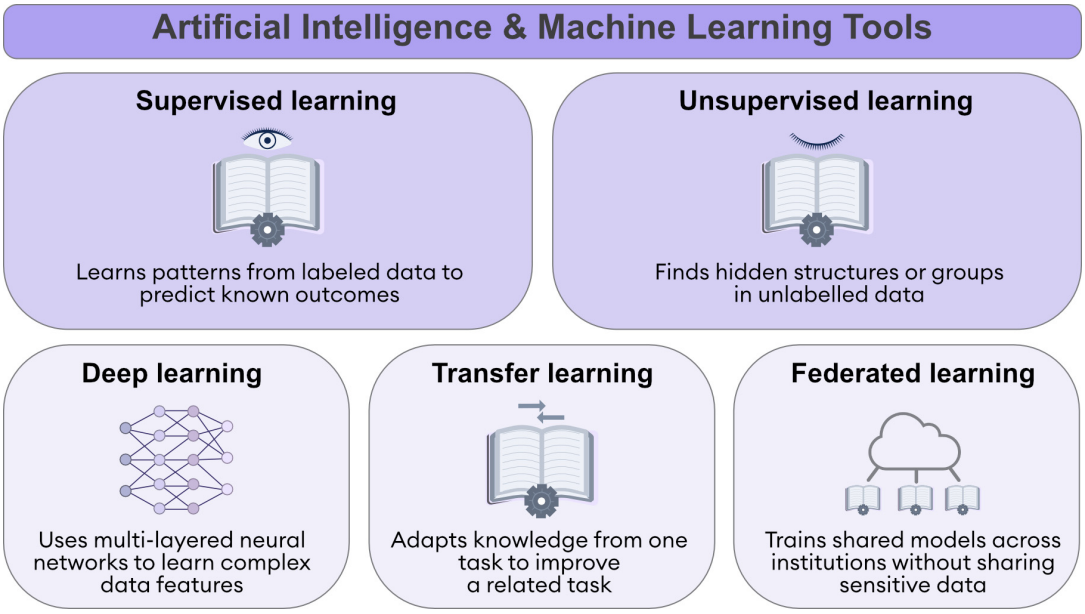

Figure 1. Artificial Intelligence (AI) and Machine Learning (ML) tools applied to patient-derived organoid (PDO) research. Supervised, unsupervised, and advanced ML approaches, including deep learning, transfer learning, and federated learning, can analyze multi-dimensional organoid datasets, integrating transcriptomic, proteomic, imaging, and drug-response data. These tools enable identification of tumor subgroups, prediction of drug sensitivity, biomarker discovery, and patient-specific therapy guidance.

2. Integration of Cancer Organoids and AI/ML

PDOs generate complex, high-dimensional datasets spanning imaging, omics, and pharmacological profiles. AI/ML methods such as random forests, CNNs, and Transformer models have successfully analyzed PDO datasets to predict drug sensitivity, identify biomarkers, and stratify patients. For example, PharmaFormer integrated > 100 PDO lines with multi-omics and pharmacogenomic data to accurately predict therapeutic response across tumor types [35]. A pipeline-based approach linking organoid data generation, computational analysis, and translational applications is summarized in Table 1.

Table 1. Pipeline-based framework for integrating cancer organoids and Artificial Intelligence (AI) and Machine Learning (ML).

Organoid Data Modality	ML/DL Approach	Analytical Endpoint	Application/ Translational Goal	Ref.
Genomic/ Transcriptomic	Random Forest, SVM, Gradient Boosting	Molecular signatures; mutation–drug associations	Drug-sensitivity prediction; Biomarker discovery	[35]
Proteomic/ Multi-omics	Deep Learning; Transformers	Integrated molecular patterns	Multi-modal prediction; Patient stratification	[35]
High-content imaging (HCI)	CNNs, autoencoders	Organoid segmentation; morphological profiling	Drug screening; cytotoxic vs. cytostatic discrimination; phenotypic clustering	[36,37]
Time-lapse imaging	RNNs, LSTMs	Growth kinetics; apoptosis; invasion dynamics	Dynamic treatment-response modeling; mechanistic insights	Longitudinal organoid tracking studies
Pharmacological dose–response	Supervised ML; regression; DL	IC50; AUC; viability changes; drug synergy	Predicting optimal therapy and hormetic effects	[38]
Multi-modal integration	GNNs, Transformers, transfer learning	Treatment-response prediction	Personalized therapy; cross-cohort generalization; clinical translation	[35,39]

2.1. Methods and Metrics for AI/ML Analysis of PDOs

High-content imaging (HCI) and time-lapse imaging capture rich phenotypic information but require preprocessing steps, including noise reduction, intensity normalization, and 3D alignment. Omics datasets undergo quality control, normalization, and batch correction, while pharmacological readouts are summarized using metrics such as IC50 or area under the curve (AUC). Standardized culture conditions and consistent metadata annotation are critical for reproducibility and cross-study comparisons.

Machine learning approaches range from supervised learning for outcome prediction to unsupervised clustering of phenotypes or molecular profiles. Deep learning architectures (CNNs, RNNs, Transformers) support hierarchical feature extraction from complex, high-dimensional inputs. Transfer learning, self-supervised learning, and federated learning improve generalization, multi-institutional analyses, and privacy protection.

Reliable AI predictions require rigorous validation, including patient-level cross-validation and testing on independent PDO cohorts. For example, a CNN trained on ovarian PDO viability achieved an internal AUC of 0.86 but dropped to 0.63 on external datasets, highlighting the necessity of external validation [40,41]. Internal validation

using patient-level splits and cross-validation reduces information leakage, while external validation across independent PDO lines evaluates generalizability. Beyond AUC, metrics such as precision–recall curves, F1 scores, calibration, and segmentation accuracy provide comprehensive assessment. Integration of multi-modal data—including imaging, omics, and pharmacology—enhances predictive reliability and translational relevance.

2.2. Applications in Preclinical Research

PDOs combined with AI/ML provide physiologically relevant, high-throughput preclinical models for drug discovery. Organoids support diverse assays, including drug screens to evaluate efficacy and toxicity of chemotherapeutics, targeted therapies, and immunotherapies across patient-derived samples [42]. These studies generate dose–response curves, viability measurements, and HCI or time-lapse imaging that captures dynamic behaviors such as proliferation, apoptosis, and morphological change [43].

Co-culture systems with stromal or immune cells allow for modeling of tumor–microenvironment interactions and immune responses [17,18]. These experiments generate large, high-dimensional datasets requiring computational approaches for analysis. Deep learning methods excel at these complex data types: for example, CNNs can segment organoid images, quantify morphological changes and distinguishing cytostatic from cytotoxic effects with greater throughput and precision than manual methods [44].

Platforms such as ACU2Net demonstrated high sensitivity, specificity, and F1-scores for bladder cancer organoid imaging [36], while OrganoID enables automated long-term tracking of organoid growth, apoptosis, and therapy response [37]. Recurrent neural networks capture temporal responses, enabling quantification of dynamic drug effects over time [45,46]. Complementary unsupervised clustering identifies phenotypic subgroups, enhancing understanding of tumor heterogeneity and therapy response [47]. A taxonomy of ML and DL approaches is presented in Table 2.

Table 2. Machine Learning (ML) and Deep Learning (DL) taxonomy and organoid-specific considerations.

ML/DL Type	Description	Typical PDO Data Regimes	Common Pitfalls/ Leakage	Preferred Validation Strategy	Evaluation Beyond AUC	Ref.
Supervised Learning	Predict outcomes from labeled data	Drug-response assays; imaging; transcriptomics	Patient leakage; batch effects; small N	Patient-level splits; external validation	PR-AUC, calibration, effect sizes	[4,23]
Unsupervised Learning	Discover patterns without labels	Morphological clustering; growth kinetics	Cluster instability; batch-driven grouping	Cluster stability indices; silhouette scores	Reproducibility metrics	[38]
Deep Learning (CNN, RNN, Transformer)	Hierarchical feature extraction	High-content imaging; time-lapse videos; multi-omics	Overfitting; interpretability limitations	External cohort validation; cross-validation	IoU, Dice, PR-AUC, segmentation accuracy	[45]
Transfer Learning	Adapts pre-trained models to PDO datasets	Small PDO biobanks; multi-tumor panels	Domain mismatch; feature drift	Evaluation on unseen PDO lines	Domain adaptation metrics	[35]

Table 2. *Cont.*

ML/DL Type	Description	Typical PDO Data Regimes	Common Pitfalls/ Leakage	Preferred Validation Strategy	Evaluation Beyond AUC	Ref.
Self-Supervised Learning	Learns representations from unlabeled data	Large imaging or genomics datasets	Unclear downstream interpretability	Downstream task performance	Embedding quality; task-specific metrics	[32]
Federated Learning	Cross-institutional model training	Multi-site PDO biobanks	Heterogeneous hardware; privacy leakage	Validation across institutions	Generalization gap; robustness metrics	[48,49]

2.3. Applications in Personalized Medicine

PDOs retain the unique molecular and phenotypic characteristics of individual patients' tumors [50]. By combining imaging, molecular, and pharmacological data with clinical information, machine learning models can identify patient-specific biomarkers predictive of therapy response, resistance, or toxicity [51]. Large, well-characterized PDO biobanks enhance these models by providing diverse patient-derived samples.

Supervised ML can stratify tumors by molecular subtype and predict sensitivity to targeted therapies. Breast cancer PDOs, for example, identified predictors of PI3K and CDK4/6 inhibitor response [4], while pancreatic PDOs enabled regression models that closely predicted clinical outcomes for gemcitabine and paclitaxel treatment [5]. Deep learning architectures, including Transformer-based models such as PharmaFormer, integrate organoid and pan-cancer pharmacogenomic datasets, improving cross-domain prediction of therapy response [35].

Beyond conventional drug-response studies, AI models can capture complex dose-dependent behaviors, including hormesis and synergistic effects, identifying optimal therapeutic windows and supporting precision oncology strategies tailored to individual patients [52–55]. Federated learning approaches further allow for multi-institutional model development while protecting patient privacy, exemplified by large-scale UK Biobank–AI initiatives [39,48,49,56].

2.4. Applications in Biomarker Discovery and Diagnostics

AI applied to PDO-derived datasets enables identification of predictive biomarkers and novel therapeutic targets. High-dimensional organoid data—including molecular profiles, imaging phenotypes, and drug responses—can be interrogated with ML to uncover patient-specific signatures that inform therapy selection and refine diagnostic pipelines.

Network-based ML frameworks have accurately predicted anticancer drug efficacy in colorectal and bladder PDOs, validated against independent clinical datasets [57]. Image analysis of organoids has revealed heterogeneity in tumor vascularization and drug delivery, challenging assumptions of uniform perfusion [58]. Single-cell RNA sequencing of organoids has enabled the development of prognostic indices, such as CAF–cancer cell crosstalk signatures predictive of immunotherapy response in head and neck cancer [59]. Collectively, these studies illustrate the potential of AI-augmented PDO platforms for biomarker discovery, patient stratification, and diagnostics.

2.5. Challenges in Translating AI-Enhanced PDOs to the Clinic

Despite their promise, AI-integrated PDO platforms face challenges in clinical translation. PDOs inherently exhibit biological variability due to patient genetics, tumor origin,

and extracellular matrix composition, which influence morphology, growth, and differentiation [60–62]. Stochastic self-organization and mass transport limitations within 3D cultures add further heterogeneity.

Harmonized culture protocols, standardized imaging methods, and consistent metadata annotation are essential to reduce variability and support reproducible, predictive AI/ML models. Multi-site collaborations require careful attention to batch effects, domain adaptation, and harmonization of technical variables. Federated learning approaches provide a framework for multi-institutional model training while preserving patient privacy, but differences in hardware, data quality, and population diversity remain potential sources of bias [39,48,49,56].

Computationally, high-dimensional PDO datasets often have limited sample sizes, increasing the risk of overfitting and data leakage. Single metrics like AUC may overestimate model performance; therefore, comprehensive evaluation with precision–recall curves, F1 scores, calibration metrics, and external validation is recommended. Robust benchmark datasets and open-access resources, such as the Organoid Data Commons, facilitate reproducibility, ethical data governance, and cross-laboratory comparisons [63,64].

3. Current Challenges and Limitations

3.1. Biological Variability and Lack of Standardization

PDOs display intrinsic heterogeneity resulting from donor genetics, tissue origin, and culture conditions. Variations in extracellular matrices, self-organization dynamics, and nutrient or oxygen gradients within 3D structures influence growth, differentiation, and morphology [60–62]. Such variability complicates reproducibility and model interpretation.

Standardizing culture protocols, imaging approaches, and metadata annotation is critical to reduce variability, enable meaningful comparisons, and support the development of robust AI-driven predictive models.

3.2. Computational Challenges and Model Evaluation

Multimodal organoid datasets are high-dimensional but often limited in sample size, making them prone to overfitting and poor external generalization. Reliance on a single performance metric, such as AUC, can be misleading. For example, a CNN trained on ovarian organoid viability achieved an internal AUC of 0.86 but dropped to 0.63 on independent datasets [40,41], highlighting the need for careful model validation.

Evaluation should include metrics reflecting class imbalance, calibration, and clinical relevance, such as precision–recall curves, F1 scores, and confidence intervals. Platforms like ACU2Net and PharmaFormer exemplify best practices, demonstrating robust performance across multiple metrics and datasets [35,36]. Future work should adopt standardized benchmarks and include external validation to ensure clinical reliability.

3.3. Data Infrastructure, Governance, and Ethical Considerations

Peer-reviewed ML/DL–PDO studies across tumor types are summarized in Table 3.

AI-PDO platforms rely on robust data infrastructure and governance frameworks. High-quality data capture, standardized metadata, secure storage, and version control are essential to minimize bias, ensure reproducibility, and protect patient privacy [63]. Initiatives such as the Organoid Data Commons provide shared benchmark datasets, ethical guidelines, and metadata standards to facilitate responsible AI development in organoid research [64].

Ethical considerations—including informed consent, privacy protection, and equitable access—remain critical for clinical translation, particularly in multi-institutional collaborations and AI-driven therapeutic decision-making.

Table 3. Representative peer-reviewed studies demonstrating the integration of ML and DL approaches with patient-derived organoid (PDO) platforms across tumor types.

Tumor Type/ Model	Data Modality	ML/DL Approach	Sample Size/Scale	Evaluation Metrics (Beyond AUC)	Key Outcome/ Biological Insight	Ref.
Breast cancer PDO biobank	Genomics + transcriptomics + drug response	Random Forest; Elastic Net	>100 PDOs across subtypes	R^2 = 0.71; feature importance; subtype reproducibility	Molecular predictors of PI3K/CDK4/6 inhibitor sensitivity	[4]
Bladder cancer PDOs	High-content imaging	ACU2Net (Deep CNN)	>20,000 images from 68 PDOs	F1 = 0.94; IoU = 0.89	Cytostatic vs. cytotoxic classification by morphology	[36]
Pan-tumor (cell lines + PDOs)	Multi-omics pharmacogenomics	Transformer (PharmaFormer) + transfer learning	>1000 cell lines + >100 PDOs	PR-AUC = 0.81; calibration error < 0.05	Improved cross-domain prediction of therapy response	[35]
Multi-tumor imaging cohorts	High-content imaging	U-Net CNN + clustering	>15,000 organoid images	Dice = 0.91; reproducibility indices	Automated phenotyping and drug-response morphotypes	[37]
Pan-cancer PDO biobank (HSP90 inhibition)	Transcriptomics + proteomics + drug response	Network-based clustering	80+ PDO lines	Silhouette = 0.72; independent xenograft validation	Identified Ganetespib-sensitive subgroups	[38]
Head & Neck squamous carcinoma PDOs	Single-cell RNA-seq + CAF co-culture	LASSO-Cox + clustering	>12,000 cells	C-index = 0.79; survival validation	CAF–tumor crosstalk genes predicting immunotherapy response	[59]

4. Emerging Directions and Future Perspectives

4.1. Advances in Organoid Models

Next-generation PDOs incorporate immune-competent and multi-lineage co-cultures, better capturing tumor–microenvironment interactions. High-content, time-lapse imaging combined with deep learning enables dynamic phenotypic profiling, accurately quantifying changes in growth, morphology, and cytotoxicity [44–46]. These innovations support mechanistic studies, drug screening, and predictive modeling.

4.2. Advances in AI and Computational Approaches

Emerging AI approaches, including self-supervised learning and foundation models, enhance generalizability across tumor types and experimental conditions. Explainable AI methods, such as SHAP values and attention-based models, allow for interpretation of biologically relevant features [65]. Integration of organoid-derived data with radiomics, liquid biopsies, and digital pathology supports multimodal pipelines for biomarker discovery, patient stratification, and adaptive clinical trial design [35,59].

Transfer learning and federated learning frameworks facilitate cross-domain and multi-institutional modeling while maintaining patient privacy, enabling more reliable predictions of therapy response and resistance mechanisms.

4.3. Translational and Industrial Applications

Several companies are implementing AI-enhanced organoid platforms for drug discovery and translational research. Recursion combines high-content imaging with AI-driven phenotypic profiling for oncology. CellPhenomics and Kyan Technologies apply AI to PD3D® organoids to optimize drug combinations across over 450 models from 20 tumor types [66]. Transformer-based frameworks, such as the TEDDY family, provide transferable representations, improving predictive modeling across PDO datasets [65]. BrainStorm Therapeutics uses patient-derived brain organoids to uncover disease mechanisms and guide precision therapeutics in neurological disorders.

These industrial applications exemplify the translational potential of AI-integrated PDO platforms in accelerating drug development and precision medicine.

4.4. Future Directions

Integrating advanced organoid models with AI has the potential to transform personalized oncology through high-throughput prediction, biomarker discovery, and adaptive therapy strategies. Key priorities include standardizing culture and imaging protocols, creating large multimodal datasets, developing explainable AI frameworks, and implementing rigorous external validation. Ethical considerations—covering informed consent, privacy, and equitable access—remain essential for responsible clinical translation [39,48,49,56].

The convergence of PDOs, AI, and robust data infrastructure promises to bridge preclinical research and clinical application, supporting precision oncology and patient-specific therapeutic strategies.

5. Conclusions

AI-enhanced PDO platforms now provide a physiologically relevant and truly scalable foundation for advancing precision oncology. As organoid protocols become standardized, biobanks expand, and multimodal data infrastructures mature, these systems will gain the reproducibility and translational strength needed for broad clinical impact. Ensuring successful adoption will require confronting biological variability, strengthening data harmonization, and embedding interpretable machine-learning frameworks at every stage of analysis. Ultimately, the full promise of AI-driven organoid research will depend on open-access resources, rigorous cross-site validation, and well-designed prospective clinical trials that can confirm real-world relevance.

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Abbreviations

The following abbreviations are used in this manuscript:

2D	Two-Dimensional
3D	Three-Dimensional

ACU2Net	Automated Convolutional U-Net
AI	Artificial Intelligence
AUC	Area Under the Curve
CAF	Cancer-Associated Fibroblast
CNN	Convolutional Neural Network
CTC	Circulating Tumor Cell
DL	Deep Learning
ECM	Extracellular Matrix
HCI	High-Content Imaging
IC50	Half-maximal inhibitory concentration
IoU	Intersection over Union
LASSO	Least Absolute Shrinkage and Selection Operator
LSTM	Long Short-Term Memory
ML	Machine Learning
PDO	Patient-Derived Organoid
PR-AUC	Precision-Recall Area Under the Curve
R^2	Coefficient of determination
RNN	Recurrent Neural Network
scRNA seq	Single-cell RNA Sequencing
SHAP	SHapley Additive exPlanations
SVM	Support Vector Machine

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