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REVIEW ARTICLE

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Organoid-based precision medicine in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) ranks among the leading causes of cancer-related deaths worldwide. Despite advances in precision oncology in other malignancies, treatment of PDAC still largely relies on conventional chemotherapy. Given the dismal prognosis and heterogeneity in PDAC, there is an urgent need for personalized therapeutic strategies to improve treatment response. Organoids, generated from patients' tumor tissue, have emerged as a powerful tool in cancer research. These three-dimensional models faithfully recapitulate the morphological and genetic features of the parental tumor and retain patient-specific heterogeneity. This review summarizes existing precision oncology approaches in PDAC, explores current applications and limitations of organoid cultures in personalized medicine, details preclinical studies correlating in vitro organoid prediction and patient treatment response, and provides an overview of ongoing organoid-based clinical trials.

KEYWORDS
drug response prediction, oncology, pancreatic ductal adenocarcinoma, patient-derived organoids, PDAC, personalized therapy, pharmacotyping, precision oncology, treatment response

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers with a 5-year survival rate of approximately 13% for all stages combined.[1] With its high mortality rate and rising incidence, PDAC poses a substantial challenge in clinical care and represents a global healthcare burden. Despite advances and successes in precision oncology in other malignancies, treatment of PDAC still heavily relies on chemotherapy, following a trial-and-error approach. Given the dismal prognosis and tumoral heterogeneity in PDAC, personalized therapeutic strategies are urgently needed to improve patient outcomes. Patient-derived organoids (PDOs) have emerged as a promising tool in cancer research for preclinical drug evaluation and individualization of treatments. This review summarizes existing

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precision oncology strategies in PDAC, explores the feasibility of organoid cultures in personalized medicine, and offers an overview of ongoing clinical trials using organoid models.

CHALLENGES AND OPPORTUNITIES FOR PRECISION ONCOLOGY IN PANCREATIC CANCER

Pancreatic tumors can be categorized as resectable, borderline resectable, locally advanced, or metastatic based on radiological criteria and involvement of local vasculature. This classification, along with biological and patient-related criteria, guides treatment options.[2] For resectable PDAC, upfront surgery is commonly followed by adjuvant therapy with (modified) FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin)[3] or gemcitabine with or without capecitabine[4] outside of clinical trials. In borderline resectable and locally advanced tumors, neoadjuvant chemo(radio)therapy is recommended, followed by surgical resection and adjuvant therapy, if feasible. Despite advances in surgical and perioperative approaches, recurrence rates after curative intended surgery remain high, with relapse rates ranging between 60% and 79% after 3 years.[3] The majority of patients (>80%) are diagnosed at an advanced tumor stage and treated with palliative multiagent chemotherapy regimens. Well-established first-line options in the advanced setting are gemcitabine with or without erlotinib,[5,6] gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel,[7] (modified) FOLFIRINOX,[8] or NALIRIFOX (nanoliposomal irinotecan, leucovorin, 5-fluorouracil, oxaliplatin).[9] Frequent mutations and deletions in cancer driver genes such as *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, accompanied by a high number of passenger alterations, generate an exceptional inter- and intra-tumoral heterogeneity. This heterogeneity induces a considerable variation in responses to antitumor therapies. Nevertheless, the choice of regimen primarily depends on clinical aspects such as patients' performance status and comorbidities, as reliable biomarkers for predicting treatment effectiveness are lacking in clinical routine. Chemotherapy is paralleled by extensive systemic toxicity, frequently requiring dose reductions and often impeding long-term treatment. Low tumor specificity and acquired resistance ultimately result in tumor progression, which is often accompanied by rapid deterioration of the patients' performance status limiting further therapeutic options.

Therefore, cancer management is increasingly shifting toward a precision oncology paradigm, which aims to individualize treatments for cancer patients based on molecular, cellular, or functional analyses of their tumor. In PDAC, targeted treatment options based on individual genomic features demonstrated survival benefits for small subgroups of patients. Erlotinib, a tyrosine kinase inhibitor of EGFR, was the first small-molecule targeted therapy in PDAC to show an overall significant but clinically not meaningful improvement in overall survival when combined with gemcitabine.[6] In 2019, the PARP inhibitor olaparib was approved as a maintenance therapy for germline *BRCA1/2* mutations, which are present in 4%–7% of PDAC patients.[10,11] Other targeted therapies for very rare molecular subgroups include larotrectinib or entrectinib in NTRK fusion-positive tumors (0.3%)[12–14]; pembrolizumab in DNA mismatch repair-deficient or microsatellite unstable tumors (1%)[15,16]; selpercatinib in RET-altered cancers (0.6%)[17]; zenocutuzumab in NRG1 fusions (0.5%)[18,19]; dabrafenib and trametinib for $BRAF^{V600}$ mutations (2%)[20,21]; and sotorasib or adagrasib for $KRAS^{G12C}$ mutations (1%–2%).[22,23] Currently, 12%–25% of pancreatic cancers harbor actionable molecular alterations. However, real-world data indicate that less than 2% of patients who were referred for molecular profiling ultimately received a matched therapy due to insufficient access to drugs, logistical issues, or physician discretion.[24]

Genomics-based precision medicine has the potential to significantly improve cancer treatment. Nevertheless, as most genetic alterations in PDAC are not (yet) clinically targetable and some patients do not respond to treatment despite carrying the relevant mutation, true benefits remain limited. Increasing evidence suggests that cancer treatment is far more complex than the "mutation-centric" precision medicine approach focusing on somatically altered genes to guide therapy selection. Advances in single-cell genomic technologies have revealed that the complexity of cancer extends beyond mutational heterogeneity to variations in cell transcriptional states. For instance, Raghavan et al. systematically profiled metastatic PDAC biopsies and matched organoid models using single-cell RNA-sequencing to examine cell states, their regulation by the tumor microenvironment (TME), and how modulating these states can influence drug responses.[25] The authors concluded that changes in transcriptional states strongly impact drug efficiency, proposing cell state as a targetable feature in cancer treatment. Given that TME signals play a major role in directing the transcriptional state, therapeutic strategies may need to target site-specific cells in the TME to control cell state evolution during treatment.

So far, unselected use of conventional chemotherapy remains the primary treatment approach for most patients. Therefore, functional precision oncology is increasingly emerging as a complementary approach that models individual tumors in vitro, aiming to integrate the complex tumor phenotype into genotype-based treatment decisions.[26]

PATIENT-DERIVED ORGANOIDS AS EMERGING MODELS IN PANCREATIC CANCER

Preclinical systems for translational research

Immortalized cell lines, primary two-dimensional cultures, cell line-derived spheroids, and xenografts have been widely employed to model and study human disease but have inherent limitations. Human pancreatic cancer cell lines, established decades ago, are suitable for rapid and scalable drug discovery but fail to adequately represent the biological heterogeneity of PDAC. Patient-derived xenograft (PDX) models are generated by subcutaneous or orthotopic engraftment of human tumor specimens into immunocompromised mice. PDX models require an average time from engraftment

to drug exposure of 3–8 months, with a take rate generally comprised between 55% and 65%.[27,28] Intra-tumoral heterogeneity is preserved in these models and PDX tumor growth regression matches clinical responses in PDAC patients.[27] However, significant drawbacks for their application in real-time precision oncology are slow growth, limitations in tumor take rate, mouse-specific genetic evolution, high costs, labor-intensive maintenance, and the inherent inability to perform high-throughput drug screenings.

Recently, PDOs have emerged as a valuable preclinical tool in precision medicine, filling the gap between in vitro and in vivo models. These three-dimensional cultures can be established from patients' tumor or metastasis within a reasonable timeframe and allow for scalable, high-throughput applications. They faithfully recapitulate the histomorphological and molecular features of the parental tumor. Strikingly, PDOs accurately capture intra-tumoral heterogeneity at a single-cell level and preserve genetic and epigenetic properties of the tumor they are derived from.[29–31] Of note, PDX-derived organoids exhibit sensitivity profiles and response rates similar to their PDX counterparts,[32,33] underlining their potential to mimic patient response.

Generation of patient-derived organoids

Organoids first emerged after the establishment of self-organizing crypt-villus units by Sato et al. in 2009.[34] Since then, several protocols for PDO generation from pancreatic tumors have been published.[35,36] For PDO isolation, patient tumor pieces are mechanically and enzymatically dissociated, embedded into a matrix that mimics the extracellular environment to allow three-dimensional growth and propagated in a culture medium to provide growth stimulation. Once established, organoid lines can be expanded indefinitely to reach the critical biomass required for downstream analysis and cryopreserved for later use. Organoid cultures can be established from the primary tumor or metastatic organ lesiona, following different methods of tissue acquisition, including surgical resections, endoscopic ultrasound-guided fine-needle biopsies, or percutaneous biopsies. PDOs have recently been generated from fluid-derived samples, such as blood, ascites, and peritoneal or pleural effusions, offering non-invasive sampling and the opportunity for continuous treatment monitoring.[37–39] Derivation efficacies range between 41% and 78% and are largely influenced by the source material, sampling method, tumor cell content, and patient treatment status (naïve vs. pre-treated).[39–47] Interestingly, a recent study found a correlation between the success rate of PDO establishment and patient survival. The study observed that patients from whom PDOs were successfully isolated had shorter survival times, suggesting that more aggressive intrinsic tumor features may facilitate organoid derivation.[39] Importantly, different definitions of PDO generation efficacies coexist, such as emergence of organoid structures within three passages,[45] expansion beyond passage three[48] or five,[40] or proportion undergoing preclinical drug testing,[44] significantly complicating comparisons between studies. The average turnaround time from biopsy collection to drug testing results ranges between 48 and 96 days,[39,44–46] but depends on multiple factors such as biopsy modality, source tissue yield and quality, isolation protocol, intrinsic organoid growth rate, and required biomass for the subsequent drug screening assay.

APPLICATIONS OF PATIENT-DERIVED ORGANOIDS IN PRECISION ONCOLOGY

Organoid technologies are among the most promising models in translational research to explore patients' susceptibility to therapeutics, study disease mechanisms, and identify novel compounds.

Organoid pharmacotyping for drug response prediction

Numerous endeavors are underway to cultivate PDOs for preclinical drug testing, a process known as pharmacotyping, to identify effective treatments for patients.[29] In this regard, Tiriac et al. generated a library of 66 PDOs derived from PDAC patients that recapitulated the mutational spectrum and transcriptomic subtype of the primary tumors.[40] PDOs were subjected to therapeutic profiling with five commonly used chemotherapy compounds (gemcitabine, paclitaxel, irinotecan/SN-38, 5-fluorouracil, and oxaliplatin) and their responses were classified as sensitive, intermediate resistant, or resistant based on the area under the curve (AUC) drug-response metric. Retrospective comparison with clinical data in nine patients provided initial evidence that organoid chemosensitivity profiles faithfully reflected patient response to therapy. Interestingly, resistant PDO lines showing poor response to conventional chemotherapeutics still exhibited susceptibilities to targeted agents, unmasking potential alternative treatment options for chemorefractory disease.[42] At our medical center, we conducted a prospective feasibility trial to assess the capability of PDOs in predicting treatment response in PDAC patients in a clinical routine setting.[44] Single agent pharmacotyping profiles from 28 PDO lines were classified as high, intermediate, or low responders based on AUCs following Jenks natural breaks classification method.[32,33] The PDO-based prediction model accurately prognosticated the response in 10 out of 11 chemotherapy-naïve patients (accuracy of 91.1%) for first-line treatment and in 4 out of 5 patients for second-line treatment (80.0%). Following a similar approach, the prospective HOPE trial (Harnessing Organoids for Personalized therapy) reported a positive correlation between PDAC PDO drug-sensitivity profiles and clinical outcomes in all 12 patients.[46] The aforementioned studies explored the feasibility of generating organoids from predominantly advanced PDAC patients and demonstrated their ability to predict patient responses to chemotherapy. A relevant drawback in the translation of organoid-based treatment selection in the palliative setting is the relatively lengthy turnaround time for obtaining pharmacotyping results, as patients need to commence chemotherapy quickly. To facilitate the

bench-to-bedside precision medicine for PDAC, a recently published study morphologically classified PDOs as gland-like or densely proliferating within two weeks after tissue sampling. The gland-like subtype showed a better in vitro response to gemcitabine and was associated with a significantly longer overall survival in patients, indicating that PDO morphological subtype determination may predict patient outcome within a short timeframe.[47]

In the resectable setting, Deyman et al. assessed the power of organoid pharmacotyping to predict response and resistance to neoadjuvant therapy in nine PDO lines isolated prior to or after treatment.[41] High concordance between organoid-predicted chemosensitivity, pathological response grading, and patient clinical response to neoadjuvant therapy was found. Interestingly, PDOs from one longitudinal patient were collected before and after neoadjuvant treatment with gemcitabine and nab-paclitaxel. The post-neoadjuvant line showed poor response to both gemcitabine and paclitaxel, indicative of acquired resistance. This mirrored the patient's clinical scenario who experienced a short recurrence-free survival of 3.7 months following continued adjuvant therapy with gemcitabine plus nab-paclitaxel.[41] In another study, Farshadi et al. used five neoadjuvant FOLFIRINOX-treated and five distinct treatment-naïve PDAC PDO lines to investigate chemoresistance to this regimen. Treated organoids exhibited higher refractoriness to oxaliplatin and irinotecan as well as to the FOLFIRINOX combination, but not to 5-fluorouracil and gemcitabine, highlighting specific acquired resistance mechanisms to this regimen. These findings prove PDOs as a robust platform to study drug resistance and suggest that the adjuvant chemotherapy for pancreatic cancer patients should be determined at the individual level, as continuing the same regimen may not benefit all patients.[41,49] A recent study demonstrated that PDO-based predictions aligned with patient outcomes in 31 out of 34 predominantly pretreated advanced PDAC patients.[39] By testing a panel of 25 approved antitumor agents, the study identified a median of three effective treatments per patient, thus offering alternative options for later-line therapies.[39]

Interestingly, mouse pancreatic tumor organoids exhibited similar growth characteristics as in vivo tumors following radiation exposure, implying that PDAC organoids may not only predict response to chemotherapy but also to radiotherapy.[50]

Organoid pharmacotyping for drug discovery and biomarker identification

Apart from evaluating individual drugs or chemotherapy combinations to predict individual treatment response, PDOs play a pivotal role as a drug screening platform to identify and validate novel pharmacological targets. For example, Driehuis et al. performed high-throughput drug screening on 30 PDO lines using 76 therapeutic agents and revealed sensitivities currently not exploited in the clinic.[29] Interestingly, organoids featured sensitivity to several agents targeting microtubule dynamics such as AURKA, PIK3CA, and TOP1 inhibitors, unmasking convergent evidence of a true biological vulnerability for this molecular pathway and highlighting the robustness of such an approach.[29] Hirt et al. established a biobank of 31 PDAC PDOs and conducted a drug repurposing screen of 1172 FDA-approved drugs using an automated pipeline.[51] The authors found that missense mutations in *ARID1A*, encoding for a subunit of the SWI/SNF chromatin remodeling complex, were linked to increased sensitivity to the kinase inhibitors dasatinib and VE-821, a known synthetic lethal interaction in ovarian clear cell carcinoma. Furthermore, they identified 26 effective compounds, including the cardiac glycoside ouabain and the anti-protozoal drug emetine, demonstrating that employing organoids to repurpose agents is much more cost-effective and resource-sparing than mouse models.[51] Intriguingly, PDOs can be generated from both tumor and healthy tissue, facilitating the identification of agents with high anti-cancer selectivity and enabling toxicity assessment in normal tissue organoids.[52]

Studying pancreatic precursor lesions is crucial for understanding the mechanisms underlying tumorigenesis and advancing early detection and prevention strategies. The development of bona fide organoids derived from intraductal papillary mucinous neoplasms (IPMNs), cystic pancreatic precursors with the potential to progress into invasive pancreatic adenocarcinoma, constitutes a unique model to interrogate cancer progression. Two studies have established a living biobank of PDOs derived from patient IPMN samples, offering a dynamic preclinical platform to study the transition of IPMNs into invasive cancer.[53,54] Histological and genomic characterization of these organoids has offered valuable insights into the various IPMN subtypes and their potential to evolve into malignancies. Another example of biomarker discovery was introduced by Huang et al., who identified extracellular vesicle protein markers using media supernatant of organoid cultures. These were validated in patient plasma and segregated PDAC patients from patients with benign gastrointestinal diseases.[32] Preclinical organoid models are promising tools for discovering novel biomarkers, refining early detection and surveillance, and developing personalized therapeutic interventions, all of which could significantly improve patient outcomes.

Organoid-based clinical trials in PDAC

The clinical utility of PDO-based treatments has mostly been investigated through retrospective or observational studies with small patient cohorts eligible for correlation between in vitro prediction and patient response. Despite positive signals for drug response prediction, these clinical correlative studies lack sufficient sample size and accessible clinical follow-up data to ensure statistical validity. Larger randomized clinical trials are urgently needed to evaluate the predictive value of employing PDOs in clinical routine. Ongoing clinical trials in PDAC assess different aspects of PDO feasibility, including organoid derivation, drug testing, correlation of chemoresponse with patient outcomes, association with genomic mutations, and pharmacotyping-guided treatment decision-making (Table 1).

TABLE 1 Clinical trials investigating organoids in pancreatic cancer.

NCT number/ name	Study title	Status	Study type	Phase	Disease	Stage	Patients to be enrolled	Aim	Primary outcome measures
UNITEPANC	Using organoids to predict efficacy of adjuvant treatment to improve outcome in resectable pancreatic cancer	Planned	Interventional	1, 2	Pancreatic cancer	Resectable	92	Organoid-based adjuvant treatment	Feasibility of treatment selection within 12 weeks, DFS at 18 months
NCT03500068	Establishing Organoids From Metastatic Pancreatic Cancer Patients, the OPT-I Study	Unknown	Interventional	N/A	Pancreatic cancer	Locally advanced, metastatic	30	Treatment response prediction	Response correlation between patients and organoids
NCT04777604	Development of a Prediction Platform for Neoadjuvant Treatment and Prognosis in Pancreatic Cancer Using Organoid	Not yet recruiting	Observational	N/A	Pancreatic cancer	Resectable after neoadjuvant therapy	300	Evaluation of adjuvant therapy response and correlation between genomic mutations	Organoid generation success
NCT05351983	Patient-derived Organoids Drug Screen in Pancreatic Cancer	Recruiting	Interventional	N/A	Pancreatic cancer	Resectable, metastatic	50	Feasibility of generating organoids	Organoid generation success, treatment effectiveness
NCT05196334	Pharmacotyping of Pancreatic Patient-derived Organoids	Active, not recruiting	Observational	N/A	Pancreatic cancer	Primary locally advanced, non-metastatic	88	Co-culturing organoids with CAFs, testing drug response	Comparison between organoid's pharmacotyping and patient's response
NCT03544255	Drug Screening of Pancreatic Cancer Organoids Developed From EUS-FNA Guided Biopsy Tissues	Unknown	Observational	N/A	Pancreatic cancer	N/A	50	Establishing organoids, testing drug sensitivity	Organoid generation success within 2 weeks, total number of organoids generated
NCT03990675	Evaluation and Comparison of the Growth Rate of Pancreatic Cancer Patient-derived Organoids	Unknown	Interventional	N/A	Pancreatic cancer	N/A	50	Comparing growth rates of organoids from matched FNA and FNB samples	Organoid growth rate
NCT04931394	Organoid-Guided Adjuvant Chemotherapy for Pancreatic Cancer	Recruiting	Interventional	3	Pancreatic Cancer	Resectable	200	Organoid-based adjuvant treatment	DFS
NCT04736043	Development of a Prediction Platform for Adjuvant Treatment and Prognosis in Resected Pancreatic Cancer Using Organoid	Recruiting	Observational	N/A	Pancreatic cancer	Resectable	300	Evaluation of adjuvant therapy response and correlation between genomic mutations	OS

(Continues)

TABLE 1 (Continued)

NCT number/ name	Study title	Status	Study type	Phase	Disease	Stage	Patients to be enrolled	Aim	Primary outcome measures
NCT04931381	Organoid-Guided Chemotherapy for Advanced Pancreatic Cancer	Recruiting	Interventional	3	Pancreatic cancer	Locally advanced, metastatic	100	Organoid-based chemotherapy regimens	Disease control rate (6 months)
NCT05571956	Establishment of Pancreas Cancer and Cancer-associated Fibroblast Using EUS-guided Biopsy Samples	Recruiting	Interventional	N/A	Pancreatic cancer	N/A	50	Establishing organoids	Establishment of pancreatic ductal adenocarcinoma organoids and cancer-associated fibroblasts
NCT02436564	In Vitro Models of Liver and Pancreatic Cancer	Unknown	Observational	N/A	Cholangiocarcinoma, Hepatocellular carcinoma, Pancreatic cancer	Resectable	75	Developing in vitro cancer models	Number of tumor-derived organoids successfully cultured in vitro for a minimum of 3 months
NCT05927298	Province of Ontario Strategy for Personalized Management of Pancreatic Cancer Trial	Recruiting	Observational	N/A	Pancreatic cancer	Resectable, borderline, advanced	200	Establishing organoids, analysis of whole genome and RNA sequencing with PDOs	Number of patients receiving precision-matched treatment based on WGS, RNAseq, and PDOs
NCT05842187	In Vitro Organoid Drug Sensitivity-Guided Treatment for Metastatic Pancreatic and Gastric Cancer	Recruiting	Interventional	N/A	Pancreatic cancer, Gastric cancer	Metastatic (after second-line therapy)	20	Evaluation of organoid-based treatment regimen	6 months PFS
NCT03140592	Pancreatic Cancer Models Developed From EUS Guided Biopsy Tissue	Unknown	Observational	N/A	Pancreatic cancer	N/A	300	Generation of pancreatic cancer models from small biopsies	Successful generation of pancreatic organoids
NCT04469556	Pancreatic Adenocarcinoma Signature Stratification for Treatment	Active, not recruiting	Interventional	2	Pancreatic cancer	Metastatic	150	Evaluation of two standard chemotherapy regimens, establishing organoids	PFS
NCT05518110	PaTcH Study: A Phase 2 Study of Trametinib and Hydroxychloroquine in Patients With Metastatic Refractory Pancreatic Cancer	Recruiting	Interventional	2	Pancreatic cancer	Metastatic (after first-line therapy)	22	Overcoming resistance by combining an established anticancer drug, trametinib, with hydroxychloroquine	PFS 12 weeks from starting treatment
NCT02869802	Prospectively Defining Metastatic Pancreatic Ductal Adenocarcinoma Subtypes by Comprehensive Genomic Analysis	Recruiting	Observational	N/A	Pancreatic cancer	Metastatic	190	Evaluating the effectiveness of identifying genetic variations and mutations, organoid generation efficacy	Feasibility of returning comprehensive genomic results within a clinically meaningful timeframe
NCT03146962	High Dose Vitamin C Intravenous Infusion in Patients	Completed	Interventional	2	Colorectal cancer, Pancreatic cancer, Lung cancer	All stages	61	Evaluating high-dose Vitamin C intravenous infusion in subjects with solid tumor malignancies	Pathological response rate in surgically resected tumor tissue

TABLE 1 (Continued)

NCT number/ name	Study title	Status	Study type	Phase	Disease	Stage	Patients to be enrolled	Aim	Primary outcome measures
	With Resectable or Metastatic Solid Tumor Malignancies								
NCT03896958	The PIONEER Initiative: Precision Insights On N-of-1 Ex Vivo Effectiveness Research Based on Individual Tumor Ownership (Precision Oncology)	Unknown	Observational	N/A	Cancer, all types	N/A	1000	Evaluation of the ability to return research and study information back to the individual patient	% of patients carry out genomic testing and functional precision testing, % of clinicians report altered clinical therapeutic regimens

Note: Ongoing, completed and planned clinical trials using organoid models in pancreatic cancer.

Abbreviations: CAFs, cancer-associated fibroblasts; CT, computed tomography; DFS, disease-free survival; EUS, endoscopic ultrasound; FNA, fine needle aspiration; FNB, fine needle biopsy; N/A, not available; OS, overall survival; PDOs, patient-derived organoids; PFS, progression-free survival; RNAseq, RNA sequencing; WGS, whole genome sequencing.

In the adjuvant setting, two studies explore the feasibility of an organoid-based selection of adjuvant therapy in resectable PDAC patients. The UNITEPANC study, conducted by the AIO Pancreatic Cancer Group and led by our institution and five academic sites in Southern Germany (Figure 1), is a single-arm trial aiming to evaluate the 18-month disease-free survival (DFS) in post-operative patients receiving chemotherapy predicted to be effective by organoid pharmacotyping. UNITEPANC will provide initial indications of whether such an organoid-based adjuvant treatment selection can achieve better outcomes than the historically reported 18-month DFS rate of 60% following six cycles of adjuvant mFOLFIRINOX.[3] Likewise, a phase 3 randomized trial is currently recruiting patients to assess the therapeutic benefit of a comparable organoid-guided strategy for additive chemotherapy selection in resectable patients (NCT04931394).

In the advanced setting, two phase 3 randomized trials, respectively single (NCT04931381) and multicenter (NCT05842187), are actively recruiting patients to investigate the effectiveness of organoid-guided treatment regimens for improving outcomes of patients in palliative care. Recently presented preliminary results from the PASS-01 trial (NCT04469556), a multicenter phase 2 study, demonstrated the feasibility of upfront multiomic profiling and PDO pharmacotyping in advanced PDAC patients. Correlative studies are underway to determine if this approach enables better precision choices.[55]

Results from these interventional trials are eagerly awaited and will hopefully license organoids as robust companion diagnostic tools and foster their integration into clinical practice.

Potential applications of PDOs in clinical care

Conceptually, using PDOs as patient avatars may aid clinicians in selecting effective chemotherapeutic drugs or targeted agents on an individual basis, prevent toxicities from ineffective compounds, and offer alternative agents in primary or acquired resistance. A potential workflow for integrating organoid-informed decision-making into clinical routine is depicted in Figure 2.

In resectable PDAC patients, organoid-based adjuvant chemotherapy may be feasible as PDOs can be expanded within 8–12 weeks of postoperative recovery. Following neoadjuvant chemotherapy, PDOs may inform decisions regarding adjuvant therapies and offer alternative regimens in cases of acquired resistance.

In the palliative setting, the time required for pharmacotyping is a crucial factor in determining its applicability for guiding treatment. Currently, first-line therapy is often initiated before pharmacotyping results are available. Decisions about whether to continue the current treatment or switch to a tumor-sensitive, predicted second-line regimen, can be made after re-staging. To effectively guide first-line treatment in the palliative setting, the development and testing of PDOs should ideally be completed within two weeks. Multiple efforts are currently underway to explore strategies for reducing turnaround times. Ideally, organoid cultures should be developed in a

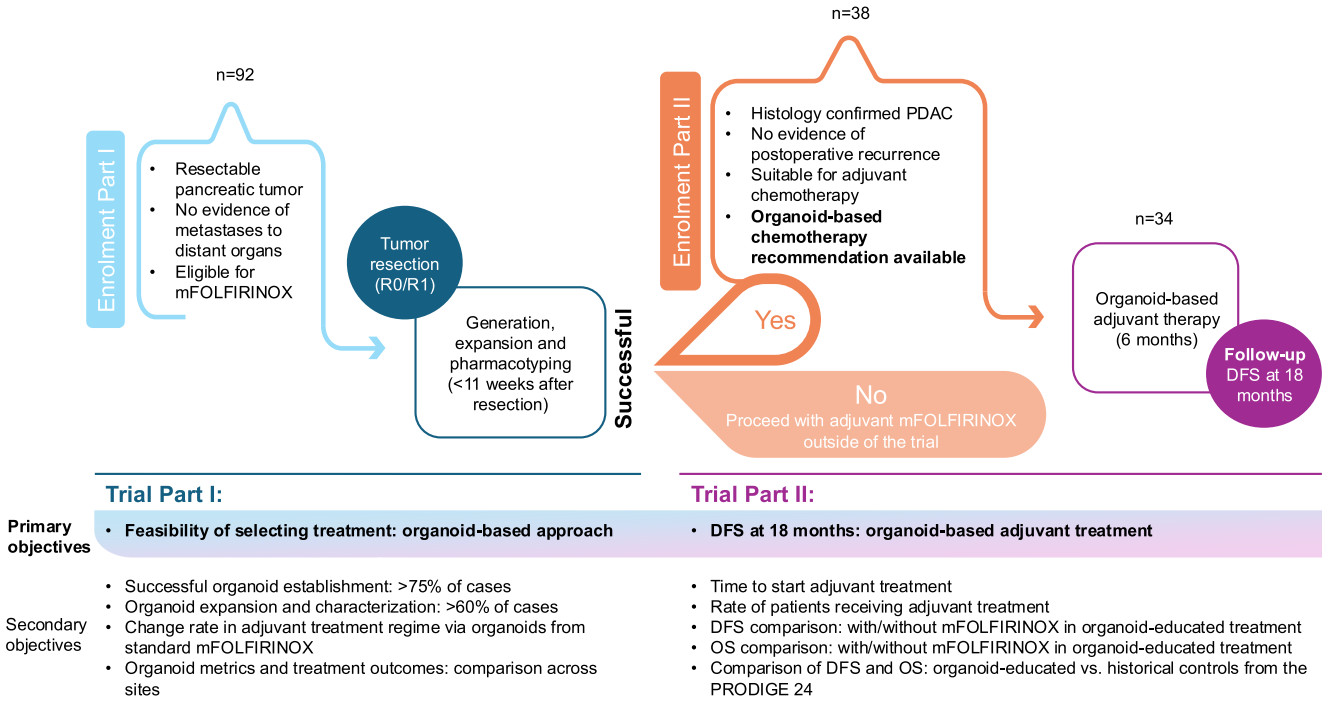

FIGURE 1 Study design of the UNITEPANC trial: Using organoids to predict efficacy of adjuvant treatment to improve outcome in resectable pancreatic cancer. The primary objectives are feasibility of selecting organoid-based adjuvant treatment (Part I) and disease-free survival at 18 months (Part II). DFS, disease-free survival; mFOLFIRINOX, modified, 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

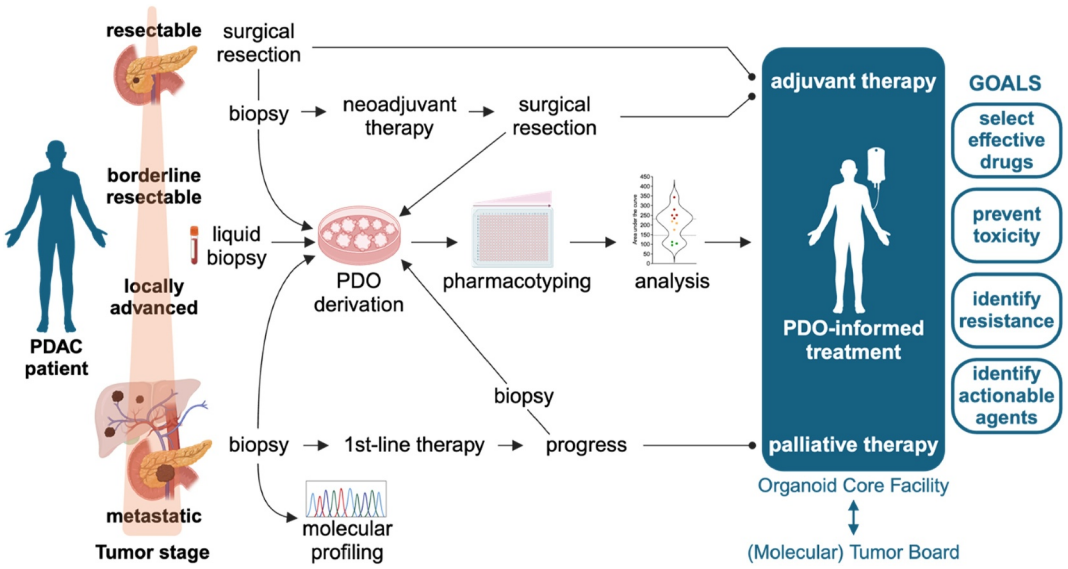

FIGURE 2 Organoid-based precision medicine in pancreatic cancer. Potential workflow to incorporate patient-derived organoids into clinical care. Organoids can be generated from surgical resections and tissue or liquid biopsies from treatment-naïve or pretreated PDAC patients. PDOs can be subjected to pharmacotyping and may inform treatment decisions. PDAC, pancreatic ductal adenocarcinoma; PDO, patient-derived organoid. *Source*: Created with BioRender.com.

specialized organoid core facility to ensure robust reproducibility. Treatment decisions should then be made in conjunction with the (molecular) tumor board or within the context of clinical trials.

CHALLENGES AND FUTURE DIRECTIONS OF ORGANOID-BASED PRECISION MEDICINE

Organoid technologies bridge the gap between conventional in vitro culture systems and translational research, but while these exciting models facilitate progress, they also reveal several limitations that require further refinement. The use of organoids as a platform for drug screening, drug repurposing, and disease modeling undoubtedly requires standardization and improvements to allow for high-throughput approaches with high reproducibility within clinically relevant timeframes.

Standardization of organoid culture and pharmacotyping

Lately, concerns were raised regarding the composition of the organoid culture medium which has been shown to impact PDO growth rates,[32,48] PDO transcriptome, and pharmacotyping results.[48] A recent study demonstrated that pharmacotyping results can vary depending on the type of media used. For example, PDO lines cultured in WNT-free PTOM (pancreatic progenitor and tumor organoid media)[36] showed increased sensitivity to 5-fluorouracil and oxaliplatin, while the same lines grown in WNT-containing culture media[35] exhibited higher sensitivity to gemcitabine and SN-38.[48] These findings underscore the significant impact of culture conditions on proliferation and pharmacotyping. However, the optimal media composition for efficient PDO growth and accurate tumor response prediction still needs to be determined.

Another concern is the widespread use of mouse-derived hydrogels or basement membrane extract matrices that vary in protein concentration and composition between batches and vendors. Standardized products and fully synthetic hydrogels from commercial suppliers are needed to circumvent inter-laboratory differences. Other parameters that merit attention to ensure comparability between laboratories are readout systems and data analysis techniques. Metabolic activity-based cell viability assays are frequently employed to assess drug response in PDOs. However, a wide variety of readout approaches exist, including cytotoxicity assays, live-cell imaging-based apoptosis tracking,[56,57] organoid morphology-based imaging[58,59] immunofluorescent imaging-based quantification of apoptotic markers,[60] and optical metabolic imaging of drug-induced changes in cell metabolism,[61] among others. Differences in drug sensitivity scoring systems that are either based on half maximal inhibitory concentration values or AUC values further contribute to variabilities between laboratories.

Standardizing organoid technology remains a critical bottleneck, and is imperative to ensure consistent, reproducible, and comparable results across laboratories. Ongoing clinical trials aim to assess applicability, standardization, and automation across multiple trial sites (NCT04469556, NCT02869802, NCT03146962, NCT04469556).

Strategies to reduce PDO turnaround times

For the organoid-based decision-making approach to be applicable in clinical settings, reducing turnaround times is critical, particularly in the advanced setting. A notable advancement in this area has been the miniaturization and automation of drug screening methods. For instance, in 2018, Hou et al. demonstrated a high-throughput pilot screen using both 384-well and 1536-well plates in primary pancreatic organoid tumor models, incorporating approximately 3300 approved drugs.[62] Such miniaturization reduces turnout times and facilitates testing of a greater number of drugs and drug combinations. In addition, automation through robot-assisted systems contributes to standardization and ensures reproducibility.

PDOs derived from circulating tumor cells (CTCs) rather than tumor tissue were reported to have relatively short expansion times. Additionally, these liquid biopsies are minimally invasive, allowing for serial sampling. In a recent study, CTC-derived PDOs were established from 31 PDAC patients within 3–4 weeks, achieving a propagation efficacy of 87.8%.[38] Drug sensitivity profiles from CTC-derived organoid cultures correlated with patient treatment response and provided actionable information consistent with the tumor genotype.[38] Undoubtedly, organoids have the potential to predict responses to targeted treatments, as sensitivities to tailored agents may vary even among patients with identical mutations.

Enhancing tumor microenvironment representation

Finally, increasing evidence indicates that responsiveness and resistance to therapeutics are not only driven by intrinsic properties of the cancer cells but also by their surrounding TME. PDAC, one of the most stroma-rich cancers, is histologically characterized by a vast desmoplastic reaction, which constitutes up to 90% of the tumor volume. This dense stroma notably collapses blood vessels, creating a hypoxic microenvironment, and limits immune cell infiltration. Cancer cells communicate with stromal cells through physical contact and paracrine signaling to support tumor progression and aggressivity. Bioengineering efforts are thus underway to advance multicellular organoid systems that could recapitulate the PDAC TME and its intricate dynamic cell-cell interactions. The importance of developing complex culture systems was recently emphasized in a study investigating the impact of cancer-associated fibroblasts (CAFs) on pancreatic cancer response to chemotherapies. Here, Schucht et al. observed increased chemoresistance in tumor organoids upon co-culture with patient-matched CAFs.[63] Similary, Raghavan et al. uncovered a relationship between the local TME and cancer cell transcriptional states that impacts drug responses.[25] Incorporating TME

cellular and non-cellular components into the current organoid systems will further enhance PDAC disease modeling and allow to investigate biologically relevant tumor-stroma interplays as well as cancer cell-immune cell crosstalks, to better comprehend response to immunotherapies.[64] Increasing efforts are also put to vascularize and innervate organoid systems to finely reconstruct pancreatic cancer TME and explore the dialog between malignant cells and cellular compartments.[64–67] Recent advances in bioengineering have led to the development of microfluidic cell culture devices that include multiple cell types, control physiological conditions, and allow high-throughput approaches. As such, Lai Benjamin et al. microengineered a three-dimensional vascularized culture system composed of PDAC PDOs, primary human fibroblasts, and endothelial cells. By co-culturing PDOs and fibroblasts within a perfusable vascular system, the authors observed that perfusing gemcitabine into the tumor stroma resulted in a reduced efficacy compared to direct application to tumor organoids. This recapitulated the inhibitory effect of desmoplasia on drug efficacy, highlighting the importance of studying the cancer cells within their TME.[68]

Despite the complex technical setups and expertise required for implementation, microfluidic chips could offer solutions to several limitations of organoid culture, such as enhancing reproducibility, improving experimental control, reducing turnaround time, and facilitating high-throughput readouts. However, as researchers develop more complex organoid models to better mimic the TME, analytical tools must also evolve in sophistication. One of the key challenges posed by the vast amount of data generated through high-throughput screenings is the need for comprehensive and effective data analysis. Artificial intelligence (AI) and machine learning algorithms can facilitate efficient processing of large datasets.[69] As an example, Matthews et al. developed the deep learning platform OrganoID, an automated image analysis tool capable of measuring live-cell organoid responses in high-throughput experiments.[59] Despite these advances, microfluidic systems, and AI-powered analytic tools are still under development and future studies will be necessary to prove their translational value.

CONCLUSION

Organoids, awarded as the Method of the Year 2017 by *Nature*,[70] have emerged as a powerful model in translational cancer research and are increasingly replacing conventional cell culture and animal models for preclinical drug evaluation. As organoid-based precision medicine continues to evolve, addressing challenges in standardization, automation, and TME simulation will be crucial to enhance its applicability in clinical settings. Many efforts are being undertaken to implement PDOs into precision medicine as retrospective and observational studies demonstrate high concordance between pharmacotyping results and patient outcomes. However, prospective validation in large, randomized clinical trials is still missing and will ultimately determine whether organoid-based decision-making should be integrated into clinical practice.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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