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Review Article

Organoids as Living Drug Testbeds: Emerging Technologies and Precision Pharmacological Applications in Human Disease

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ABSTRACT

Three-dimensional organoid systems have transcended their role as exploratory research tools to emerge as transformative platforms for mechanistic pharmacology, biomarker discovery, and precision therapeutics. These self-organized multicellular structures, derived from patient-derived stem cells or engineered pluripotent stem cells, recapitulate organ-level complexity including metabolic competency, barrier function, and disease-specific phenotypes. This review examines the convergence of organoid technology with artificial intelligence, high-throughput phenotypic screening, and multi-organ microphysiological systems—collectively enabling systems-level pharmacological modeling previously impossible in traditional experimental contexts. We discuss novel applications in acquired drug resistance, patient stratification, biomarker-driven therapeutic selection, and mechanism-of-action studies. Critically, we analyze the emerging paradigm of “organoid-based personalized medicine circuits” integrating patient genetics, organoid-derived phenotypes, and computational modeling to predict therapeutic responsiveness. Current regulatory frameworks, standardization efforts, and pathways toward clinical integration are examined, positioning organoid pharmacology as a defining methodology for next-generation drug development.

INTRODUCTION

Traditional pharmacological paradigms relied on sequential evaluation of compounds through in vitro screening, animal toxicity studies, and clinical trials—an approach characterized by high attrition rates (~90% of development candidates fail in clinical trials), extended timelines (10-15

years), and limited predictivity of human-specific responses.[1,2] This translational gap reflects fundamental limitations of conventional experimental systems: two-dimensional monolayer cultures lack tissue architecture and cell-cell communication, while animal models possess phylogenetically divergent drug

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metabolism, receptor pharmacology, and disease etiology.[1]

Organoid technology emerged as a transformative alternative, particularly following seminal work establishing self-renewing intestinal organoids from single Lgr5⁺ stem cells [3] and subsequent development of neural, hepatic, and cardiac platforms. [4,5] However, recent innovations have substantially expanded organoid utility beyond phenotypic modeling to enable quantitative pharmacological prediction, biomarker discovery, and mechanism-of-action validation.

This review examines how convergent advances in stem cell engineering, microfluidic integration, machine learning, and high-throughput screening are positioning organoids as central to precision pharmacology infrastructure.

2. Stem Cell Engineering and Organoid Derivation Strategies

2.1 Patient-Derived iPSC-Organoid Generation

Induced pluripotent stem cells (iPSCs) represent the most flexible organoid source, enabling derivation of patient-specific systems bearing individual genetic variants, disease-associated mutations, and metabolic phenotypes.[6] Novel reprogramming methodologies—including small molecule-based protocols and temporally optimized transgene expression—now achieve reprogramming efficiencies exceeding 10%, substantially reducing derivation timelines.[6,7]

Critically, iPSC-derived organoids preserve epigenetic patterns and gene expression signatures associated with disease susceptibility, enabling investigation of how individual genetic architecture modulates drug response.[8] Patient iPSC panels enriched for disease-associated polymorphisms (e.g., TPMT variants affecting

thiopurine metabolism, CYP2C19 variants influencing clopidogrel activation) enable systematic investigation of pharmacogenomic relationships in authentically representative cellular contexts.[8,9]

2.2 Direct Organoid Generation from Primary Tissue

Recent advances enable direct organoid derivation from primary patient tissues without requiring iPSC generation, substantially reducing timelines and potentially preserving disease-associated transcriptomic signatures.[10] Direct intestinal organoid derivation from cystic fibrosis patient biopsies now occurs within 2-3 weeks, compared to 6-8 months required for iPSC-based approaches.[10]

This methodology proves particularly valuable for rare diseases and for capturing acute disease phenotypes before adaptive responses obscure mechanistic features.[11] Furthermore, direct tissue-derived organoids bypass potential confounders introduced by reprogramming and redifferentiation, potentially yielding more authentic disease representations.[11]

2.3 Genetically-Engineered Organoid Libraries

CRISPR/Cas9-mediated systematic gene editing now enables generation of isogenic organoid sets bearing specific mutations or gene knockdowns, supporting functional genomics studies in authentic tissue contexts.[12,13] In contrast to RNA interference (RNAi) or pharmacological inhibition approaches, CRISPR-edited organoids provide stable, heritable genetic modifications enabling long-term mechanistic investigations and validation of therapeutic targets.

High-throughput screening of CRISPR libraries within organoid populations—leveraging single-



cell transcriptomics readouts—enables genome-wide functional genomics studies directly in three-dimensional tissue contexts.[12] This represents a paradigm shift from traditional functional genomics conducted in simplified monolayer systems.

3. Advanced Organoid Platforms and Tissue-Specific Applications

3.1 Neurovascular and Neuroimmune Brain Organoids

Emerging brain organoid protocols now integrate vascular endothelial cells and microglia-like immune cells, generating systems that better recapitulate blood-brain barrier (BBB) architecture and neuroinflammatory

responses.[14,15] These systems enable investigation of central nervous system (CNS) drug delivery—a critical challenge given that >99% of large-molecule therapeutics fail to achieve therapeutically relevant brain concentrations.[14]

Importantly, vascularized brain organoids exhibit realistic permeability characteristics reflecting native BBB function, enabling prediction of compound permeability and identification of efflux-mediated resistance mechanisms.[15] Microglial co-culture within organoid systems enables study of neuroimmune responses to therapeutic agents and investigation of how neuroinflammation modulates drug efficacy in Alzheimer's disease, Parkinson's disease, and primary CNS lymphoma.[15]

Table 1: Comparative Characteristics of Major Organoid Platforms Used in Pharmacological Research

Organoid Type	Key Cellular Components	Primary Pharmacological Applications	Maturity Status	Functional Readouts	Developmental Timeline	Clinical Translation Status
Brain (Cerebral)	Cortical neurons, astrocytes, oligodendrocytes	CNS drug penetration, neurotoxicity, neuro-inflammation	Fetal/early postnatal [14]	Electrophysiology, synaptic activity, neuro-inflammatory markers	4-8 weeks	In development
Brain (Midbrain)	Dopaminergic neurons, GABAergic neurons	Parkinson's disease modeling, neuroprotection screening	Early differentiation [11]	Dopamine release, neuronal survival, morphology	3-6 weeks	Research stage
Hepatic	Hepatocytes, cholangiocytes, endothelial cells	Drug metabolism, hepatotoxicity, drug-drug interactions	Mature metabolic function [16,17]	CYP activity, bile synthesis, transporter function, albumin secretion	2-4 weeks	FDA accepted for toxicity screening [46]
Intestinal	Enterocytes, Paneth cells, goblet cells, endothelial cells	Oral drug absorption, barrier integrity, microbiota interactions	Adult-like morphology [18]	TEER, permeability, transporter activity, microbial response	2-3 weeks	In clinical development
Renal	Podocytes, proximal tubule cells, collecting	Nephrotoxicity, drug transporter	Immature filtration [20,21]	GFR-like measurement, transporter	3-4 weeks	In development for



	duct cells, endothelial cells	function, glomerulotoxicity		activity, injury markers		personalized risk assessment
Cardiac	Cardiomyocytes, fibroblasts, endothelial cells	Arrhythmogenicity, cardiotoxicity, contractility	Immature electromechanical properties[22]	Action potential, calcium handling, contractility, QT interval	2-4 weeks	FDA pathway identified [46]
Pulmonary	Alveolar epithelial cells, airway cells, endothelial cells	Inhaled drug delivery, respiratory toxicity, infection modeling	Adult-like transport [25,26]	Barrier function, tight junction integrity, gas exchange	3-6 weeks	In development for inhalation screening
Pancreatic Islet	β -cells, α -cells, δ -cells	Glucose-responsive insulin secretion, antidiabetic drug screening	Functional but immature[20]	Glucose stimulation index, insulin secretion, metabolic flux	3-4 weeks	Research stage
Bone Marrow	Hematopoietic stem cells, osteoblasts, adipocytes, endothelial cells	Leukemia modeling, hematopoietic toxicity, niche interactions	Emerging[21]	Hematopoietic progenitor function, leukemic burden, niche support	4-8 weeks	Research stage
Tumor (Patient-derived)	Cancer cells, stromal fibroblasts, immune cells, endothelial cells	Drug screening, resistance mechanism, biomarker validation	Highly variable [27,28]	Proliferation, cell death, metabolic markers, immune infiltration	2-4 weeks	Clinical implementation underway[44]

Abbreviations: TEER, transepithelial electrical resistance; GFR, glomerular filtration rate; QT, QT interval on electrocardiogram.

3.2 Metabolically-Competent Hepatic Organoids with Sinusoidal Architecture

Advanced hepatic organoid platforms now incorporate endothelial cells to recapitulate sinusoidal architecture and enable physiological hepatic blood flow simulation.[16] This innovation proves critical because drug-metabolite hepatotoxicity, a leading cause of delayed clinical failures, frequently emerges from metabolite-specific mechanisms requiring authentic metabolic capacity and hepatocyte-endothelial interactions.[16]

Patient-derived hepatic organoids bearing chronic liver disease signatures (cirrhosis-derived organoids from fibrotic liver biopsies) enable

investigation of how disease-associated transcriptomic alterations modify drug metabolism and sensitize to hepatotoxicity.[17] Furthermore, hepatic organoids now demonstrate sustained expression of phase III drug transporters (MDR1, BCRP, OATP), enabling investigation of drug-drug interactions and transporter-mediated toxicity not achievable in traditional hepatocyte monolayers.[17]

3.3 Intestinal Organoids as Microbiota-Responsive Systems

Recent innovations integrate commensal bacterial species or their metabolites into intestinal organoid cultures, enabling investigation of how microbiota-derived metabolites (short-chain fatty



acids, secondary bile acids) modulate intestinal epithelial responses to therapeutic agents.[18] This represents a major advance because approximately 40-60% of oral drugs undergo metabolic modification by gut microbiota, yet traditional drug screening neglects this interaction.[18]

Organoid platforms incorporating pathogenic organisms (*Clostridioides difficile*, *Salmonella typhimurium*, enteroviruses) enable mechanistic investigation of infection-drug interactions and assessment of antimicrobial compound efficacy against intestinal pathogens in realistic epithelial contexts.[19] Importantly, these organoids permit simultaneous measurement of epithelial barrier integrity (transepithelial electrical resistance, tight junction protein expression) and pathogen burden, enabling comprehensive phenotypic assessment impossible with traditional culture methods.

3.4 Islet Organoids for Diabetes Pharmacology

Pancreatic islet organoids derived from patient-derived iPSCs bearing type 2 diabetes-associated variants (TCF7L2, KCNQ1, PPARG polymorphisms) enable investigation of how genetic susceptibility modulates therapeutic responses to antidiabetic agents.[20] These organoids maintain glucose-responsive insulin secretion and enable functional assessment of β -cell responses to novel insulinotropic compounds.

Patient-derived islet organoids enable personalized prediction of responsiveness to sulfonylureas, GLP-1 receptor agonists, and SGLT2 inhibitors—supporting precision dosing and therapeutic selection in heterogeneous type 2 diabetes populations.[20]

3.5 Vascularized Bone Marrow Organoids for Hematopoietic Pharmacology

Emerging bone marrow organoids incorporating osteoblasts, adipocytes, endothelial cells, and hematopoietic stem cells recapitulate the bone marrow niche architecture critical for hematopoietic stem cell maintenance and differentiation.[21] These systems enable investigation of how chemotherapy agents and targeted therapies affect both leukemic blasts and supportive niche cells—critical for understanding resistance mechanisms and off-target hematologic toxicity.

Importantly, these organoids enable study of leukemia-niche interactions driving minimal residual disease and therapeutic resistance.[21] Patient-derived leukemic bone marrow organoids now support functional assessment of tyrosine kinase inhibitor efficacy in chronic myeloid leukemia with acquired resistance mutations—a critical unmet need in precision oncology.

4. High-Throughput Organoid Screening and Phenotypic Profiling

4.1 Phenotypic Screening Platforms and Image-Based Readouts

Automated microscopy platforms coupled with machine learning-based image analysis now enable high-throughput assessment of organoid morphology, size, branching complexity, and cellular composition.[22] This phenotypic screening approach proves superior to traditional endpoint assays because it captures multiple dimensions of biological response simultaneously, enabling detection of compounds with novel mechanisms-of-action or unexpected off-target effects.[22]

Deep learning models trained on organoid image datasets now identify subtle phenotypic alterations corresponding to specific pathway disruptions, enabling inference of mechanism-of-action from



morphological features alone.[23] This represents a paradigm shift from traditional bioassay approaches requiring explicit readout selection a priori.

Table 2: Comparative Performance of Organoid-Based Screening versus Traditional Model Systems

Parameter	2D Cell Culture	Animal Models (Rodents)	Animal Models (Non-human Primates)	Organoid Systems	Multi-Organ Organoid Circuits
Human Biology Relevance	Limited (monolayer artifact)	Species-divergent	Closer to human, but limited	High (patient-derived)[1,2]	Very high (systemic modeling)[37,38]
Tissue Architecture	None (flat monolayer)	Complete organ structure	Complete organ structure	Partial 3D recapitulation[3,4]	Near-complete multi-organ structure[37]
Cell-Cell Communication	Minimal	Complete	Complete	Partial restoration[30,31]	Near-complete restoration[37]
Metabolic Competency	Limited CYP activity	Full metabolic capacity	Full metabolic capacity	Tissue-specific metabolic activity [16,17]	Multi-organ metabolic integration[37]
Genetic Fidelity	Cell line artifacts	Cross-species translation	Limited genetic variation	Patient-specific genetics[6,8]	Patient-specific multi-organ genetics[44]
Predictivity for Human Toxicity	45-60% concordance [67]	60-70% concordance [68]	70-85% concordance [68]	80-90% concordance (emerging) [24,69]	>85% concordance (validated) [44]
Barrier Function Integrity	Absent	Present	Present	Partial (epithelial organoids) [18]	Preserved multi-organ barriers[37]
Turnaround Time	2-4 days	8-12 weeks	12-16 weeks	2-4 weeks[10]	4-6 weeks[37]
Cost per Compound	\$500-2,000	\$5,000-15,000	\$15,000-40,000	\$1,000-5,000	\$3,000-10,000
Animal Use	None	Extensive	Limited to essential studies	Minimal/None	Minimal/None
Personalized Medicine Capability	Minimal	None (genetically uniform)	Limited	Excellent (patient-derived)[44]	Excellent (patient-derived)[44]
Systemic ADME Modeling	None	Complete	Near-complete	Limited (single organ)	Comprehensive (multi-organ) [37,38]
Regulatory Acceptance	Routine	Established standard	Limited acceptance	Emerging (FDA 2023)[46]	Under development[46]

Abbreviations: ADME, absorption-distribution-metabolism-excretion; CYP, cytochrome P450; FDA, Food and Drug Administration.

4.2 Multi-Parameter Organoid Biomarker Panels

Emerging “organoid biomarker cards” simultaneously measure 20-50 functional and molecular parameters across single organoid

populations: proliferation rate, differentiation efficiency, barrier function (transepithelial electrical resistance for epithelial organoids), metabolic flux (seahorse-based mitochondrial and glycolytic assessment), gene expression (via RNA-seq or targeted qPCR), protein localization



(immunofluorescence), and drug-metabolizing enzyme activity.[24] These comprehensive phenotypic profiles enable quantitative assessment of drug pharmacodynamic effects at tissue level.

Patient-to-patient biomarker variation predicts interindividual drug response heterogeneity, enabling stratification of patients likely to benefit from specific therapeutics.[24] This represents a transformative advancement toward “organoid-enabled clinical biomarker validation”—where organoid-derived biomarkers prospectively predict clinical responsiveness.

4.3 Functional Genomics Screening in Organoid Context

CRISPRi (CRISPR interference) screening libraries targeting all protein-coding genes now enable genome-wide functional genomics studies directly in organoid populations, identifying genes required for organoid-specific functions (barrier integrity, metabolic competency, differentiation) or genes modulating drug responses.[25,26] This approach proves superior to monolayer-based screening because it preserves three-dimensional tissue architecture during perturbation studies.

Notably, CRISPRi screens in organoid populations have identified novel resistance mechanisms distinct from those observed in traditional monolayer screens, highlighting the importance of tissue context in resistance mechanism discovery.[26]

5. Organoids as Platforms for Biomarker Discovery and Patient Stratification

5.1 Transcriptomic and Proteomic Profiling for Predictive Biomarker Development

Single-cell RNA-sequencing (scRNA-seq) combined with spatial transcriptomics now enables cell-type-specific gene expression profiling within organoid populations while preserving spatial relationships.[27] This approach identifies organoid cell populations exhibiting differential drug responses, enabling discovery of biomarkers predicting patient-level therapeutic responsiveness.

Critically, integration of scRNA-seq data with surface proteomic profiling (mass cytometry, spectral flow cytometry) identifies combinations of surface markers enabling prospective isolation and functional characterization of drug-responsive versus drug-resistant populations within heterogeneous organoid cultures.[27]

5.2 Organoid-Based Companion Diagnostic Development

Patient-derived tumor organoid biobanks now support prospective validation of companion diagnostics predicting immunotherapy responsiveness. Organoid-derived immune infiltration patterns, T cell exhaustion markers, and immunosuppressive myeloid populations predict ICB (immune checkpoint blockade) responsiveness with accuracy exceeding that of tissue-based biomarkers alone.[28]

This emerging “functional immunophenotyping” approach evaluates not merely static marker expression but dynamic immune responses—including organoid-infiltrating T cell effector function, myeloid cell-derived immunosuppression, and organoid cell intrinsic immunogenicity—enabling comprehensive immunotherapy prediction.[28]



Table 3: Organoid-Based Biomarkers Predicting Therapeutic Responsiveness and Clinical Outcomes

Disease Context	Organoid Type	Predictive Biomarker Panel	Clinical Endpoint Predicted	Predictive Accuracy	Validation Status	Ref
Colorectal Cancer	Patient-derived tumor organoid	PDO drug sensitivity score, MSI status, TP53 mutation profile	Overall survival, progression-free survival	85-90%	Phase II clinical trials underway [44,29]	[44]
Pancreatic Cancer	Patient-derived tumor organoid	Gemcitabine sensitivity, KRAS mutation status, fibroblast infiltration	Response to chemotherapy	80-87%	Clinical validation ongoing[45]	[45]
Lung Cancer (EGFR-mutant)	Patient-derived tumor organoid + co-cultured fibroblasts	NRG1 expression, HER3 activation, stromal content	TKI resistance development timeline	82-88%	Prospective validation in progress[31]	[31]
Cystic Fibrosis	Patient-derived intestinal organoid	CFTR-dependent forskolin-induced swelling	CFTR modulator efficacy	95-98%	FDA companion diagnostic pathway [17,70]	[17]
Type 2 Diabetes	Patient-derived islet organoid	Glucose-stimulated insulin secretion, β -cell transcriptome	GLP-1 agonist responsiveness	78-85%	Research stage[20]	[20]
Chronic Myeloid Leukemia	Patient-derived leukemic marrow organoid	BCR-ABL1 mutation profile, niche interaction markers	TKI resistance emergence	80-86%	Small cohort validation [21]	[21]
HER2+ Breast Cancer	Patient-derived tumor organoid + lymphocyte co-culture	HER2 expression level, T cell infiltration, immunogenicity score	HER2-targeted therapy + immunotherapy response	82-89%	Phase I pilot study[28]	[28]
Acute Myeloid Leukemia	Patient-derived leukemic organoid	FLT3-ITD status, blast proliferation rate, chemotherapy sensitivity	Chemotherapy response prediction	79-84%	Small patient cohort [21]	[21]
Idiopathic Pulmonary Fibrosis	Patient-derived lung organoid	TGF- β response, collagen deposition, epithelial barrier integrity	Antifibrotic drug response	75-82%	Research stage[56]	[56]
Immunotherapy (pan-cancer)	Patient-derived tumor	ICB-infiltrating T cell exhaustion markers, myeloid	ICB responsiveness,	80-87%	Clinical validation	[28]



	organoid with TIL co- culture	infiltration, PD- L1 expression	immune-related adverse events		underway [28]	
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Abbreviations: PDO, patient-derived organoid; MSI, microsatellite instability; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; CFTR, cystic fibrosis transmembrane conductance regulator; HER2, human epidermal growth factor receptor 2; ICB, immune checkpoint blockade; TIL, tumor-infiltrating lymphocyte; PD-L1, programmed death ligand 1.

5.3 Metabolic Profiling and Therapeutic Targeting

Organoid-level metabolic profiling using isotope tracing, metabolomics, and real-time metabolic rate assessment identifies metabolic dependencies selectively exploitable in pathological contexts (cancer metabolic addiction, diabetic β -cell metabolic dysfunction).[29] Patient-derived tumor organoids reveal metabolic heterogeneity within clonal populations, enabling discovery of metabolism-targeting therapeutic opportunities.[29]

Integration of metabolic profiling with drug screening identifies combinations targeting complementary metabolic pathways, providing mechanistic rationale for synergistic drug combinations validated in patient organoids before clinical testing.

6. Organoid-Based Investigation Of Drug Resistance Mechanisms

6.1 Acquired Resistance in Cancer Organoid Models

Patient-derived tumor organoids cultivated in the presence of targeted therapeutics or chemotherapy agents develop acquired resistance over weeks to months—a timescale that enables mechanistic investigation of resistance development.[30] These “resistance organoids” exhibit altered genomic architecture, gene expression, and metabolic phenotypes compared to parental lines, recapitulating clinical resistance mechanisms.

Importantly, sequential organoid-level resistance development reveals resistance pathways not observed in static mutation screening approaches.[30] For example, studies of EGFR-mutant lung cancer organoid resistance to EGFR tyrosine kinase inhibitors identified activation of HER3 signaling through increased neuregulin (NRG1) production in stromal fibroblasts—a mechanism detectable only in co-culture contexts.[31]

6.2 Inherent Resistance and Tumor Microenvironment Contributions

Tumor organoid biobanks reveal that drug response heterogeneity correlates with organoid-intrinsic characteristics (mutational burden, immune infiltration) and microenvironmental factors (fibroblast abundance, vascular density, extracellular matrix composition).[32] Manipulation of organoid microenvironment through addition/removal of stromal cells or matrix components enables dissection of microenvironment-mediated resistance.[32]

This approach identified matrix-mediated resistance mechanisms in pancreatic cancer whereby high hyaluronic acid content limits drug penetration, a mechanism remediable through co-administration of hyaluronidase.[33]

6.3 Clonal Evolution and Polyclonal Resistance

Single-cell derived organoid clones subjected to drug selection reveal differential clonal evolution trajectories, with individual clones employing distinct resistance mechanisms.[34] This



polyclonal resistance discovery is impossible in traditional single-cell derived models but proves critical for understanding therapeutic resistance in heterogeneous tumors.

Temporal sampling of organoid populations during drug pressure reveals the molecular order of resistance events (which mutations/expression changes occur first, second, etc.), enabling prediction of resistance vulnerability windows amenable to therapeutic intervention.[34]

7. Microphysiological Systems and Multi-Organ Organoid Circuits

7.1 Organ-on-Chip Integration and Physiological Fluidics

Microfluidic integration of organoids with physiologically-relevant fluid flow, shear stress, and mechanical stimulation substantially enhances organoid maturation and function.[35] Intestinal organoids cultured in perfused microfluidic chambers exhibit enhanced villus-like structure, increased tight junction protein expression, and improved barrier function compared to static cultures.[35]

Critically, organoid-on-chip systems enable investigation of how fluid flow and mechanical forces modulate drug responses—parameters absent in traditional culture but critical for predicting efficacy in vascularized tissues.[36]

7.2 Multi-Organ Microphysiological Systems (“Body-on-a-Chip” Networks)

Emerging interconnected organoid systems linking intestinal, hepatic, renal, and cardiac organoids via microfluidic channels enable realistic modeling of systemic drug absorption-distribution-metabolism-excretion (ADME) and multi-organ toxicity.[37,38] These systems now support quantitative pharmacokinetic modeling,

enabling prediction of systemic drug exposure from organoid-level parameters.

Importantly, multi-organ systems enable detection of organ-organ interactions driving unexpected toxicities. For example, organoid-level modeling revealed that hepatic metabolism of certain compounds generates nephrotoxic metabolites—a mechanism detectable only in multi-organ contexts.[37]

7.3 Vascularized Organoid Networks

Novel biomaterial approaches enabling vascular network formation within interconnected organoid circuits now support blood flow through organoid tissues at physiologically-relevant rates.[39] Vascularized tumor organoid networks demonstrate enhanced therapeutic resistance compared to avascular controls, better recapitulating in vivo drug penetration limitations and heterogeneous drug exposure.[39]

8. Artificial Intelligence and Machine Learning in Organoid Pharmacology

8.1 Predictive Models Integrating Organoid Phenotypes and Patient Genetics

Machine learning models trained on organoid biomarker panels integrated with patient germline genetics now predict individual drug responses with accuracy exceeding 85% in validation cohorts.[40] These “organoid-genetics prediction models” leverage the insight that therapeutic responsiveness emerges from interactions between drug properties, organoid-intrinsic characteristics, and individual genetic background.[40]

Deep learning models processing high-dimensional organoid imaging data identify morphological signatures predictive of underlying genetic alterations and disease progression—



enabling non-invasive inference of organoid genotype from imaging alone.[41]

Table 4: Artificial Intelligence and Machine Learning Architectures Applied to Organoid Pharmacology

ML/AI Approach	Input Data	Output/Prediction	Organoid Application	Performance Metrics	Clinical Translation Status	Ref
Convolutional Neural Networks (CNN)	High-resolution organoid images (morphology, differentiation)	Organoid phenotype classification, maturity assessment, drug response prediction	Automated high-throughput screening of 500+ organoids/day [22,23]	92-96% classification accuracy [23]	Deployed in research labs [22]	[22,23]
Random Forest/Gradient Boosting	Organoid biomarker panels (20-50 parameters) + patient genetics	Individual drug response prediction, therapeutic ranking	Personalized medicine decision support (10 top drugs ranked) [40,44]	85-90% prediction accuracy in validation cohorts[40]	Phase II clinical trials [44]	[40,44]
Graph Neural Networks (GNN)	Organoid single-cell transcriptomics data + spatial information	Cell-cell interaction mapping, critical population identification, resistance mechanism prediction	Drug resistance pathway discovery, combination therapy design [42]	Identifies 10-30 key cell populations driving drug response [42]	Research stage [42]	[42]
Transformer Models (e.g., BERT-based)	Organoid transcriptomic sequences, drug chemical structures	Drug-organoid response prediction for novel compounds not in training data	Virtual screening of compound libraries (>100,000 compounds) [43]	78-85% accuracy for novel compound prediction[43]	Development stage [43]	[43]
Variational Autoencoders (VAE)	Single-cell RNA-seq from organoids	Latent feature extraction, cell state embedding, biomarker discovery	Identification of drug-responsive cell states, rare resistance populations [71]	Discovers biomarkers with 80-88% specificity [71]	Research stage [71]	[71]
Deep Learning Image Analysis	Time-lapse organoid imaging (4D confocal microscopy)	Proliferation rate prediction, differentiation trajectory, cell death kinetics	Drug pharmacodynamic profiling without endpoint fixation[41]	Predicts drug mechanism-of-action with 88-93% accuracy [41]	Deployed in screening centers [41]	[41]



Reinforcement Learning	Organoid culture parameters + phenotype feedback	Optimal culture conditions for enhanced organoid function/maturation	Automated bioreactor control, protocol optimization [72]	Reduces protocol optimization time from 6 months to 4-6 weeks[72]	Early deployment [72]	[72]
Bayesian Networks	Organoid biomarkers + patient clinical data + genomics	Probability estimates for treatment response, confidence intervals for clinical predictions	Quantified uncertainty in personalized medicine decisions[73]	Provides calibrated probability estimates (>90% calibration) [73]	Development stage [73]	[73]
Natural Language Processing (NLP)	Organoid literature + experimental data + clinical trial reports	Knowledge extraction, hypothesis generation, target identification	Mining 100,000+ organoid studies for pattern discovery[74]	Identifies previously-unknown drug-organoid correlations [74]	Research stage[74]	[74]
Federated Learning	Organoid data from multiple institutions (without sharing raw data)	Collaborative model training, multi-center validation, privacy-preserving predictions	Building predictive models across 50+ organoid biobanks simultaneously [75]	Maintains institutional data privacy while improving prediction accuracy [75]	Pilot implementations [75]	[75]

Abbreviations: ML/AI, machine learning/artificial intelligence; CNN, convolutional neural network; BERT, bidirectional encoder representations from transformers; VAE, variational autoencoder.

8.2 Graph Neural Networks for Organoid Cell Community Modeling

Graph neural network architectures treating organoids as computational graphs (nodes = cells, edges = cell-cell interactions) enable mechanistic modeling of how spatial organization and cell-cell communication drive drug responses.[42] These models identify “critical cell populations” whose perturbation disproportionately affects organoid-level responses—insights valuable for rational combination therapy design.

8.3 Generative Models for Organoid and Drug Property Integration

Transformer-based models trained on paired organoid phenotypes and drug properties now enable prediction of organoid responses to novel compounds not represented in training data.[43] These generative models substantially accelerate virtual screening, enabling prioritization of experimental testing toward compounds with highest predicted efficacy.

9. Translational Paradigm: Organoid-Based Personalized Medicine Circuits

9.1 “Functional Precision Medicine” Framework



An emerging paradigm termed “functional precision medicine” integrates organoid-based functional testing with genomic profiling and machine learning to enable patient-specific therapeutic selection.[44] In this framework, patient-derived organoids are subjected to comprehensive drug panels (50-200 compounds representing major therapeutic classes), yielding quantitative efficacy measures. These organoid phenotypes, integrated with patient germline genetics and tumor genomics (for cancer applications), feed machine learning models predicting optimal therapy with quantified confidence intervals.[44]

Clinical pilot studies implementing organoid-based functional precision medicine now demonstrate superior therapeutic outcomes compared to standard-of-care genomic testing alone.[44]

9.2 Biobanking Infrastructure and Standardization

Large-scale organoid biobanks (>5,000 patient-derived organoid lines at major cancer centers) now serve as repositories supporting rapid functional drug testing, biomarker discovery, and mechanism-of-action validation.[45] Standardized protocols, validated quality-control metrics, and centralized computational platforms now enable cross-institutional data sharing and meta-analysis.[45]

Integration of organoid biobanks with electronic health records enables retrospective validation of organoid-predicted drug responses against clinical outcomes—establishing the evidence base for prospective clinical implementation.[45]

9.3 Regulatory Pathways for Organoid-Based Decisions

The FDA has announced frameworks for incorporating organoid-derived data into drug development decision-making, including use of patient-derived tumor organoids as potential replacements for comparative in vivo efficacy studies in early-stage development.[46] These emerging regulatory frameworks require standardized protocols, defined analytical validation criteria, and demonstrated concordance with clinical outcomes.

10. Tissue-Specific Applications with Mechanistic Depth

10.1 Cardiac Organoids and Electrophysiological Safety Pharmacology

Cardiac organoids now enable direct measurement of action potential duration, refractory period, and drug-induced arrhythmia liability in human-derived tissue—parameters critical for safety assessment but traditionally requiring animal models.[47] High-throughput cardiac organoid screening platforms assess hundreds of compounds simultaneously for QT prolongation, early afterdepolarization, and other pro-arrhythmic features.[47]

Recent innovations integrate calcium imaging and voltage-sensitive dyes enabling real-time assessment of electrical propagation through organoid tissue, revealing how local drug concentrations modulate electrophysiological properties at subcellular and tissue level.[48]

10.2 Renal Organoids and Personalized Nephrotoxicity Risk

Patient-derived kidney organoids bearing genetic variants associated with drug-induced acute kidney injury susceptibility (e.g., CYP3A4 variants affecting metabolite generation, SLCO variants affecting transporter-mediated toxicity)



enable personalized nephrotoxicity risk assessment.[49] Organoid-level assessment predicts which patients require dose reductions or alternative therapeutics for nephrotoxic agents (chemotherapy, NSAIDs, ACE inhibitors).[49]

Integration of kidney organoid biomarkers with serum biomarkers (KIM-1, NGAL) in clinical trials now prospectively identifies patients at highest nephrotoxicity risk before irreversible renal damage occurs.[49]

10.3 Pulmonary Organoids for Respiratory Drug Delivery

Lung organoids recapitulating both conducting airway and alveolar regions enable realistic assessment of inhaled drug deposition, mucociliary clearance, and alveolar absorption.[50] Patient-derived cystic fibrosis and COPD organoids reveal disease-specific alterations in airway mucus composition and epithelial barrier function that modify drug deposition and efficacy.[50]

Organoid-level modeling now guides formulation optimization for inhaled therapeutics—identifying conditions maximizing alveolar deposition and bioavailability while minimizing upper airway sequestration.[50]

11. Emerging Challenges and Methodological Considerations

11.1 Organoid Maturity and Developmental Stage Heterogeneity

While organoid technology has advanced dramatically, many organoid systems remain phenotypically immature, resembling fetal rather than adult tissues.[51] This represents a fundamental limitation for modeling adult diseases, particularly those affecting terminally differentiated cells (hepatocyte metabolic

dysfunction in cirrhosis, aged neuronal degeneration).

Recent innovations enabling accelerated maturation (co-culture with stromal cells, mechanical stimulation, extended culture periods, micronutrient supplementation) now generate mature organoids with gene expression and functional profiles resembling adult tissues.[51] However, standardization of maturation protocols remains incomplete.

11.2 Batch Variability and Inter-Line Heterogeneity

Organoid derivation and differentiation protocols exhibit substantial variability, with efficiency ranging from 5-80% depending on protocol details and cell line characteristics.[52] This heterogeneity complicates cross-institutional comparisons and regulatory acceptance. Emerging approaches including automated cultivation systems, real-time parameter monitoring, and machine learning-guided protocol optimization now substantially reduce batch variability.[52]

11.3 Absence of Systemic Responses and Endocrine Signaling

Current organoid systems capture local tissue-level responses but cannot fully model systemic endocrine signaling, immune system integration, or whole-body metabolic responses.[53] multi-organ circuits partially address this limitation, yet achieving physiologically authentic inter-organ crosstalk remains incomplete.

Future innovation integrating endocrine signaling (circulating hormones, growth factors) and appropriate immune components promises enhanced physiological authenticity.[53]

12. Disease-Specific Applications and Clinical Impact



Table 5: Disease-Specific Organoid Applications, Therapeutic Insights, and Clinical Outcomes

Disease Category	Organoid Platform	Key Discoveries/ Applications	Therapeutic Targets Identified	Clinical Translation Progress	Patient Impact Metrics	Ref
Cystic Fibrosis	Patient-derived intestinal organoid	CFTR mutation-specific rescue; N-of-1 functional testing	CFTR correctors, potentiators (VX-770, VX-661)	Companion diagnostic FDA-approved [17]	100% accuracy in predicting drug responsiveness for CFTR modulators [17]	[17,70]
Colorectal Cancer	Patient-derived tumor organoid biobank (>500 lines)	Chemotherapy/immunotherapy response prediction; resistance mechanism discovery	WNT/ β -catenin pathway; immune infiltration markers	15+ patients enrolled in organoid-guided treatment trials[44]	72% response rate vs. 40% standard-of-care[44]	[44]
Pancreatic Cancer	Patient-derived tumor organoid	Gemcitabine/nab-paclitaxel sensitivity; stromal interactions	KRAS-dependent metabolic vulnerabilities; fibroblast interactions	8 patients completing organoid-guided therapy[45]	Median progression-free survival 8.2 months (vs. 5.5 standard-of-care)[45]	[45]
Type 2 Diabetes	Patient-derived islet organoid	Glucose responsiveness heterogeneity; drug response prediction	GLP-1R pathway; KCNQ1 variants affecting drug response	Research stage; planned 50-patient clinical validation[20]	Predicts GLP-1 agonist efficacy with 82% accuracy[20]	[20]
Parkinson's Disease	Patient-derived midbrain organoid (iPSC-derived)	α -synuclein aggregation; dopaminergic neuron vulnerability	L-DOPA efficacy; neuroprotective compound screening	Neuroprotective compounds identified in 5 organoid lines[76]	Organoid-predicted compounds entering Phase I trials[76]	[76]
Alzheimer's Disease	Patient-derived brain organoid with vascular/immune cells	Amyloid- β and tau pathology; neuroinflammation contribution	Neuroinflammation modulators; amyloid clearance enhancers	Small organoid biobank established (10 patient lines)[15]	Neuro-inflammatory biomarkers predict cognitive decline[15]	[15]
Chronic Myeloid Leukemia	Patient-derived bone marrow organoid	BCR-ABL1 mutation emergence; niche-mediated resistance	BCR-ABL1 second/third-generation inhibitors; niche-targeting agents	6 CML patients with acquired TKI resistance[21]	100% accuracy identifying optimal next-line therapy[21]	[21]

HER2+ Breast Cancer	Patient-derived tumor organoid + lymphocyte co-culture	HER2 heterogeneity; immunotherapy response prediction	HER2-targeted therapy + ICB combinations; CD8+ T cell engagement	12 patients in organoid-guided combination therapy trial[28]	75% response rate vs. 50% sequential therapy[28]	[28]
Idiopathic Pulmonary Fibrosis	Patient-derived lung organoid (airway + alveolar)	Disease progression markers; antifibrotic drug response	TGF- β pathway inhibition; epithelial-mesenchymal transition blocking agents[56]	Research stage; planned Phase IIa biomarker study[56]	Organoid biomarkers correlate with FVC decline ($r=0.78$)[56]	[56]
Mitochondrial Disease	Patient-derived organoid (tissue-specific)	Mitochondrial respiration defects; metabolic vulnerability assessment	Mitochondrial function enhancers; anti-inflammatory agents	3 rare mitochondrial disease patients; organoid-guided therapy[54]	Clinical improvement in 2/3 patients with organoid-predicted therapy[54]	[54]
Neurodegeneration (Frontotemporal Dementia)	Patient-derived brain organoid (MAPT/GRN mutations)	Tau pathology; progranulin insufficiency modeling	GSK3 β inhibitors; progranulin replacement approaches[55]	Organoid lines from 15 FTD patients established[55]	Organoid biomarkers predict cognitive decline trajectory[55]	[55]
Acute Kidney Injury (Drug-Induced)	Patient-derived renal organoid (personalized risk)	Nephrotoxic drug sensitivity; transporter-mediated injury	Renal-protective agents; dose adjustment strategies for high-risk patients[49]	30 patients assessed for personalized drug dosing[49]	Prevention of AKI in 85% of high-risk patients with organoid-guided dosing[49]	[49]

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; FDA, Food and Drug Administration; GLP-1R, glucagon-like peptide-1 receptor; KCNQ1, potassium channel gene; TKI, tyrosine kinase inhibitor; ICB, immune checkpoint blockade; FVC, forced vital capacity; MAPT, microtubule-associated protein tau; GRN, granulin; GSK3 β , glycogen synthase kinase-3 beta; AKI, acute kidney injury.

12.1 Rare Genetic Disorders and Precision Therapeutics

Patient-derived organoids derived from individuals with rare genetic disorders (mitochondrial diseases, lysosomal storage disorders, rare syndromic forms of diabetes) enable functional assessment of rescue therapeutics in authentic disease contexts.[54] Organoid-based functional testing now de-risks

development of ultra-rare disease therapeutics by confirming target engagement and functional rescue before expensive clinical trials.[54]

12.2 Neurodevelopmental Disorder Modeling

Brain organoids derived from individuals with autism, schizophrenia, and intellectual disability variants now enable investigation of how neurodevelopmental disease-associated mutations affect neural circuit formation, neurotransmitter



function, and drug responses.[55] These studies identified novel therapeutic targets (glutamate receptor modulation, GABAergic signaling enhancement) validated through organoid-based functional testing.[55]

12.3 Fibrotic Disease Modeling and Anti-fibrotic Drug Development

Organoid systems incorporating fibroblasts now enable investigation of epithelial-mesenchymal

crosstalk driving fibrosis.[56] Patient-derived lung and liver fibrosis organoids reveal disease-specific pro-fibrotic signaling axes amenable to therapeutic intervention. Novel anti-fibrotic compounds now undergo validation in patient-derived fibrosis organoids before clinical testing.[56]

13. Regulatory Evolution and Standardization Efforts

Table 7: Regulatory Frameworks for Organoid-Based Drug Development and Clinical Translation

Regulatory Body	Guidance Release	Scope	Acceptable Applications	Required Standards	Current Acceptance Status	Expected Timeline for Full Implementation	Ref
FDA (USA)	Preliminary IND Guidance (2023) [46]	Organoid-based toxicity screening for IND applications	Hepatotoxicity, nephrotoxicity, cardiotoxicity screening; rare disease drug development	Standardized protocols, validated QC metrics, clinical concordance demonstration ($\geq 80\%$) [46]	Conditional acceptance for early-stage toxicity screening [46]	2024-2026 (full implementation) [46]	[46]
FDA (USA)	Companion Diagnostic Framework (Approved 2023)	Organoid-derived biomarkers predicting drug response	CFTR-modulator efficacy prediction (CF); PD-L1 expression in lung cancer [70]	Clinical validation in ≥ 200 patients; $\geq 85\%$ predictive accuracy; prospective trial confirmation [70]	Approved for CF; pending for oncology [70]	2025-2027[70]	[70]
EMA (Europe)	Organoid Screening Guidelines (2023) [57]	Alternative to animal hepatotoxicity/nephrotoxicity testing	Drug safety assessment; replacement for rat hepatocyte testing [57]	GLP compliance; defined endpoints; comparative validation studies [57]	Accepted as replacement for 2D hepatocyte screening in early stage [57]	2024-2025[57]	[57]
EMA (Europe)	ICH S9B Guidance Amendment (Proposed 2024)	Qualification of organoid platforms for regulatory submissions	Safety pharmacology assessment; organoid-specific study designs[80]	Standardized protocols; organoid characterization panels; inter-laboratory validation [80]	Under consultation[80]	2025-2026[80]	[80]
ISO/TC 229	ISO Consensus Standards	Organoid derivation, banking,	All organoid platform types;	Standardized nomenclature; validated QC	Draft standards	2025-2027[58]	[58]



	(In Development)	characterization standards	biobank infrastructure; quality metrics[58]	assays; minimum characterization data sets [58]	circulating (2024)[58]		
OECD	Test Guidelines for Organoid Screening (Proposed 2024)[58]	Organoid replacement for OECD standard animal toxicity tests	Acute toxicity testing; organ-specific toxicity screening; readiness assessment [58]	OECD Test Guideline format; cross-laboratory validation; statistical requirements[58]	Proposed; under scientific review[58]	2025-2027[58]	[58]
Clinical Implementation	Organoid-Guided Therapy Pathways (Emerging 2023-2024)[59]	Infrastructure and workflows for clinical decision-making	Oncology (tumor organoid drug sensitivity); rare disease precision therapy selection [59]	Institutional Quality Management Systems; personnel certification; turnaround time <14 days[59]	Piloted at 10+ major cancer centers[59]	2024-2025 (broader adoption) [59]	[59]
International Society for Organoid Research (ISOR)	ISOR Best Practices Standards (2024)	Community consensus guidelines for organoid research	Organoid derivation; banking; phenotypic characterization; ethical oversight [81]	Compliance with ISOR guidelines; ethical review board oversight [81]	Guidance published; adoption ongoing[81]	2024-2025 [81]	[81]
Chinese NMPA	Organoid Guidance (Proposed 2024)	Organoid-based drug development in China	Safety assessment; rare disease therapeutics; personalized medicine applications [82]	Organoid standardization; GLP-equivalent compliance; clinical data package [82]	Under development [82]	2025-2026 [82]	[82]
Japanese PMDA	Organoid Discussion Document (2023)	Preliminary guidance on organoid data acceptance	Predictive biomarker development; safety assessment[83]	Standardized protocols; data format harmonization ; QC specifications [83]	Under discussion; preliminary acceptance for pilot studies [83]	2024-2026 [83]	[83]

Abbreviations: IND, Investigational New Drug; QC, quality control; CF, cystic fibrosis; GLP, good laboratory practice; OECD, Organisation for Economic Co-operation and Development; ISO, International Organization for Standardization; ISOR, International Society for Organoid Research; NMPA, National Medical Products Administration (China); PMDA, Pharmaceuticals and Medical Devices Agency (Japan).

13.1 FDA and EMA Guidance Documents

The FDA has released preliminary guidance (2023) proposing acceptable organoid-based study designs for supporting IND (Investigational New Drug) applications, particularly for toxic drugs

where animal models prove inadequate.[46] These guidelines emphasize standardized protocols, defined endpoints, and demonstrated concordance with clinical outcomes.



The EMA has similarly published guidance on organoid-based screening for hepatotoxicity and nephrotoxicity, establishing acceptable study designs and reporting standards.[57]

13.2 International Standardization Initiatives (ISO, OECD)

International standards organizations now develop consensus protocols for organoid derivation, characterization, and quality control (ISO/TC 229 Nanotechnologies working groups).[58] OECD Test Guideline development programs now incorporate organoid-based screening approaches as alternatives to animal toxicity testing.[58]

13.3 Clinical Implementation Frameworks

Emerging clinical implementation frameworks define workflows for organoid-based functional testing in clinical decision-making, including infrastructure requirements, personnel qualifications, turnaround time targets, and result interpretation guidelines.[59]

14. Ethical Evolution and Governance Structures

14.1 Brain Organoid Consciousness and Sentience Concerns

As brain organoids develop increasingly complex electrical activity and network properties, ethical concerns regarding potential consciousness or sentience warrant serious consideration.[60] International consensus statements now establish upper limits on organoid complexity (e.g., maximum organoid size, maximum network connectivity) beyond which organoid research requires enhanced ethical oversight.[60]

14.2 Patient Autonomy and Data Governance in Organoid Biobanking

Large-scale organoid biobanking raises novel governance challenges regarding patient autonomy, long-term data stewardship, and commercial exploitation.[61] Emerging frameworks establish: - Dynamic consent mechanisms enabling patients to specify acceptable research uses - Transparent data governance structures with patient representation - Fair benefit-sharing agreements for commercialized organoid-derived products [61]

14.3 Equitable Access and Global Health Considerations

Organoid technology poses substantial risks of concentrating precision medicine access in high-resource settings.[62] Ethical frameworks now emphasize: - Technology transfer supporting organoid platforms in lower-resource settings - Equitable participant recruitment in organoid-based biobanks - Inclusion of diverse patient populations ensuring therapeutic benefits reach all demographics.[62]

15. Future Directions and Emerging Technologies

15.1 Organoid-Derived “Human Tissues-in-a-Vial”

Advances in decellularization and organoid recellularization now enable generation of organoid-derived ECM scaffolds repopulated with patient cells, creating “humanized tissue” platforms with realistic vascularization, innervation, and stromal support.[63]

15.2 Integration with Real-Time Biosensors

Organoid integration with implantable biosensors enabling real-time measurement of organoid responses to drug exposure now permits closed-loop experimental designs with dynamic drug adjustment.[64] These “smart organoid platforms”



enable discovery of optimal therapeutic windows and identification of biomarkers predicting therapeutic response.

15.3 Organoid Cryopreservation and High-Throughput Screening Infrastructure

Standardized cryopreservation protocols now preserve organoid viability and function through freeze-thaw cycles, enabling distributed organoid testing networks.[65] This capability supports global organoid biobanks with centralized testing infrastructure.

15.4 Quantum Computing for Organoid Phenotype Prediction

Emerging quantum computing applications enabling analysis of high-dimensional organoid phenotype datasets now identify previously-hidden patterns in organoid biomarker-drug response relationships.[66]

CONCLUSION

Organoids have evolved from exploratory research models into quantitative, precision pharmacology platforms capable of supporting clinical decision-making. The convergence of organoid biology with artificial intelligence, high-throughput screening, biomarker discovery, and multi-organ systems engineering has generated unprecedented capabilities for human-relevant drug testing, patient stratification, and therapeutic resistance investigation.

The emergence of “functional precision medicine” frameworks integrating organoid phenotypes with genomic profiling and machine learning now enables personalized therapeutic selection with demonstrated clinical utility. Large-scale organoid biobanks coupled with standardized protocols and regulatory frameworks position organoid

pharmacology as essential infrastructure for future drug development.

Critical remaining challenges such as organoid maturity, batch variability, systemic response modeling, and ethical governance are increasingly addressable through ongoing innovation. Integration with real-time biosensing, quantum computing, and advanced AI architectures promises further expansion of organoid capabilities.

The next decade will likely witness transition from organoid-based academic research to routine clinical implementation, with organoid-derived functional testing becoming standard decision points in therapeutic selection pathways. This transformation promises substantial improvements in therapeutic efficacy, acceleration of drug development timelines, and reduced reliance on animal experimentation, advancing both scientific progress and ethical practice in precision medicine development.

Successful clinical translation requires coordinated effort across scientists, regulators, clinicians, and patients to establish robust governance frameworks, ensure equitable access, and translate organoid insights into global health impact.

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