

REVIEW

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Organoids in translation: a bench-to-bedside framework for pancreatic cancer precision medicine

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Abstract

Introduction Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a 5-year survival rate of < 13%. Standard treatments such as FOLFIRINOX or gemcitabine/nab-paclitaxel yield modest response rates, underscoring the urgent need for precision oncology approaches. Patient-derived organoids (PDOs) preserve the genomic, phenotypic, and histopathological features of the source tumor and offer a promising platform for drug screening, biomarker development, and personalized therapy. However, a systematic evaluation of their translational capacities is lacking.

Methods A systematic review was conducted according to the PRISMA 2020 guidelines (PROSPERO registration pending) using PubMed, EMBASE, and Cochrane CENTRAL (December 10, 2024) to identify English-language PDAC PDO studies that incorporated therapeutic testing. Ninety-five studies met the inclusion criteria. Data extraction captured >75 variables per study, including spanning culture methodology, therapeutic profiling, biomarker integration, and clinical correlation. A 13-domain weighted Translatability Scoring Framework adapted from Wehling et al. assessed predictive validity, biomarker strength, pharmacogenetics, and clinical trial alignment. Scores ranged from 0 to 5 and were categorized as good (>4.0), moderate (3.0–4.0), or low (<3.0) translational potential.

Results Of the 95 studies, 70.5% have been published since 2021, reflecting the rapid growth in this field. The mean PDO generation success rate was 89.7%, with the primary tumor tissue being the predominant source (48.4%). Only 24.8% were directly linked to clinical trials and 5.3% incorporated multi-omic profiling. The median translatability score was 3.13 (range, 1.72–4.59): 45.3% of the studies had low translatability, 50.5% moderate, and only 4.2% had good translational potential. High-scoring studies consistently combine multi-omic biomarker platforms, in vivo validation, clinical outcome correlation, and prospective trial integration. Conversely, the weakest domains were pharmacogenetics, endpoint strategies, and biomarker validation, limiting their overall clinical relevance.

Conclusions PDOs have demonstrated strong feasibility and in vitro clinical correlation in PDAC; however, their clinical translation remains constrained by limited multi-omic integration, absence of pharmacogenomic modeling, and sparse clinical trial embedding. Standardization of protocols, adoption of harmonized and clinically relevant endpoints, and systematic incorporation of biomarker-driven co-clinical trial frameworks are urgently needed to

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transition PDOs from promising experimental surrogates to validating precision oncology tools capable of informing therapeutic decision-making in PDAC.

Keywords Pancreatic ductal adenocarcinoma, Patient-derived organoids, Precision oncology, Translational research, Drug screening, Biomarker development, Systematic review

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignancies worldwide, with only modest gains in survival despite decades of research. In the United States, the Surveillance, Epidemiology, and End Results (SEER) program projects more than 67,000 new cases and over 51,000 deaths by 2025, and PDAC is the third leading cause of cancer mortality, despite accounting for only 3.3% of diagnoses and 8.4% of deaths [1, 2]. Its disproportionate fatality burden reflects its aggressive biology, late detection, and poor responsiveness to current therapies. PDAC is expected to become the second leading cause of cancer-related deaths by 2030 [3].

Curative potential is limited to a minority (10–20%) of patients eligible for surgical resection using a multimodal approach involving chemotherapy, surgery, and radiation [1, 4]. Most patients present with advanced disease (stages III–IV), rendering chemotherapy the primary option; however, response rates to standard regimens, such as FOLFIRINOX or gemcitabine/nab-paclitaxel, remain modest (~30%), undermined by chemoresistance, toxicity, and rapid progression [4]. Even within these regimens, wide inter-patient variability exists due to underlying molecular subtypes, tumor-stroma interactions, and treatment-induced adaptive resistance, highlighting the inadequacy of “one-size-fits-all” therapeutic strategies [5–7]. These limitations underscore the urgent need for precision oncology approaches that can tailor therapy to tumor-specific biology.

Given PDACs marked heterogeneity and genomic complexity of PDAC, patient-derived organoids have emerged as powerful preclinical models for dissecting tumor biology, therapeutic response, and resistance. [8–10] (Fig. 1B). These three-dimensional cultures preserve the genetic, phenotypic, and histopathological fidelity of the original tumors, with high establishment rates from surgical resections (~85%) and endoscopic biopsies (~70%) [11, 12]. PDO platforms have been successfully expanded to ascites and pleural fluid [13], fine-needle biopsies [14–16], and even metastatic lesions [17, 18]. This approach broadens their applicability to advanced-stage patients who are rarely represented in surgical cohorts. PDOs also enable high-throughput drug testing, providing clinically relevant data to guide precision oncology research. [12, 19]. Beyond PDAC, organoid technology has advanced disease modeling across colorectal, gastric, breast, liver, and prostate cancers, as well as non-malignant conditions, such as cystic fibrosis [20].

Notably, multiple studies have shown that PDO-based *ex vivo* drug sensitivity correlates strongly with clinical response (AUC 0.80–0.90), particularly for FOLFIRINOX- and gemcitabine-based regimens [12, 19]. Prospective trials have confirmed that PDO pharmacotyping can predict neoadjuvant chemotherapy response [13]. Pharmacogenomic integration further enhances the predictive validity [21–23]. PDOs have also supported the functional validation of KRAS-targeted therapies and enhanced genomic resolution by selectively expanding the malignant epithelium while reducing stromal contamination [11, 12, 19, 20]. This capacity improves the detection of clinically relevant alterations that are often missed in conventional biopsies. For example, PDO-based sequencing has uncovered resistant subclones [24] and enhanced mutation detection compared with standard diagnostic pipelines [25].

Despite these advances, systematic evaluation of PDOs’ translational utility—particularly their capacity to predict survival, therapeutic efficacy, and trial integration, remains limited. The reporting of critical metrics, such as reproducibility, scalability, pharmacokinetic/pharmacodynamic (PK/PD) modeling, and toxicity assessment, has been inconsistent. Moreover, trial-linked PDO studies remain relatively rare, with only a few efforts formally integrating PDO pharmacotyping into clinical decision-making frameworks [26–28]. This review addresses these gaps by applying a structured translatability framework encompassing predictive validity, biomarker integration, safety data, and co-clinical trial concordance [8, 9].

By synthesizing existing evidence, we aimed to define when and how PDOs can be optimally leveraged in precision-driven translational oncology for patients with PDAC.

Materials and methods

Systematic review

This meta-analysis was prospectively registered with PROSPERO and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. To evaluate the translational relevance of patient-derived pancreatic ductal adenocarcinoma organoid models, we conducted a systematic review according to the PRISMA 2020 guidelines (Fig. 1A). A comprehensive literature search was performed using PubMed, EMBASE, and Cochrane CENTRAL on December 10, 2024, using a combination of Medical Subject Headings terms and keywords related

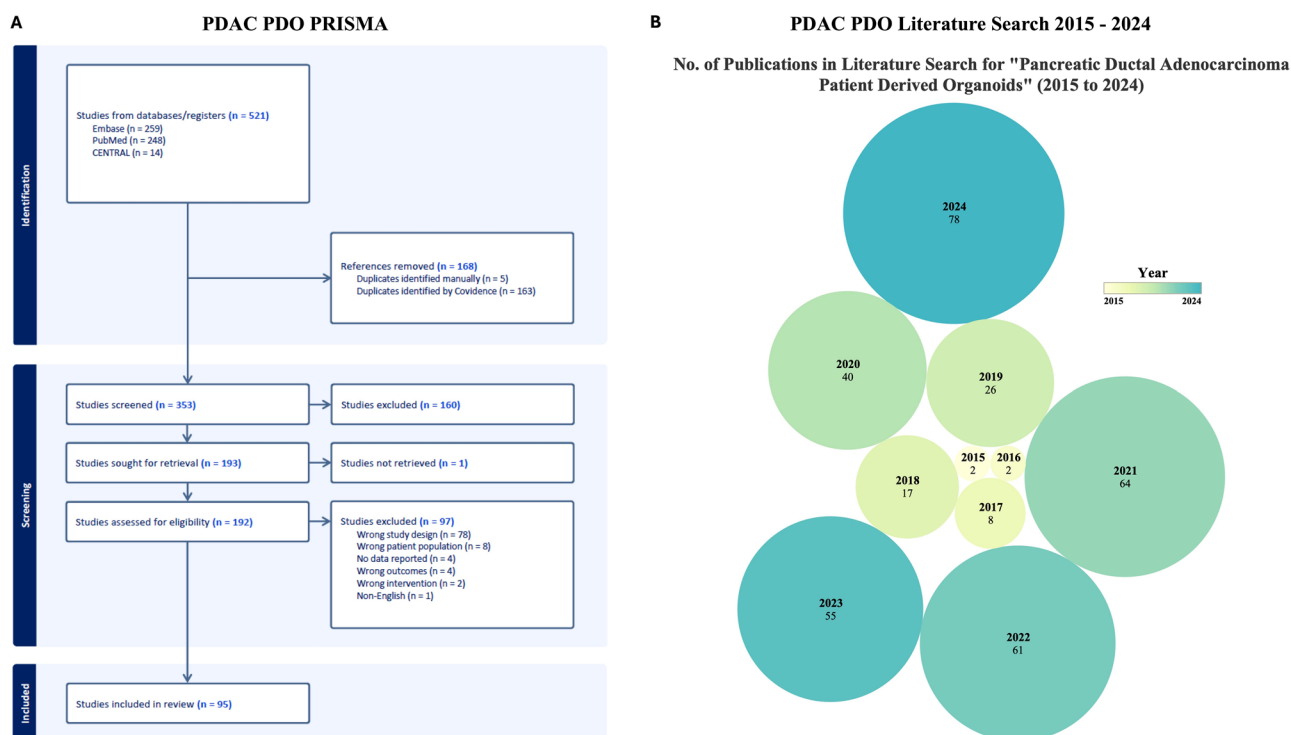


Fig. 1 A PRISMA 2020 flow diagram for study selection in the systematic review of patient-derived organoids (PDOs) in pancreatic ductal adenocarcinoma (PDAC). Database searches (PubMed, embase, central) yielded 521 records, with 168 duplicates removed. After screening 353 unique records, 193 full texts were sought, of which 192 were retrieved. Following eligibility assessment, 97 studies were excluded for reasons including study design ($n=78$), patient population ($n=8$), lack of data ($n=4$), irrelevant outcomes ($n=4$), intervention mismatch ($n=2$), or non-English language ($n=1$). A total of 95 studies met inclusion criteria and were analyzed. B: annual publication trends for pancreatic ductal adenocarcinoma patient-derived organoids (2015–2024). Bubble plot shows yearly publication counts (bubble size) with a color gradient by year (light yellow = earliest; dark teal = most recent). Data were obtained from PubMed, embase, and Cochrane central (December 10, 2024) using PDAC-, organoid-, and drug-screening-specific MeSH/EMTREE terms. The progressive enlargement and darker hue of recent bubbles underscore the marked surge in PDAC PDO publications over the past five years, reflecting accelerating translational and clinical momentum in this field

to pancreatic ductal adenocarcinoma, organoids, and drug screening (Supplemental Appendix A). The search was restricted to English-language studies with no limitations on the publication year. The complete search strategy for all databases is provided in the appendix.

A total of 521 studies were retrieved from all the databases. After deduplication, 353 unique records were screened based on their titles and abstracts (Fig. 1B). The inclusion criteria were as follows: (i) use of PDO models from PDAC tissues, (ii) preclinical drug screening or pharmacotyping, and (iii) data relevant to therapeutic outcomes, biomarker validation, or translational potential. The exclusion criteria were reviews, non-English articles, non-peer-reviewed studies, non-PDAC models, and/or studies without drug-testing data. Screening was completed in duplicate, and conflicts were resolved by consensus.

Following title and abstract screening, 193 articles underwent a full-text review using the same screening process. One article was not retrievable, and 97 were excluded for reasons such as irrelevant population (e.g., not PDAC patients), incorrect study design (e.g., review

articles, did not pharmacotype PDOs), or missing outcomes. Ultimately, 95 studies met all the inclusion criteria for the final analysis, as shown in the PRISMA diagram (Fig. 1A.). [5–7, 13–19, 21–104].

Data extraction

Data were extracted in duplicate with consensus from reviewers (DM and RCGM) using a standardized Excel-based template comprising over 75 variables per study across the domains of clinical metadata, experimental conditions, translational metrics, and outcome correlation. For each eligible study, data were extracted based on the translatability of PDO studies using a structured framework that included organoid sources (e.g., surgical resection and EUS-FNA), culture methods (e.g., matrix, media, and time to passage), screening (e.g., IC50, viability, and AUC), molecular profiling (e.g., KRAS and TP53 mutations), and clinical correlations. This review emphasized studies that incorporated translational endpoints, such as PDO response, in concordance with clinical treatment response or survival outcomes.

Translatability scoring heuristic

To systematically assess the clinical relevance and predictive capacity of patient-derived organoid (PDO) models in PDAC, we applied a structured Translatability Scoring System adapted from Wehling et al. [10, 11] for oncology and precision medicine [12]. This framework evaluates the robustness of evidence across domains, which is essential for bridging preclinical models to clinical applications.

The scoring system comprises 13 weighted domains: (i) In Vitro Application, (ii) In Vivo Efficacy, (iii) Human Pathophysiological Rationale, (iv) Model Compounds, (v) Genetic Evidence, (vi) Surrogate/Endpoint Strategy, (vii) Biomarker Strategy, (viii) Biomarker Grading, (ix) Biomarker Development, (x) Pharmacogenetics, (xi) Clinical Trials, (xii) Regulatory/Guideline Relevance, and (xiii) External Validation. Each domain was scored from 0 to 5, multiplied by its weight, and summed to generate a composite score (0–5) (Fig. 2A).

Biomarker evaluation followed Wehling’s grading framework, encompassing ten criteria: proximity to disease biology, supporting animal and human data, cross-species relevance, sensitivity, specificity,

reproducibility, validation status, ease of measurement, and clinical accessibility. Domain scores were normalized (1–5) and weighted to the maximum of each subdomain (2–24% of the total score).

$$\text{Translatability Score} = \sum \left[\frac{(\text{Domain Score from 1 – 5}) \times (\text{Domain Weight} \div 100)}{\text{Domain Weight} \div 100} \right]$$

All 95 included studies were independently reviewed by two evaluators (DM and RCGM) using a standardized extraction form and scoring criteria. Discrepancies were resolved by consensus, and justifications were recorded for transparency. Scores were entered into an Excel template with automated weighting formulas, yielding both continuous translatability scores and categorical classifications: good (>4.0), moderate (3.0–4.0), or low (<3.0) translational potential (Fig. 2B–D).

It should be noted that the translatability scoring framework used in this review, while adapted from the conceptual model proposed by Wehling (2009), has not been formally validated as a standardized or statistically

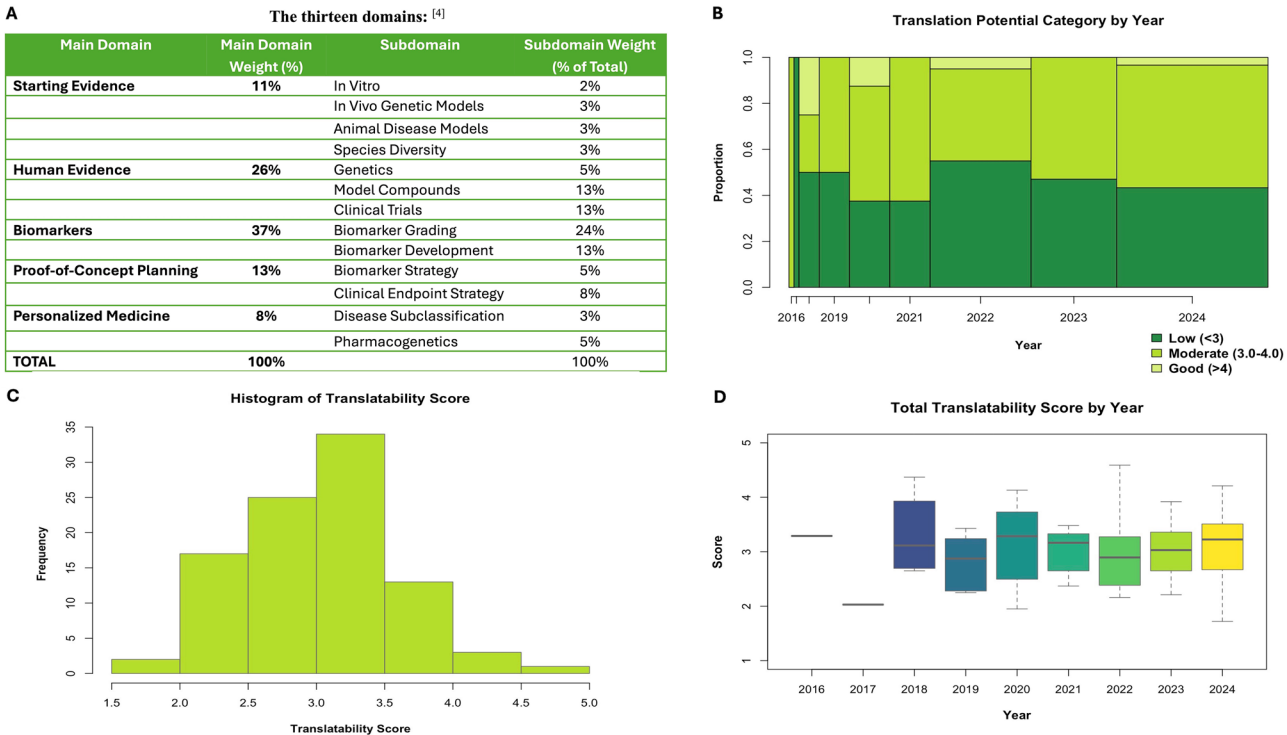


Fig. 2 (A) summarizes the translatability assessment of 95 PDAC PDO studies (2016–2024) using a five-domain, 13-subdomain framework adapted from Wehling (2009). Scores (1–5) were weighted to yield a composite value (max = 5.00), classifying studies as good (> 4.0), moderate (3.0–4.0), or low (< 3.0) translational potential. Most studies were preclinical, derived from primary or metastatic samples, with staging and prior treatment extracted as reported. Temporal analysis (B) shows a shift from low-to-moderate scores before 2021 toward predominantly moderate studies thereafter, while high-quality studies (> 4.0) remain rare (< 5%). The score distribution (C) was unimodal around 3.13 (IQR 2.72–3.52), with 46% low, 49% moderate, and 4% good translatability. Yearly trends (D) reveal modest but steady improvement, with isolated outliers in 2018, 2020, 2022, and 2024. Overall, PDAC PDO research shows gradual methodological refinement yet limited consistency in achieving high translational rigor

verified assessment tool. The scoring system was applied to ensure a structured, comparative evaluation across studies, but the results should be interpreted with caution. Future work involving inter-rater reliability testing, external benchmarking, and validation against prospective clinical outcomes is essential to establish its scientific robustness and predictive accuracy in organoid-based translational research.

Statistical analysis

All statistical analyses were performed using R, version 4.2.2. To evaluate the relationship between the translatability score and study-level features, the manuscripts were stratified into three ordinal tiers: low (<3.00), moderate ($3.00\text{--}3.99$), and high (≥ 4.00) translatability scores. This stratification is grounded in the methodology published by Wehling (2009), wherein a score ≥ 4.0 is defined as indicative of fair to good translational potential. Scores below 3.00 typically reflect critical deficits across core domains, and scores in the 3.00–3.99 range represent intermediate feasibility. These bins are intended to reflect real-world translational readiness, rather than arbitrary quantiles.

To compare features across translatability strata, continuous variables were analyzed using one-way ANOVA when normality assumptions were satisfied; otherwise, the Kruskal-Wallis test was used. Normality was visually assessed. Binary and categorical variables were evaluated using Fisher's exact test, which was chosen over Pearson's chi-squared test to account for the small sample sizes in some groups. Associations between the continuous translatability scores were considered using Spearman's correlation for continuous features and ANOVA for categorical features. Statistical significance was defined as $p < 0.05$. Importantly, features marked as "Not Reported" were not treated as missing data, but were retained as a distinct analytical category. This approach is consistent with the principle that non-reporting may signal methodological opacity or quality limitation. Treating "Not Reported" as a separate level allows for the evaluation of whether the absence of information systematically correlates with lower translatability or inferior outcomes. Sensitivity analyses were performed to determine whether the exclusion of "Not Reported" observations altered the significance of the findings.

Results

Literature features

Our systematic review identified 95 published studies using patient-derived organoids (PDOs) to model pancreatic ductal adenocarcinoma (PDAC), reflecting the rapid maturation of the field. Most studies (70.5%, $n = 67$) were published between 2021 and 2024, coinciding with the emergence of standardized protocols, commercial

media, and biobanking initiatives. This shift marks a clear evolution from early proof-of-concept efforts toward integration with translational and precision oncology frameworks. Across all studies, the mean translatability score was 3.0 ± 0.6 , with 46% classified as low, 49% as moderate, and only 4% as high (Fig. 3A). The majority (85%) were preclinical, and all high-translatability studies (≥ 4.0) fell within this category, indicating that direct clinical application remains in its infancy. The median publication year was 2022, and the translatability scores showed no temporal trends ($\rho = 0.06$, $p = 0.56$). Patient enrollment ranged from 3 to 85 years (median = 8 years), with no correlation between cohort size and translatability ($\rho = 0.14$, $p = 0.20$). No significant correlation was observed between cohort size and translatability score ($\rho = 0.14$, $p = 0.20$), suggesting that the translational value was not strictly determined by the sample size (Supplemental Table 1A).

The PDO establishment success averaged 89.7% (range, 70–100%), affirming procedural feasibility across platforms. However, an inverse correlation between the success rate and translatability ($\rho = -0.32$, $p = 0.015$) suggests potential reporting bias; studies claiming near-perfect success may overestimate feasibility, whereas moderate success rates may better reflect clinical heterogeneity and logistical barriers. These findings emphasize the need for standardized metrics and transparent reporting to ensure that PDO-based studies yield realistic and reproducible insights for translational and clinical applications.

Source of organoids

The tissue origin of PDOs markedly influences their translatability. Primary tumor resection was the most common source (48.4%, $n = 46$), followed by mixed cohorts (22.1%, $n = 21$), metastatic lesions (13.7%, $n = 13$), and unspecified sources (15.8%, $n = 15$) (Supplemental Table 1A). PDOs derived from primary or mixed tissues achieved higher mean translatability scores (3.1 ± 0.6 and 3.1 ± 0.4 , respectively) compared with metastatic (3.0 ± 0.6) or unspecified sources (2.7 ± 0.5) ($p = 0.067$), suggesting that precise documentation of tissue origin enhances translational robustness. All high-translatability studies (≥ 4.0) relied exclusively on primary tumor resections, whereas metastatic and mixed sources appeared only in low-to-moderate tiers, and unspecified sources were confined to the lowest-scoring studies (Supplemental Table 1B). Autopsy-derived tissue was used solely for moderate quality work. Collectively, these findings underscore the importance of using well-characterized, biologically representative, and meticulously documented source materials to strengthen the translational relevance of PDO-based research.

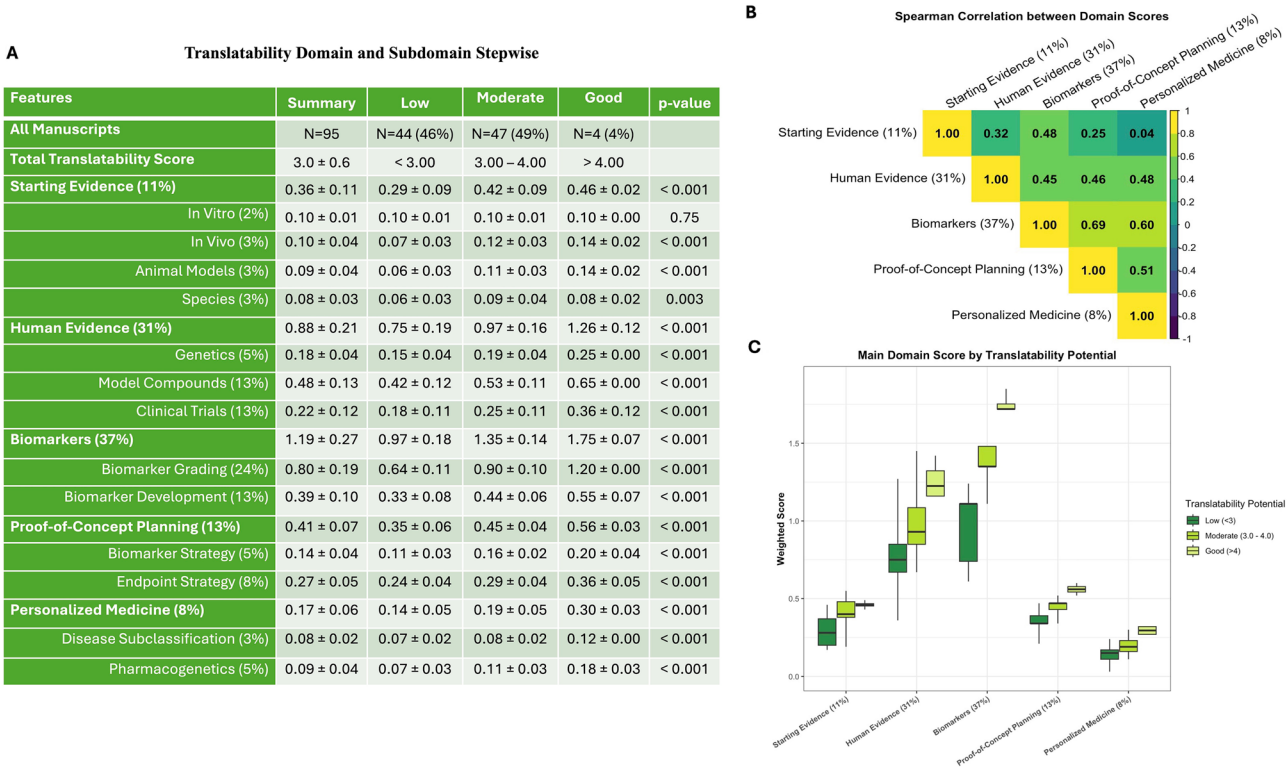


Fig. 3 A compares weighted domain scores across 95 PDAC PDO studies stratified by translatability (low < 3.0, moderate 3.0–4.0, good > 4.0). The median total score was 3.0 ± 0.6, with 46% low, 49% moderate, and 4% good potential. Stepwise increases were observed across most domains, including human evidence, in vivo validation, biomarker integration, proof-of-concept planning, and personalized medicine (all $p < 0.001$, except in vitro $p = 0.75$). Biomarkers had the strongest influence (37% weight), followed by human evidence (31%) and proof-of-concept planning (13%). Boxplots (B–C) show that good studies consistently scored higher in biomarker rigor, clinical trial linkage, and translational design, while starting evidence contributed minimally to discrimination across categories. Overall, biomarker robustness and clinical correlation were the principal determinants of high translatability, underscoring the growing importance of molecular validation and patient-centered study design in advancing PDO models toward clinically predictive precision oncology

Establishment and culture fidelity

Across 95 studies, the median PDO establishment time was 14 days (IQR: 7–21), although durations varied widely owing to differences in tissue origin, assay design, and laboratory workflow. While establishment time did not correlate significantly with translatability ($p = 0.18$, $p = 0.18$), higher scoring studies consistently provided clearer and more standardized reporting. Matrigel was the dominant extracellular matrix (88%), with BME and synthetic alternatives rarely used (8 and 3%, respectively) (Supplemental Table 2A).

All high-scoring studies in our analysis utilized Matrigel, reflecting its current effectiveness and technical reliability under research conditions. However, its animal-derived origin introduces batch-to-batch variability in growth factor content and extracellular matrix components, which complicates reproducibility, standardization, and inter-laboratory consistency. These factors, combined with undefined biochemical composition and limited Good Manufacturing Practice (GMP) compliance, hinder scalability and regulatory approval for clinical-grade PDO applications. Thus, reliance on Matrigel,

while practical, underscores the need for xeno-free, chemically defined extracellular matrices that can sustainably improve quality control and meet the regulatory standards required for translational and clinical applications deployment.

Fidelity validation was heterogeneous; 75% of studies performed genomic confirmation—typically of KRAS, TP53, CDKN2A, and SMAD4—alongside histopathology, whereas 24% relied solely on histology. Multimodal validation approaches were uniformly present across high-scoring studies and associated with greater translatability, although the difference was not statistically significant ($p = 0.93$). PDO source further influenced outcomes; most were derived from resection specimens (59%), whereas autopsy-derived PDOs, though rare (4%), achieved the highest mean translatability scores (3.5 ± 0.7), highlighting their value for modeling late-stage disease and therapy resistance (Supplemental Table 2A–B).

PDO establishment success rates across studies were high (median 91% [range 70–100%]), but showed an inverse correlation with overall translatability ($\rho = -0.32$,

$p=0.015$). While this pattern may suggest that studies reporting moderate success rates adhere to stricter quality controls or inclusion criteria, such an interpretation remains speculative without direct evidence of methodological rigor or external benchmarking. Alternatively, this trend could reflect a reporting bias, as studies emphasizing feasibility may preferentially publish higher success rates. By contrast, those focusing on translational endpoints may report more stringent criteria for culture fidelity or downstream validation. Future meta-analyses linking success rates to objective reproducibility metrics, such as long-term culture stability or drug-response concordance, will be critical to clarify whether lower success rates genuinely indicate higher rigor simply reflect different study aims and publication practices.

Translational design features

Of the 95 manuscripts reviewed, 85% were preclinical and only 15% included retrospective clinical correlations, such as outcome-linked analyses or patient stratification. Despite this imbalance, translatability scores were similar between the groups (3.0 – 3.1 , $p=NS$), indicating that *in vivo* experimental rigor, rather than the presence of clinical data, primarily drives translational value. Studies incorporating direct clinical correlations (62%) scored higher (3.1 ± 0.5) than those relying on indirect inferences (32%, 2.9 ± 0.6 ; $p=0.026$). Notably, all high translatability studies included direct validation, whereas the absence of predictive accuracy strategies (6%) was confined to the lowest-scoring tier, emphasizing the importance of linking PDO-based results to patient outcomes.

Clinical trial integration remained limited: only 24.8% of the studies were linked to formal trials, 32% demonstrated retrospective or structured associations, and 41% offered only implied co-clinical support. Critically, only 3% incorporated true co-clinical frameworks involving real-time PDO applications within active trials, even among top performers. These findings underscore a key translational bottleneck—without systematic clinical trial embedding—PDO research remains scientifically robust, but lacks regulatory grounding. Rigorous validation and biomarker strategies can yield clinically meaningful insights, but scalable co-clinical trial models are essential to advance PDOs from exploratory tools to standardized precision oncology platforms.

Therapeutic modeling and functional readouts

Across studies, therapeutic interrogation was central to PDO applications, with 54% testing standard cytotoxic regimens (e.g., gemcitabine, FOLFIRINOX, and irinotecan) and 42% evaluating combination therapies incorporating targeted or immunologic agents. Despite heterogeneity, translatability scores were similar between chemotherapy-only and mixed regimens (3.0 ± 0.6 vs.

3.1 ± 0.5 , $p=0.79$), indicating that treatment type alone does not determine translational strength.

However, the methodological depth strongly influenced the outcomes. Studies that quantified IC_{50} or AUC values and employed CellTiter-Glo assays reported slightly higher translatability scores, underscoring the cumulative benefits of quantitative approaches. Similarly, studies using continuous response modeling (66%) achieved higher scores (3.1 ± 0.6) than those using binary response classification (8%, 2.7 ± 0.6 ; $p=0.083$). All high-scoring studies incorporated quantitative readouts, highlighting the importance of detailed phenotypic profiling of categorical responses.

Across the 95 included studies, PDO performance was most commonly quantified using drug-response metrics such as IC_{50} (58%), area under the curve (AUC; 27%), and percentage growth inhibition or viability index (15%). Less than 10% reported a normalized growth rate (GR_{50}) or time-to-event measures. Studies employing IC_{50} or AUC values generally achieved higher translatability scores (median 3.24 vs. 2.91), likely due to improved comparability with pharmacologic reference standards and clinical dose–response data. However, heterogeneity in the assay design, normalization methods, and viability thresholds limits cross-study reproducibility.

These findings emphasize that methodological consistency in quantifying PDO responses is as critical as endpoint selection on the clinical side. Standardized dose–response modeling, ideally incorporating GR metrics and pharmacodynamic benchmarks, is essential for improving the predictive alignment between organoid pharmacotyping and patient outcomes, thereby strengthening the translational reliability of PDO-based platforms.

High-throughput screening (HTS) further distinguished high-performing studies, present in 38% of investigations and associated with significantly greater scores (3.2 ± 0.6 vs. 2.9 ± 0.5 ; $p=0.006$). Collectively, these findings show that functional rigor, defined by quantitative phenotyping and scalable HTS platforms, rather than the therapeutic class, drives translatability. Therefore, integrating high-content and reproducible pharmacologic evaluation frameworks is essential for advancing PDOs as clinically meaningful drug-testing systems.

Translatability outcomes

Clinical correlation strategies varied substantially in terms of depth and precision across the 95 studies. The translatability scores ranged from 1.72 to 4.59 , with a mean of 3.0 ± 0.6 and a median of 3.13 , reflecting a field of moderate maturity. When stratified, nearly half of the studies (45.3%, $n=43$) were in the low translatability tier, 50.5% ($n=48$) were in the moderate tier, and only a small

fraction (4.2%, $n=4$) achieved high translatability (Supplemental Table 4A).

This disparity highlights a critical gap; while PDO platforms are technically feasible and widely utilized, their clinical applicability is limited to a minority of rigorously conducted studies. Importantly, concordance analysis revealed that 40% ($n=38$) of the manuscripts demonstrated only a partial alignment between PDO-derived responses and patient outcomes, 31% ($n=29$) achieved strong concordance, and 29% ($n=28$) reported no concordance (Supplemental Table 4A). Although these differences were not statistically significant ($p=0.34$), studies with strong concordance demonstrated modestly higher mean translatability scores (3.1 ± 0.5) than those with partial (2.9 ± 0.6) or no concordance (3.0 ± 0.5) (Supplemental Table 4B).

Collectively, these findings emphasize that while PDOs are widely applied as translational tools, most studies remain limited by incomplete or absent patient-level correlations, restricting their advancement toward regulatory or clinical utility.

Research endeavors that consistently demonstrated superior translatability showed a convergence of multi-dimensional validation, clinical alignment, and methodological innovation, thereby distinguishing themselves from broader cohorts. Several features emerged as statistically and conceptually significant contributors to the high scores.

Multi-omic biomarker integration

Only a small subset of studies (5.3%, $n=5$) incorporated integrated multi-omic profiling, combining genomic, transcriptomic, and proteomic analyses within their PDO frameworks. Although limited in number, these studies demonstrated an enhanced capacity to identify resistance mechanisms, therapeutic vulnerabilities, and molecular correlates of drug response compared to mutation-based stratification alone. Matsumoto et al. (2024) and VandeWall et al. (2023) employed multi-omic integration to delineate subtype-specific signaling dependencies and predict clinical outcomes with greater precision. Although these examples highlight the promise of comprehensive molecular annotation, current evidence remains preliminary and insufficient for definitive conclusions. Therefore, rather than representing a proven “transformative” advance, multi-omic integration should be regarded as an emerging area with substantial potential to improve predictive accuracy once standardized pipelines, larger sample sizes, and clinical concordance metrics are systematically implemented.

Clinical correlation

A direct correlation between PDO drug response and patient-level outcomes was reported in 62% of studies

($n=59$) and was significantly associated with higher translatability scores (3.1 ± 0.5 vs. 2.9 ± 0.6 , $p=0.026$). In contrast, indirect inference strategies (32%, $n=30$) underperformed, and the absence of predictive accuracy (6%, $n=6$) was confined to the lowest scoring tier (mean score of 2.5 ± 0.4). The inclusion of validated clinical biomarkers, such as CA19-9 (16%, $n=15$) and RECIST criteria (20%, $n=19$), conferred a further 0.3-point advantage ($p=0.017$ and $p=0.028$, respectively) (Supplemental 4A-B). Conversely, reliance on long-term endpoints, such as PFS (27%) or OS (46%), failed to enhance the scores (both $p>0.5$), likely reflecting the mismatch between real-time PDO outputs and prolonged clinical follow-up.

In vivo validation

PDO studies incorporating xenograft models (15.8%, $n=15$) reported improved biological fidelity but did not exhibit statistically significant improvements in translatability (3.0 ± 0.5 vs. 3.0 ± 0.6 ; $p=0.97$) (Supplemental Table 4B). Moreover, none of the high-scoring studies employed parallel PDX validation (Supplemental 4A), underscoring that, while in vivo confirmation may augment mechanistic insights, it does not independently elevate translational performance without a standardized framework for its implementation.

Clinical trial embedding

Formal clinical trial associations were identified in 30 (32%) of the studies (Supplemental Table 4A). Although these studies trended toward higher scores (3.1 ± 0.6 vs. 3.0 ± 0.6 , $p=0.57$) (Supplemental Table 4B), only three (3%) demonstrated true co-clinical trial frameworks, prospectively aligning PDO testing with patient enrollment or treatment arms. Intriguingly, these rare trial-embedded designs exhibited paradoxically lower mean scores (2.8 ± 0.6) than those with implied (2.9 ± 0.6) or no trial linkage (3.1 ± 0.5) ($p=0.064$) (Supplemental Table 4B). This reflects the feasibility-driven nature of early co-clinical studies, which remain underpowered to demonstrate substantial translational gains, but represent the most rigorous blueprint for future adoption.

Advanced experimental platforms

High-throughput screening (HTS) was employed in 38% of the studies ($n=36$) and yielded significantly higher translatability scores (3.2 ± 0.6 vs. 2.9 ± 0.5 , $p=0.006$) (Supplemental Tables 3 B and 4 B). All high-scoring studies (100%) used HTS platforms (Supplemental Table 3A), underscoring their role as methodological accelerators for enhancing reproducibility and prioritizing drugs. Emerging technologies, including AI-based predictive analytics, have been exclusively observed among high-scoring studies, suggesting an untapped frontier for future PDO trial designs.

Domain-level performance

Clinical correlation analyses revealed marked heterogeneity across the 95 studies. Only 31% demonstrated strong concordance between PDO drug responses and patient outcomes, 40% showed partial concordance, and 29% did not. Although the differences were not statistically significant ($p=0.34$), studies with strong concordance achieved higher mean translatability scores (3.1 ± 0.5 vs. 2.9 ± 0.6). Incorporation of validated surrogate biomarkers further distinguished high-performing studies, those using CA19-9 or RECIST criteria demonstrated significantly greater translatability (3.3 ± 0.5 – 0.6 ; $p<0.03$) than studies relying on PFS or OS, which showed no benefit to translatability.

Despite their translational potential, their clinical integration remains limited. Only 32% of the studies were directly linked to clinical trials, and only 3% used co-clinical trial frameworks, neither of which significantly improved the scores. Similarly, parallel validation with patient-derived xenografts (42%) did not enhance translatability (3.0 ± 0.5 vs. 3.0 ± 0.6 ; $p=0.97$), and none of the top-scoring studies used PDX. Collectively, these data suggest that rigorous patient-level correlation and biomarker alignment, and not trial linkage or animal validation, are the strongest predictors of PDO translatability.

Biomarker strategies and clinical correlations

Genomic fidelity was consistent across the 95 included studies. Nearly all PDO models preserved the canonical mutational spectrum of PDAC, including recurrent alterations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, confirming their reliability as translational PDAC models. However, beyond this baseline genetic preservation, biomarker exploration has been limited and inconsistent in literature. While 39% ($n=37$) of the studies employed mutation-based stratification, a greater proportion (60%, $n=57$) performed a multi-omic biomarker evaluation. Upon closer inspection, only five studies (5.3%) implemented accurate integrated profiling that combined transcriptomic, proteomic, and metabolomic datasets (Supplemental 3A–B).

This discrepancy between the reported and executed analyses contributed to the lack of a significant difference in translatability scores between mutation-based approaches (3.1 ± 0.6) and multi-omic strategies (2.9 ± 0.5 ; $p=0.18$, Supplemental Table 3B). Moreover, multi-omic inclusion was paradoxically more common in low-scoring manuscripts (68%) than in high-scoring ones (25%), suggesting that the presence of “omics” data alone—without rigorous integration or clinical validation—does not have a meaningful impact. In contrast, the few high-performance studies that employed authentic multi-omic integration demonstrated the transformative potential

of comprehensive molecular annotation when executed properly.

Summary

This systematic evaluation highlights both the maturity and vulnerability of the existing PDAC PDO translational pipelines. Although the processes of organoid establishment, drug screening, and genetic fidelity are consistently reliable, the field continues to face limitations due to insufficient biomarker validation, inadequate endpoint harmonization, underdeveloped pharmacogenomic modeling, and limited integration with co-clinical trials. These shortcomings restrict the predictive capacity of PDOs and hinder their acceptance as genuine precision medicine platforms for precision medicine.

The limited number of high-quality studies illustrates that multilayered translational integration is both feasible and influential, establishing replicable frameworks that connect PDO multi-omic patient outcomes via multi-omic biomarker strategies, sophisticated functional modeling, and the integration of prospective clinical trials. These exemplars serve as blueprints for next-generation translational oncology pipelines, whereby PDOs are regarded not only as experimental surrogates but also as validated regulatory-grade tools.

To fully realize their clinical potential, future studies must focus on harmonized fidelity benchmarks, standardized reporting of clinically relevant endpoints, and the systematic incorporation of multi-omic and pharmacogenomic strategies. Equally critical is the prospective integration of PDOs into co-clinical trial designs to enable real-time therapeutic predictions and validation in patient cohorts. By closing these methodological and structural gaps, PDO platforms can evolve into validated clinical companions capable of guiding individualized therapeutic decisions, informing rational drug development, and ultimately advancing precision oncology in pancreatic ductal adenocarcinoma, which is one of the most lethal human malignancies.

Discussion

Bridging resistance and response

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most treatment-refractory malignancies, with a 5-year survival rate of 13% [1]. Its poor prognosis reflects both intrinsic and acquired resistance to systemic therapy, driven predominantly by activating *KRAS* mutations (>90%), most commonly *KRAS*^{G12D} and *KRAS*^{G12V} [12, 17, 19]. These mutations hyperactivate MAPK and PI3K–AKT signaling, promoting proliferation, immune evasion, and apoptosis resistance [28, 76]. While mutation-specific inhibitors, such as sotorasib (*KRAS*^{G12C}) and MRTX1133 (*KRAS*^{G12D}), show promise, their benefits are frequently transient due to adaptive resistance [4, 40,

54, 94]. Resistance is further compounded by complex genomic, epigenomic, and stromal interactions, including chromosomal instability, aberrant DNA methylation, and a dense, immunologically “cold” tumor microenvironment (TME) that impairs drug delivery and T-cell infiltration [22, 67, 72].

Despite the comprehensive genomic characterization of PDAC, the clinical impact of genomics-driven therapies remains modest compared with that of other cancer types. To date, only two molecularly guided strategies have received regulatory approval: the addition of erlotinib for *EGFR*-mutant PDAC, which confers minimal benefit when combined with gemcitabine [34, 47], and PARP inhibitors for germline *BRCA1/2* mutation carriers, which improve progression-free but not overall survival [52, 71]. Additionally, most recurrent mutations (*KRAS*, *TP53*, *CDKN2A*, and *SMAD4*) remain non-actionable, underscoring the gap between mutational discovery and therapeutic applicability.

This disconnect limits the immediate clinical utility of PDOs as pharmacogenomic models, as a few existing genomic alterations directly inform targeted therapy selection. However, PDOs offer a functional complement to purely genomic profiling by linking molecular signatures to phenotypic drug responses, thereby enabling the discovery of context-specific vulnerabilities. The paradigm lies in integrating multiomic data with PDO-based pharmacotyping to reveal actionable synthetic lethal interactions and identify molecular predictors of therapeutic response, bridging the current divide between genomic annotation and clinically meaningful precision oncology in PDAC.

PDO models have demonstrated concordance with chemotherapy responses and can incorporate immune and stromal co-cultures to interrogate resistance pathways [7, 22, 35, 43, 45, 57, 58, 92, 95]. However, only 4% of the studies achieved “good” translational potential, underscoring that biological realism alone is insufficient for clinical utility. Integrating PDO-derived pharmacotyping with multi-omic and biomarker-guided frameworks is a critical fore existing models of therapeutic resistance and the transformation of PDOs into predictive instruments for precision oncology [6, 51, 62].

Standardization of surrogate endpoints is essential for enhancing comparability and reproducibility across PDO studies, yet few investigations have explicitly defined which metrics should be prioritized. Based on the present analysis, the most consistently applied clinical surrogates were **CA19-9 response** and **RECIST-based radiologic assessment**, both reported in >60% of clinically correlated studies [41, 68, 93]. These measures enable the short-term alignment of PDO pharmacotyping with patient response, although their interpretive limitations have been discussed above with studies relying on PFS

or OS, showing no benefit to translatability. From the experimental side, **IC₅₀** and **AUC-based viability curves** were the most frequently used and provided the clearest linkage with therapeutic dose–response data [19, 43, 57]. Therefore, these endpoints represent realistic initial harmonization targets for bridging laboratory and clinical outcomes.

Emerging molecular and functional biomarkers, including *KRAS* mutant allele frequency [17, 70], DNA damage response (DDR) signatures [71, 78], γ H2AX immunofluorescence assays for DNA repair activity [80], and metabolic imaging correlates, such as FDG-PET or hyperpolarized MRI [84, 89], offer promising avenues for standardization but remain underreported. Prioritizing these molecular- and imaging-based readouts in future protocols could establish a unified translational framework linking PDO functional outputs with clinically actionable biomarkers, thereby strengthening reproducibility and predictive validity.

Precision without compromise

The emergence of PDO technology has catalyzed a paradigm shift in preclinical cancer modeling, particularly in PDAC, where traditional approaches have been inadequate for predicting clinical efficacy. Accumulating evidence suggests that PDOs are not only scientifically robust, but also ethical and regulatory-aligned tools for accelerating translational medicine.

Animal models, which are historically central to cancer research, often fail to predict human treatment outcomes accurately. The failure rate during translation from pre-clinical to clinical stages is notably high, with less than 8% of oncology drugs proving effective in humans after successful animal testing [10, 12]. This gap is due to the key differences between species in the TME, immune system structure, and drug processing. Conversely, PDOs retain the original tumor’s genomic, histological, and functional traits, including somatic mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* [33, 40, 61]. They reliably demonstrated the ability to predict patient responses to drugs, with studies showing positive and negative predictive values of 88% and 75%, respectively, for chemotherapy effectiveness [39, 70, 74, 86].

VandeWall et al. demonstrated that PDOs can undergo integrated multi-omic analysis, encompassing transcriptomics, proteomics, pharmacogenomics, and spatial imaging, to identify evolving biomarker-response links and uncover resistance mechanisms [105]. This versatility is enhanced by co-culture methods that incorporate immune and stromal cells, enabling the modeling of immunotherapy responses and interactions within the tumor microenvironment [18, 27, 65, 79, 94]. These features directly address the shortcomings of reductionist

models, making PDOs highly relevant for future clinical trials.

Recent regulatory changes have highlighted the importance of shifting toward human-relevant animal models. In 2024, the U.S. Food and Drug Administration (FDA) announced plans to phase out mandatory animal testing for monoclonal antibodies and other biologics, citing issues with predictive accuracy and increased trust in human-based technologies [106]. Simultaneously, the National Institutes of Health (NIH) pledged to increase funding for platforms such as organoids that better replicate human disease processes [107]. These regulatory statements align with the ethical recommendations of the AMA Journal of Ethics, which advocates the replacement of animal models with scientifically equivalent or superior human tissue-derived alternatives [108].

Thus, PDOs offer substantial ethical advantages. They can be obtained from patient biopsies or surgical resections with informed consent, and do not involve the moral burden of animal use, including pain, distress, and euthanasia. Moreover, their scalability, compatibility with high-throughput platforms, and direct derivation from human tumors enable their use in rapid turnaround functional diagnostics, offering tangible benefits to individual patients, while advancing generalizable knowledge.

Collectively, the scientific, regulatory, and ethical advantages of PDOs render them indispensable tools for precision oncology. High-performance studies have demonstrated their utility in modeling therapeutic responses, stratifying patient populations, and informing clinical decision-making [35, 36, 45, 65, 67, 74]. However, challenges persist, including standardization of protocols across institutions, reproducibility of multi-omic outputs, and scalability for large cohort applications. Nevertheless, these limitations are surmountable and are being actively addressed through harmonized consortium efforts and the development of organoid biobanks in Japan.

Conclusion

Although PDOs demonstrate strong predictive value and faithfully recapitulate PDAC biology, the present findings do not imply that they can fully replace *in vivo* validation. Although translatability scores did not show a significant benefit from xenograft or parallel PDX confirmation, this absence reflects limited reporting standardization, rather than definitive redundancy. PDOs offer scalable and ethically favorable advantages as human-relevant models; however, their predictive accuracy is maximized when complemented by *in vivo* or multisystem validation, particularly for assessing pharmacokinetics, immune dynamics, and toxicity. Thus, rather than serving as standalone surrogates, PDOs should be viewed as central components within an integrated translational

framework that combines molecular fidelity and physiological validation. A harmonized approach incorporating organoid–animal–clinical cross-validation will more accurately capture therapeutic efficacy and accelerate bench-to-bedside translation of PDAC discoveries.

PDOs offer promise as functional diagnostics and potential pre-enrollment screening tools, and their integration into frontline PDAC decision-making is constrained by the rapid clinical progression of the disease. Neoadjuvant therapy is typically initiated within 3–4 weeks of diagnosis, and first-line palliative regimens often begin within 2 weeks, leaving limited time for individualized pharmacotyping. In our review, the median reported turnaround for PDO establishment and drug testing was approximately 28 days (range, 14–56 days), suggesting that pre-treatment functional testing remains largely impractical for most advanced PDAC cases.

Given these constraints, near-term feasibility may be greater in adjuvant or maintenance settings, where treatment windows are less compressed, and PDO-guided secondary screening could refine subsequent therapeutic decisions. Emerging rapid-culture methods, including microfluidic bioreactors and accelerated growth media, have reduced establishment times to 10–14 days in select studies [27, 63, 89]; however, these approaches remain investigational. Therefore, PDOs currently function best as co-clinical or post-treatment validation tools, with future integration into prospective clinical workflows dependent on further reductions in culture and testing times.

Based on the aggregate evidence from this systematic analysis, several recommendations have emerged to enhance the translational relevance of future PDO-based PDAC studies (Fig. 4).

- I. *Integration with clinically validated biomarkers and outcomes:* PDO findings should be systematically linked to established clinical biomarkers (e.g., CAMulti-omicRECIST) and extended to multiomic analyses to capture the full complexity of tumor biology.
- II. *Incorporation of pharmacogenomics:* Germline and somatic pharmacogenomic data should be embedded into therapeutic response models to enable patient stratification and personalized therapeutic predictions.
- III. *Endpoint harmonization:* Surrogate and clinically meaningful endpoints must be standardized across PDO studies to better mimic clinical trial outcomes and to improve predictive validity.
- IV. *Co-clinical trial embedding:* PDO platforms should be prospectively integrated into clinical trial pipelines to serve as pre-enrollment screening tools,

Translational Integration of PDAC Patient-Derived Organoids (PDOs) into Clinical Care



Fig. 4 Workflow for integrating pancreatic ductal adenocarcinoma (PDAC) patient-derived organoids (PDOs) into clinical practice. Tumor tissue from biopsies is used to establish and expand PDOs with genomic, phenotypic, and histological profiling. PDOs undergo high-throughput drug screening and functional assays integrated with multi-omics data. Findings are reviewed by a multidisciplinary tumor board (oncology, radiology, surgery) to inform patient management. Applications include drug screening, spatial multi-omics, biomarker discovery, machine learning-based predictive analytics, and personalized medicine. Outputs (IC₅₀, tumor microenvironment modeling, artificial intelligence-driven (AI) predictions, using machine learning (ML)) generate a clinical feedback loop, enabling real-time therapy guidance and advancing precision oncology

real-time treatment predictors, or the basis for developing companion diagnostics.

Our systematic review refines this paradigm by revealing that across 95 PDAC PDO studies, resistance mechanisms are well recapitulated biologically but infrequently validated clinically. The median translatability score was 3.13 indicates moderate fidelity without consistent integration of patient-level outcomes or pharmacogenomic modeling. High-scoring studies uniquely combined multi-omic profiling, validated biomarkers (CA19-9, RECIST), and co-clinical trial alignment, features essential for bridging molecular resistance mechanisms to therapeutic prediction. However, domains such as pharmacogenetics and endpoint harmonization remain underdeveloped, which limits the translation of PDO findings into clinically actionable strategies.

This review highlights the duality of PDO research in PDAC: strength in laboratory feasibility, but fragility in clinical applicability. Although nearly all studies have successfully established PDOs and applied them to therapeutic testing, only a small fraction demonstrated high translatability, characterized by multi-omic integration, clinical concordance, and co-clinical validation.

To transform PDOs from experimental avatars into regulatory-grade platforms, the field must converge on harmonized endpoints, validated biomarkers, pharmacogenomic modeling, and systematic clinical trial integration.

Supplementary Information

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Supplementary material 1
Supplementary material 2
Supplementary material 3
Supplementary material 4
Supplementary material 5
Supplementary material 6
Supplementary material 7

Author contributions

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Declaration

Consent to participate

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Competing interests

Authors declare that they have no competing interests.

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