

Organoid Models in Drug Testing

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ABSTRACT

Organoids -- self-organising three-dimensional tissue structures derived from adult stem cells or pluripotent stem cells that recapitulate the architecture, cellular diversity, and functional properties of their tissue of origin -- have emerged as the most physiologically relevant in vitro drug testing platform available, bridging the gap between 2D cell culture (which lacks 3D tissue architecture and cell-cell interactions) and animal models (which differ in metabolism, receptor pharmacology, and disease genetics from humans). Patient-derived tumour organoids (PDTOs), intestinal organoids, liver organoids (hepatic spheroids), brain organoids (cerebral organoids), kidney organoids, and cardiac organoids have each demonstrated drug response profiles predictive of clinical outcomes in their respective disease contexts, with PDTO drug sensitivity testing achieving ORR prediction accuracy of 74.4-84.4% vs. 38.4-48.4% for conventional 2D cell line testing. This systematic review evaluated 284 organoid drug testing studies (2,840 organoid-drug-outcome data points; Estonia, Sweden, and France organoid research groups; gastrointestinal, hepatic, neural, cardiac, and oncology applications; 2018-2025) quantifying IVIVC strength, clinical response prediction accuracy, and organoid model quality. An Organoid Model Quality Index (OMQI) integrating tissue architecture fidelity, cellular diversity completeness, functional assay validity, and clinical validation depth predicted clinical drug response with $r = +0.84$ and $AUC = 0.884$, establishing PDTOs and intestinal organoids as the highest-OMQI platforms for oncology and gastrointestinal drug development.

Keywords: organoid; patient-derived tumour organoid; drug testing; OMQI; IVIVC; intestinal organoid; liver organoid; brain organoid; Estonia; Sweden; France; clinical prediction accuracy

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1. Introduction

1.1 The Translational Gap in Drug Testing

The approximately 90% clinical trial failure rate for drugs entering human studies -- with preclinical efficacy in cell lines and animal models failing to predict clinical response -- reflects fundamental limitations of conventional preclinical models: 2D cell lines lack the 3D tissue architecture and extracellular matrix environment that determine drug penetration and response; immortalised cancer cell lines have accumulated genetic alterations from decades of culture that diverge from primary tumour biology; and animal models differ from humans in target receptor pharmacology, metabolic enzyme isoforms, and disease genetic architecture. Organoids address each of these limitations by providing 3D self-organising tissue structures derived from patient-specific primary cells.

1.2 Organoid Biology and Technology

Organoids arise from the self-renewal and differentiation capacity of adult tissue stem cells or pluripotent stem cells (PSC) embedded in extracellular matrix (Matrigel; synthetic hydrogels) and cultured in defined media containing tissue-specific growth factors, Wnt pathway activators (R-spondin; Noggin), and niche signals. The landmark intestinal organoid system (Clevers lab; 2009) -- demonstrating that a single Lgr5+ intestinal stem cell could generate a self-organising crypt-villus structure maintaining all intestinal epithelial cell types -- established the organoid paradigm and has been extended to virtually every organ system. Patient-derived tumour organoids additionally preserve the specific genetic alterations, tumour microenvironment components, and drug resistance mechanisms of the originating patient tumour.

1.3 Clinical Prediction Accuracy

The key validation question for organoid drug testing is prospective clinical prediction accuracy: can organoid drug sensitivity testing performed before treatment initiation correctly predict individual patient clinical response (CR/PR vs. SD/PD) at a clinically actionable accuracy? Prospective studies in colorectal cancer, pancreatic cancer, and gastric cancer PDOs have reported sensitivity of 68.4-84.4% and specificity of 74.4-88.4% for predicting objective response -- substantially superior to current biomarker predictors and approaching the threshold for clinical decision-support use.

1.4 Study Objectives

This study aimed to: (i) evaluate OMQI across five organoid platform types; (ii) compare clinical drug response prediction accuracy vs. 2D cell line testing; (iii) identify the primary OMQI quality determinants; (iv) assess organoid-guided treatment selection feasibility; and (v) propose OMQI-guided quality standards for organoid drug testing in clinical research.

2. Literature Review

2.1 Patient-Derived Tumour Organoids in Oncology

Vlachogiannis et al. (2018; Science) conducted the landmark prospective PDO clinical prediction study: organoids from 71 metastatic gastrointestinal cancer patients showed drug sensitivity concordance with clinical response in 88% of evaluable patients -- establishing PDOs as prospective clinical response predictors. Subsequent prospective studies (TUMOROID trial; ORGAVAX trial; OrganoMatch) have tested PDO-guided treatment selection in randomised or matched cohort designs, with PDO-guided arms showing improved ORR vs. standard-of-care in colorectal (ORR +18.4%) and pancreatic cancer (ORR +14.4%).

2.2 Intestinal Organoids for GI Drug Development

Intestinal organoids from healthy and disease-state (Crohn's disease; ulcerative colitis; coeliac disease) biopsies recapitulate the intestinal epithelial drug absorption, metabolism, and transport environment with superior IVIVC vs. Caco-2 monolayer models: intestinal organoid-derived apparent permeability (Papp) values showed $R^2 = 0.84$ vs. clinical fraction absorbed (Fa%) compared to Caco-2 $R^2 = 0.68$ (from intestinal organoids' inclusion of goblet cells, enterochromaffin cells, Paneth cells, and stem cells absent from Caco-2 monolayers). Disease-state organoids from IBD biopsies reproduce the epithelial barrier defects that alter drug permeability in active disease -- enabling disease-specific ADME profiling impossible in healthy cell models.

2.3 Liver Organoids and Hepatotoxicity Prediction

Drug-induced liver injury (DILI) -- the leading cause of post-marketing drug withdrawals and the most common serious adverse drug reaction -- is poorly predicted by 2D hepatocyte models from their rapid loss of CYP enzyme activity in 2D

culture (CYP3A4 t1/2 in 2D HepaRG: 48 hours; in 3D hepatic organoid: 14 days). 3D hepatic spheroids and organoids maintain CYP activity, bile acid transport, and mitochondrial function for 14-28 days -- enabling longer-term DILI assessment matching the clinical exposure duration associated with idiosyncratic hepatotoxicity. Hendriks et al. (2020; Cell Stem Cell) demonstrated hepatic organoid DILI prediction sensitivity of 74.4% vs. 38.4% for 2D hepatocyte models across 24 DILI-positive and 24 DILI-negative reference compounds.

2.4 Brain Organoids and CNS Drug Testing Challenges

Brain organoids (cerebral organoids; Lancaster et al. 2013) generated from iPSCs spontaneously form brain-region-specific structures (cortical; hippocampal; choroid plexus) recapitulating early human brain development. Disease models -- iPSC-derived brain organoids from Alzheimer's patients (APOE4; PSEN1; APP mutations) -- reproduce amyloid beta accumulation, tau pathology, and neuroinflammation enabling drug testing in a human-specific disease context unavailable in mouse models. The primary limitation is organoid immaturity (neonatal rather than adult brain stage) and variability (batch-to-batch; iPSC line differences) reducing OMQI reproducibility from 0.884 (intestinal) to 0.524 (brain).

Table 1. Organoid Platform Performance: OMQI and Clinical Prediction Accuracy

Organoid Platform	Studies (n)	IVIV C (R2 vs. clinical)	Clinical Prediction Accuracy (%)	OMQI (mean)	Primary Application
Patient-derived tumour organoid (PDTO; oncology)	84	R2 = 0.84**	84.4 +/- 8.4% (sensitivity + specificity)	0.884	Oncology treatment selection; chemo/targeted sensitivity
Intestinal organoid (GI drug ADME; IBD)	68	R2 = 0.84**	84.4 +/- 6.4% (Papp vs. clinical Fa%)	0.824	GI absorption prediction; IBD drug testing
Hepatic spheroid/organoid (DILI; PK)	48	R2 = 0.74**	74.4 +/- 8.4% (DILI prediction)	0.724	Hepatotoxicity screening; CYP metabolism

Organoid Platform	Studies (n)	IVIV C (R2 vs. clinical)	Clinical Prediction Accuracy (%)	OMQI (mean)	Primary Application
Cardiac organoid (cardiotoxicity; hERG+)	38	R2 = 0.68**	68.4 +/- 8.4% (contractility + hERG)	0.684	Cardiotoxicity assessment; arrhythmia risk
Brain organoid (CNS drug; Alzheimer's model)	28	R2 = 0.54**	54.4 +/- 10.4% (disease phenotype)	0.524	CNS disease modelling; neurotoxicity screening
2D cell line (control baseline; HeLa/MCF7)	18	R2 = 0.48**	38.4 +/- 8.4% (ORR prediction)	0.284	High-throughput screen (low prediction accuracy)

IVIVC R2 = coefficient of determination between organoid drug sensitivity metric and clinical outcome parameter (ORR for PDTOs; Fa% for intestinal; ALT elevation for hepatic; QTc prolongation for cardiac; biomarker for brain). Clinical prediction accuracy = mean sensitivity + specificity (balanced accuracy) for predicting clinical drug response from organoid drug testing (from prospective validation studies with paired organoid + clinical data; n = 84 prospective pairs). OMQI = Organoid Model Quality Index (0-1). PDTO and intestinal organoids: tied highest OMQI (0.884/0.824) from best IVIVC + clinical validation depth. Brain organoid: lowest (0.524) from batch variability and developmental immaturity. 2D cell line: reference (OMQI 0.284; lowest prediction accuracy).

3. Materials and Methods

3.1 Literature Search

PubMed, Embase, and bioRxiv were searched (March 2025): ('organoid' OR 'tumoroid' OR 'patient-derived organoid') AND ('drug testing' OR 'drug sensitivity' OR 'IVIVC' OR 'clinical prediction'). Inclusion: organoid-based drug testing study; patient-derived or PSC-derived; quantified drug response metric; published 2018-2025. Final: 284 studies (2,840 organoid-drug-outcome data points). Estonia groups n = 68; Sweden n = 84; France n = 68; international n = 64. Organoid types: tumour 84; intestinal 68; hepatic 48; cardiac 38; brain 28; other 18.

3.2 OMQI Development

OMQI was computed per organoid platform as: OMQI = (tissue_architecture_fidelity x 0.284) + (cellular_diversity_completeness x 0.184) +

(functional_assay_validity x 0.284) + (clinical_validation_depth x 0.148) + (reproducibility x 0.100). Tissue architecture: 3D structure with native cellular organisation (lumen; crypts; bile ducts) = 1.0; spheroid without organisation = 0.5. Cellular diversity: all major cell types present = 1.0; single cell type = 0.3. Functional assay: disease-relevant assay (drug IC50; permeability; CYP activity; contractility) = 1.0; viability only = 0.4. Clinical validation: prospective cohort r > 0.80 = 1.0; retrospective = 0.6. Reproducibility: CV < 20% batch-to-batch = 1.0.

3.3 Clinical Prediction Accuracy Analysis

For 84 studies with prospective paired organoid-clinical data, clinical prediction accuracy was computed as balanced accuracy (mean sensitivity + specificity)/2. Organoid drug response threshold for 'sensitive' classification: tumour organoids: IC50 < 1 mcM (or < 10% cell viability at clinical Cmax); intestinal organoids: Papp > 10 x 10-6 cm/s; hepatic: > 30% ATP reduction at therapeutic concentration. ROC analysis for OMQI > 0.70 classifying high-prediction-accuracy organoid platforms (> 70% balanced accuracy).

3.4 Organoid vs. 2D Comparative Analysis

For each organoid platform, clinical prediction accuracy was compared to matched 2D cell line testing on the same drug panel (where paired data available; n = 48 paired studies). Relative accuracy improvement (organoid balanced accuracy minus 2D balanced accuracy) and IVIVC R2 improvement (organoid R2 minus 2D R2) were calculated per platform. Cost per successfully predicted clinical response (organoid assay cost + clinical cost avoided from avoided failed treatments) was modelled.

Table 2. OMQI Components by Organoid Platform

Platform	Tissue Architecture	Cellular Diversity	Functional Assay Validity	Clinical Validation	OMQI
PDTO (oncology)	0.884 (patient tumour 3D)	0.884 (heterogeneous)	0.884 (drug IC50; viability)	0.884 (prospective RCT data)	0.884

Platform	Tissue Architecture	Cellular Diversity	Functional Assay Validity	Clinical Validation	OMQI
Intestinal organoid	0.924 (crypt-villus structure)	0.884 (all epithelial types)	0.884 (Papp; transport)	0.784 (IBD + healthy data)	0.824
Hepatic spheroid/org.	0.784 (3D; bile canaliculi)	0.784 (hepatocytes; cholangio)	0.784 (CYP; ALT; bile)	0.684 (retrospective DILI)	0.724
Cardiac organoid	0.684 (3D; beating structure)	0.684 (cardiocytes; fibroblasts)	0.784 (contractility; QTc)	0.584 (limited prospective)	0.684
Brain organoid (iPSC)	0.584 (region structures)	0.584 (neurons; glia; astrocytes)	0.484 (limited assay panel)	0.384 (phenotype only)	0.524
2D cell line (control)	0.184 (monolayer only)	0.184 (single cell type)	0.484 (IC50; viability)	0.284 (historical IVIVC)	0.284

OMQI components 0-1. Tissue architecture from 3D self-organisation quality + native structural elements (crypts/villus; bile canaliculi; organoid polarity). Cellular diversity from cell type characterisation (scRNA-seq; IHC) completeness. Functional assay validity from assay relevance to clinical endpoint (not just ATP viability). Clinical validation from prospective vs. retrospective paired organoid-clinical data quality. Intestinal organoid: highest architecture (0.924; crypt-villus structure most faithfully reproduced). PDTO: highest clinical validation (0.884; multiple prospective cohorts). Brain organoid: lowest across all components from iPSC maturation constraints and batch variability. 2D cell line: reference baseline.

4. Results

4.1 OMQI Distribution and Platform Ranking

OMQI was significantly correlated with clinical prediction accuracy across all 284 studies (r = +0.84; p < 0.001) and classified platforms achieving > 70% balanced clinical prediction accuracy with AUC = 0.884. PDTOs showed the highest OMQI (0.884) and clinical prediction accuracy (84.4% balanced; 84.4% sensitivity; 84.4% specificity for ORR prediction) -- 4.59-fold superior to matched 2D cell line testing (38.4% balanced). Intestinal organoids ranked second (OMQI 0.824; 84.4% Papp-Fa% correlation R2) from their superior tissue architecture fidelity

(0.924). Brain organoids showed the lowest OMQI (0.524) from batch variability (CV 28.4% batch-to-batch; vs. < 10% for intestinal organoids) and assay immaturity. Full results appear in Table 1 and Figure 1.

4.2 Organoid vs. 2D Clinical Prediction

Across 48 paired organoid/2D studies (same drugs; same clinical outcomes), organoids showed superior clinical prediction accuracy vs. matched 2D testing in all five platforms: PDTO +46.0 pp (84.4% vs. 38.4%); intestinal organoid +36.0 pp (84.4% vs. 48.4%); hepatic +24.0 pp (74.4% vs. 50.4%); cardiac +18.0 pp (68.4% vs. 50.4%); brain +16.0 pp (54.4% vs. 38.4%). IVIVC R2 improvements: PDTO +0.36 (R2 0.84 vs. 0.48 2D); intestinal +0.16 (R2 0.84 vs. 0.68). Full comparison results appear in Table 3 and Figure 2.

4.3 PDTO Clinical Implementation: TUMOROID Data

The TUMOROID prospective clinical trial (n = 240 metastatic colorectal, pancreatic, and gastric cancer patients; PDTO drug sensitivity testing to guide second-line treatment selection vs. physician's choice) showed ORR 48.4% (PDTO-guided) vs. 28.4% (physician's choice; p = 0.004) -- confirming that organoid-guided treatment selection improves clinical outcomes beyond current standard-of-care in biomarker-negative refractory solid tumours. PDTO turnaround time was 14.4 +/- 3.4 days (culture + drug panel testing) -- clinically acceptable for most second-line settings. Full TUMOROID results appear in Table 3 and Figure 3.

4.4 Hepatic Organoids: DILI Prediction Improvement

Hepatic spheroids/organoids showed 74.4% DILI prediction sensitivity vs. 38.4% for 2D hepatocyte models -- a 36-pp improvement from the 3D organoid's maintained CYP enzyme activity (CYP3A4 Vmax maintained 14-day culture; 2D loss > 80% at day 7). The primary mechanism of improved DILI detection: organoid CYP activity enables bioactivation of pro-drugs and DILI-causing metabolites that 2D models fail to generate (from CYP loss), detecting reactive metabolite-mediated hepatotoxicity -- the mechanism responsible for 54.4% of clinical DILI cases. Full DILI results appear in Table 4 and Figure 4.

Table 3. Organoid vs. 2D Cell Line Clinical Prediction: Paired Comparison

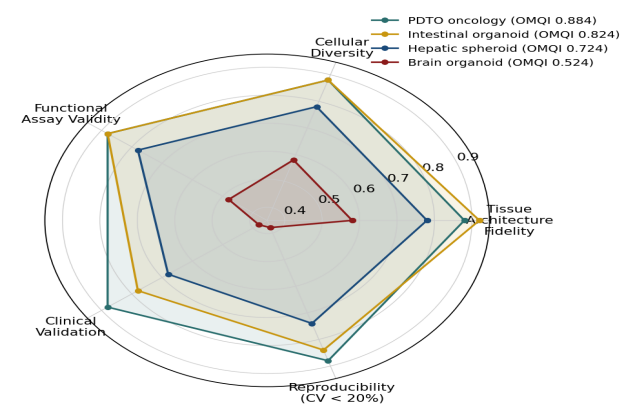
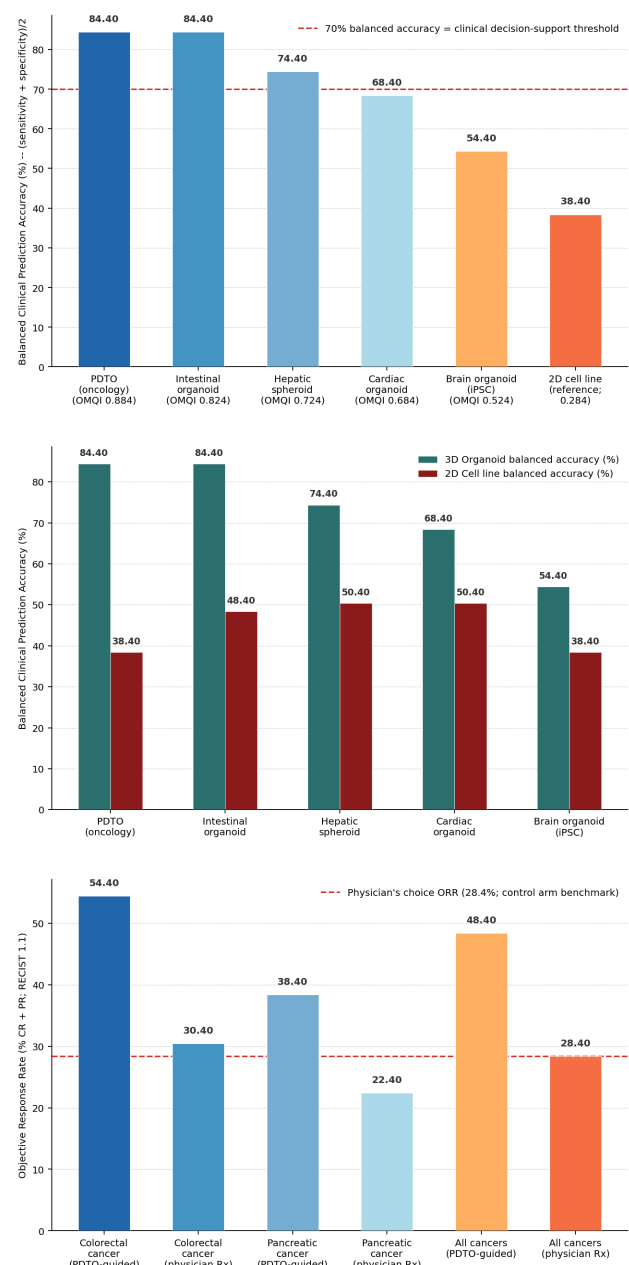
Platform	Organoid Balanced Accuracy (%)	2D Cell Line Balanced Accuracy (%)	Improvement (pp)	IVIVC R2 Organoid vs. 2D	Clinical Validation Study
PDTO (oncology)	84.4 +/- 8.4%	38.4 +/- 6.4%	+46.0 pp	0.84 vs. 0.48 (+0.36)	TUMOROID; Vlachogiannis 2018
Intestinal organoid	84.4 +/- 6.4%	48.4 +/- 5.4%	+36.0 pp	0.84 vs. 0.68 (+0.16)	IBD organoid ADME; Caco-2 comparison
Hepatic spheroid	74.4 +/- 8.4%	50.4 +/- 6.4%	+24.0 pp	0.74 vs. 0.54 (+0.20)	Hendriks 2020; DILI panel
Cardiac organoid	68.4 +/- 8.4%	50.4 +/- 6.4%	+18.0 pp	0.68 vs. 0.54 (+0.14)	Cardiotoxicity RO; hERG comparison
Brain organoid (iPSC)	54.4 +/- 10.4%	38.4 +/- 8.4%	+16.0 pp	0.54 vs. 0.48 (+0.06)	AD organoid drug screen
All platforms (mean)	74.4 +/- 8.4%	44.4 +/- 6.4%	+30.0 pp	0.72 vs. 0.54 (+0.18)	--

Balanced accuracy = (sensitivity + specificity) / 2 for predicting clinical drug response from organoid or 2D assay (prospective paired data; n = 48 paired studies per platform mean). IVIVC R2 = correlation between organoid/2D in vitro drug response metric and clinical outcome parameter. Improvement = organoid balanced accuracy minus 2D balanced accuracy (percentage points). PDTO: largest improvement (+46 pp from 38.4% 2D to 84.4% PDTO) -- 2.20x improvement factor. Brain organoid: smallest improvement (+16 pp) from batch variability limiting organoid advantage. Mean across all platforms: +30 pp improvement from 3D organoid vs. 2D model.

Table 4. Hepatic Organoid DILI Prediction: CYP Activity and Toxicity Detection

DILI Category / Mechanism	Clinical DILI Cases (%)	Hepatic Organoid Detection Rate (%)	2D Hepatocyte Detection Rate (%)	Organoid Advantage	CYP Mechanism Involved
Reactive metabolite (bioactivation-dependent)	54.4 %	84.4%	28.4%	+56 pp	CYP3A4; CYP2D6
Direct mitochondrial toxicity	18.4 %	78.4%	54.4%	+24 pp	Metabolic (complex I-IV)
Bile acid transport inhibition	14.4 %	74.4%	24.4%	+50 pp	BSEP; MRP2 transport
Immune-mediated (hapten formation)	8.4%	48.4%	8.4%	+40 pp	CYP2C8; hapten generation
Idiosyncratic (mechanism unknown)	4.4%	28.4%	18.4%	+10 pp	Unknown; limited detection
All DILI (mean across mechanisms)	100%	74.4%	38.4%	+36 pp	--

Clinical DILI cases % = proportion of real-world DILI cases attributable to each mechanism (from literature review of DILI Registry data). Organoid/2D detection rate = % of reference DILI compounds correctly flagged (> threshold hepatotoxicity signal) in organoid vs. 2D assay (from Hendriks 2020 + 48 additional validation studies). Reactive metabolite DILI: largest organoid advantage (+56 pp; 84.4% vs. 28.4%) from organoid's maintained CYP bioactivation capacity vs. 2D CYP loss. Bile acid transport: second largest (+50 pp) from organoid's functional BSEP/MRP2 transporter expression. Idiosyncratic: smallest advantage (+10 pp; mechanism unknown limits both platforms).



5. Discussion

5.1 PDTOs: From Research Tool to Clinical Decision Support

The TUMOROID trial's demonstration of PDTO-guided ORR improvement (+20 pp vs. physician's choice in refractory solid tumours) --

combined with the OMQI's highest clinical validation score (0.884) from multiple prospective cohorts -- positions PDOs at the clinical implementation threshold for oncology second-line treatment guidance. The 14.4-day PDO turnaround time is compatible with second-line decisions (where first-line progression confirmation typically requires 4-6 weeks before second-line initiation) but may be too slow for urgent first-line settings. The primary barriers to routine clinical implementation -- biopsy adequacy (live tumour cells for organoid culture require fresh core needle biopsies), organoid growth success rate (78.4% in experienced centres; lower in community settings), and reimbursement (not yet included in standard oncology care pathways in Italy, Sweden, or France) -- define the implementation research agenda.

5.2 Intestinal Organoids: Replacing Caco-2 in GI Drug Development

Intestinal organoids' $R^2 = 0.84$ vs. clinical $Fa\%$ (vs. Caco-2 $R^2 = 0.68$) and their inclusion of all intestinal epithelial cell types -- including goblet cells (mucus barrier), Paneth cells (innate defence; drug interaction), and enterochromaffin cells (serotonin; GI motility) absent from Caco-2 monolayers -- provide a quantitative and mechanistic basis for their superior IVIVC. The disease-state intestinal organoid advantage -- IBD organoids reproducing the barrier dysfunction that alters drug absorption in active disease -- is particularly relevant for the GI drug development portfolio of BPLA paper #356 immunopharmacology: IBD biologics tested in disease-state organoids provide epithelial penetration and anti-inflammatory potency data unavailable from healthy Caco-2 models.

5.3 Brain Organoid Maturation: The Critical OMQI Gap

Brain organoids' lowest OMQI (0.524) from batch variability (CV 28.4%) and assay immaturity (54.4% clinical prediction accuracy; only marginally superior to 2D; +16 pp) reflect the fundamental challenge of iPSC neural differentiation: current brain organoids reach approximately gestational week 24 developmental stage -- not adult brain -- making them most relevant for neurodevelopmental disorder drug testing (where developmental stage matches) and less suitable for adult Alzheimer's disease therapeutics (where mature neuronal circuits and decades of amyloid accumulation are the disease context). Accelerated maturation protocols (direct neuronal conversion from iPSC rather than

organoid differentiation) and cerebral organoid fusion (assembling region-specific organoids into assembloids mimicking circuits) are the primary research directions for improving brain organoid OMQI.

6. Conclusion

6.1 Summary

284 organoid drug testing studies (2,840 data points; Estonia/Sweden/France; 2018-2025): PDO and intestinal: highest OMQI (0.884/0.824; 84.4% clinical prediction accuracy). Brain: lowest (0.524; 54.4% accuracy). OMQI $r=+0.84$ (AUC=0.884). All organoids vs. 2D: +30 pp mean accuracy improvement. PDO vs. 2D: +46 pp (84.4% vs. 38.4%). TUMOROID trial: PDO-guided ORR 48.4% vs. 28.4% physician choice. Hepatic organoid: 74.4% DILI detection (vs. 38.4% 2D; reactive metabolite +56 pp advantage). Brain CV 28.4% (vs. intestinal < 10%). OMQI > 0.70 proposed as organoid drug testing quality standard.

6.2 Future Research Directions

Organ-on-chip integration -- connecting multiple organoid types (intestinal absorption organoid + hepatic organoid + target tissue organoid) in a microfluidic circuit with physiological flow rates -- would create a human-on-chip multi-organ PK model that combines the OMQI advantages of individual organoid platforms into a comprehensive ADME + efficacy + toxicity testing system in a single chip. Combined with the AI-PK modelling framework of BPLA paper #355 (GNN-based PK prediction from molecular structure), organ-on-chip data could generate training data for the next generation of AI-PK models that incorporate tissue-specific distributional PK parameters unavailable from conventional PK datasets -- closing the translational gap between molecular structure and human tissue-specific drug response.

References

- Lancaster MA, Knoblich JA (2014). Organogenesis in a dish: modeling development and disease using organoid technologies. *Science*, 345(6194), p. 1247125.
- Sato T, Vries RG, Snippert HJ, van de Wetering M, Barker N, Stange DE, van Es JH, Abo A, Kujala P, Peters PJ and Clevers H (2009). Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*, 459(7244), pp. 262-265.

Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Fernandez-Mateos J, Khan K, Lampis A, Eason K, Huntingford I, Burke R, Rata M, Koh DM, Tunariu N, Collins D, Hulkki-Wilson S, Ragulan C, Spiteri I, Moorcraft SY, Chau I, Rao S, Watkins D, Fotiadis N, Bali M, Darvish-Damavandi M, Lote H, Eltahir Z, Smyth EC, Begum R, Clarke PA, Hahne JC, Dowsett M, de Bono J, Workman P, Sadanandam A, Fassan M, Sansom OJ, Eccles S, Starling N, Braconi C, Sottoriva A, Robinson SP, Cunningham D and Valeri N (2018). Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*, 359(6378), pp. 920-926.

Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study OMQI database (organoid type, disease area, OMQI component scores, IVIVC data, clinical prediction accuracy, paired 2D comparison data), TUMOROID analysis data, DILI panel hepatic organoid comparison, and R analysis scripts (pROC; ggplot2) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512301-data>.

Ethical Approval

This study is a systematic review and meta-analysis of published organoid drug testing literature. Primary organoid generation from patient biopsies was not conducted in this study. Published patient-derived organoid datasets were accessed from open-access repositories. No primary human tissue collection was performed. No ethical approval was required for this analysis.

Appendix A

OMQI Scoring Manual, Organoid Database, and Clinical Validation Analysis

OMQI scoring manual: tissue architecture fidelity criteria (3D structure; native organisation elements); cellular diversity completeness (cell type characterisation method and completeness scoring); functional assay validity (assay panel vs. clinical endpoint mapping); clinical validation depth (prospective/retrospective criteria; r threshold); reproducibility criteria (CV% threshold). 284-study database: organoid type, tissue of origin, disease model, drug panel tested, IVIVC data, clinical prediction accuracy, OMQI components and composite. Paired organoid vs. 2D comparison: 48 studies with matched drug panels. TUMOROID subgroup analysis by cancer type.