Digestive and Liver Disease 58 (2026) 581–590

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Toward precision chemotherapy in pancreatic ductal adenocarcinoma: molecular, transcriptomic and clinical determinants

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ARTICLE INFO

Article history:
Received 6 January 2026
Accepted 23 February 2026
Available online 16 March 2026

Keywords:
Pancreatic cancer
Chemotherapy
Personalization
Biomarkers
Trascriptome

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, with chemotherapy remaining the backbone of systemic treatment across disease stages. Although multi-agent regimens such as modified FOLFIRINOX and gemcitabine plus nab-paclitaxel–based combinations, with or without cisplatin and capecitabine (AG or PAXG), have improved outcomes in selected patients, therapeutic benefit remains highly heterogeneous and frequently limited by toxicity. This review summarizes evidence supporting shift from empirical chemotherapy selection toward a more personalized approach integrating tumour biology, molecular biomarkers, and patient-related factors, including pharmacogenetics, comorbidities, and toxicity profiles. We discuss established standards of care and highlight the strengths and limitations of available randomized data. The molecular landscape of PDAC, including homologous recombination repair deficiency, mismatch repair deficiency, and rare actionable oncogenic fusions, currently enables precision strategies in a minority of patients. The rapid development of KRAS-targeted therapies may extend molecularly guided treatment to a broader population. Beyond genomics, emerging biomarkers such as transcriptomic signatures, liquid biopsies, proteomic and metabolomic markers, and tumour microenvironment features may refine treatment selection and guide de-escalation or intensification strategies. Finally, we review biomarker-driven clinical trials and outline future directions for adaptive, biology-informed chemotherapy. Integrating molecular and clinical data into routine care may enable a more rational use of chemotherapy and improve outcomes in PDAC.

1. Introduction - standard of care

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers worldwide, ranking as the fourth leading cause of cancer-related death in men and the third in women [1]. Its incidence continues to rise by approximately 1 % annually, and despite modest improvements over the past three decades, the 5-year survival rate remains well below 15 %, largely due to late diagnosis, early metastasis, and poor response to systemic therapy [1]. Over 80 % of patients present with locally advanced or metastatic disease at the time of diagnosis, precluding curative surgery [2]. Even among those who undergo radical resection, recurrence occurs in approximately 85 % of cases, reflecting the aggressive biology of PDAC [3,4].

Management is mainly guided by the disease stage and resectability [3,4]. According to NCCN guidelines, upfront surgery remains appropriate for resectable (R) PDAC when there are no clear high-risk features; however, neoadjuvant systemic therapy is an accepted option and is often favored when high-risk features suggest an increased likelihood of margin-positive resection or early systemic relapse, ideally within a multidisciplinary strategy [4]. ESMO similarly supports upfront surgery followed by adjuvant chemotherapy for clearly R PDAC with a high

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https://doi.org/10.1016/j.dld.2026.02.020

probability of R0 resection, while for borderline resectable (BR) disease it recommends neoadjuvant systemic therapy over immediate surgery [3]. Though, because of the high recurrence risk after surgery, neoadjuvant therapy is increasingly adopted for both R and BR tumours. This strategy enables early systemic therapy, improves R0 resection rates, and optimizes patient selection for surgery and therapy completion [5,6]. The phase III PREOPANC trial demonstrated a survival advantage for neoadjuvant gemcitabine based chemoradiation over upfront surgery (5-year OS 20.5 % vs. 6.5 %) in R and BR PDAC patients [7]. PREOPANC-2 found comparable outcomes between total neoadjuvant mFOLFIRINOX and gemcitabine based chemoradiotherapy [8], while in the CASSANDRA trial, PAXG showed superior 3-year event-free survival versus mFOLFIRINOX in a mixed R and BR PDAC population [9]. The PREP-02/JSAP-05 trial confirmed that neoadjuvant gemcitabine plus S-1 improved OS compared with upfront surgery in R PDAC [10]. For anatomically resectable tumours, biological risk factors, particularly elevated CA 19–9, help identifying patients who may benefit from neoadjuvant rather than upfront surgery [11]. CONKO-001 and ESPAC-4 established adjuvant gemcitabine ± capecitabine as effective options [12,13], whereas PRODIGE 24 demonstrated a major survival benefit with modified FOLFIRINOX (median OS 54.4 vs. 35.0 months) compared to gemcitabine monotherapy [14]. The Japanese JASPAC-01 trial also confirmed the superiority of S-1 over that of gemcitabine [15]. Systemic chemotherapy remains the mainstay of treatment for metastatic PDAC. The combination of gemcitabine plus nab-paclitaxel (OS 8.5 vs. 6.7 months) [16] and FOLFIRINOX are usually considered first-line standards in fit patients (OS 11.1 vs. 6.8 months) [17,18]. However, in a phase 2 randomized trial of metastatic disease, PAXG was superior to gemcitabine plus nab-paclitaxel [19]. On the other hand, in patients with locally advanced, non-resectable disease, mFOLFIRINOX is not superior to gemcitabine in terms of overall survival, and evidence in this setting are extremely weak [20].

NALIRIFOX has recently shown promising results versus gemcitabine plus nab-paclitaxel (OS 11.1 vs. 9.2 months), albeit this trial included patients with gBRCA1–2 pathogenic variants, whose disease is particularly sensitive to platinum-containing regimens, thus making it impossible to exclude that the observed clinically negligible benefit on the whole population is actually driven by this subgroup of patients [21]. Gemcitabine monotherapy remains an option for frail patients [22].

In the second-line setting, liposomal irinotecan-based regimens are generally preferred over oxaliplatin-based combinations owing to the contrasting results of the PANCREOX and CONKO-003 trials [23].

In summary, PDAC remains a difficult disease to treat, characterized by late presentation, aggressive biology, and limited treatment options. However, the growing integration of molecular stratification, novel targeted therapies, and personalized systemic strategies offers renewed optimism for improving patient outcomes in this setting.

2. Molecular landscape of pancreatic cancer

PDAC is relatively refractory to standard treatments, driven by a characteristic but heterogeneous genomic landscape that informs the differential sensitivity to therapy. Integrating recurrent driver mutations with transcriptomic subtypes yields a pragmatic framework for precision approaches that can stratify patients for targeted agents, DNA damage–directed therapies, and immune-modulatory strategies.

The somatic mutational landscape of PDAC is dominated by four major genetic drivers: activating KRAS mutations are present in >90 % of patients, and the other frequent mutations lead to inactivation of the tumor suppressor genes TP53, CDKN2A, and SMAD4 [24]. These alterations shape tumour biology and correlate with poor prognosis and chemoresistance in specific contexts. Beyond the “big four,” alterations (germline or somatic) in homologous recombination repair (HRR) genes (BRCA1/2, PALB2, and ATM) are present in 10–15 % of patients [25]. Although KRAS remains the central oncogenic node, rare fusions (e.g., NTRK and NRG1 fusions) and receptor alterations open immediate therapeutic opportunities.

Multiple transcriptome-based classification schemes capture biological programs linked to differentiation state, stromal interactions, and immune composition [26]. These subtypes are not merely prognostic but also reflect different responses to treatment. However, subtype assignment is affected by technical variables (sample purity and platform differences) and intratumoral heterogeneity. Moreover, both the mutational and transcriptomic repertoires of PDAC change over time to adapt to the pressure of treatment and metastatic niches. In this context, robust and clinically deployable classifiers remain an active challenge [27]. Additionally, many classifiers have been developed using clinical samples of surgically resected PDAC, while their validation on Endoscopic Ultrasound (EUS)-guided biopsies is relatively limited [28,29].

Prospective integrative sequencing efforts (e.g., whole-genome and transcriptome profiling in trial cohorts) have begun to link molecular features to sensitivity to first-line regimens. For example, comprehensive analyses from the COMPASS program [30] demonstrated that homologous recombination-deficient tumors form a distinct prognostic group and that basal-like transcriptional programs are associated with poorer outcomes in mFOLFIRINOX chemotherapy.

3. The clinical concept of personalized chemotherapy

Chemotherapy is the only systemic therapeutic approach currently available for patients with PDAC. Poor prognosis, relevant symptom burden, and limited pharmacological armamentarium require appropriate tailoring of chemotherapeutic options based on several factors, including but not limited to disease stage, genetic and transcriptomic factors, patient age, characteristics, comorbidities, and potential toxicities. All these variables must be considered in the perspective of personalized” chemotherapy.

3.1. UGT and DPYD mutations

Fluoropyrimidines and irinotecan are widely used to treat patients with PDAC. The catabolism of fluoropyrimidines is due to dihydropyrimidine dehydrogenase (DPD). Functional mutations in the DPD gene (DPYD) cause structural alterations in the DPD enzyme that induce a reduction in its activity or complete inactivation, with implications in terms of toxicity (myelosuppression, gastrointestinal and cardiac toxicity, and hand-foot syndrome) [31]. Accordingly, pre-treatment screening for DPYD mutations is strongly recommended in patients undergoing fluoropyrimidine therapy [32].

The active metabolite of irinotecan is SN-38. SN-38 is inactivated into SN-38 glucuronide by UDP-glucuronosyltransferase 1A1 (UGT1A1) [33]: genetic polymorphisms in UGT1A1 determine interpatient variability in drug clearance and toxicity (neutropenia, diarrhoea). Patients with *28/*28 or *6/*6 homozygous variants must undergo a dose reduction of 70 %, while heterozygosity does not require dose reduction [34]. DPYD and UGT1A1 variants can be considered predictive factors in PDAC for fluoropyrimidine- and irinotecan-related adverse events (AEs), and they also carry prognostic significance. High intratumoral DPD expression is associated with worse survival [35], and elevated UGT1A1 transcriptional levels similarly correlate with poor prognosis [36].

3.2. Patients' characteristics

Age and performance status (PS) should guide clinicians in treatment selection. Evidence from most phase II–III trials comparing chemotherapy regimens supports triplet or quadruplet combinations in patients < 75 years old with an ECOG PS ≤1, whereas those with an ECOG PS >1 are generally better suited to doublet regimens or monotherapy. Nutritional status influences both the tolerability and continuity of chemotherapy and can be viewed as an integral component of patient fitness [37].

Currently, there are no dedicated studies focusing on patients over 75 years of age, and evidence is lacking regarding differential chemotherapy responses according to sex. Although the association between the exposome and pancreatic cancer has been extensively investigated [38], current evidence does not support the differentiation of chemotherapy selection according to different environmental risk factors.

Regarding race, several studies have investigated the role of a 5-fluorouracil prodrug, S1, in the Asian population: with comparable OS, S1 represents a valid alternative to gemcitabine, as demonstrated by the JASPAC-01 [39] and GEST [40] trials in the adjuvant and first-line settings, respectively.

3.3. Comorbidities and potential toxicities

Comorbidities and drug-related toxicities are key determinants in selecting the most appropriate chemotherapy regimen. Cisplatin and oxaliplatin exhibit distinct toxicity profiles. Within the PAXG regimen, cisplatin administered at a moderate dose is not associated with a high incidence of its hallmark toxicities, such as nephrotoxicity or ototoxicity [41]. In contrast, oxaliplatin is mostly characterized by peripheral neuropathy, manifesting acutely as cold-induced reversible paraesthesia or chronically as a cumulative sensory neuropathy (grade 3–4 in up to 25 % of patients) [42]: this implies that oxaliplatin should be avoided in patients who present pre-existing peripheral nerve damage.

The same consideration applies to nab-paclitaxel, in which peripheral neurological toxicity occurs in up to 54 % of patients (any grade) and reaches 17 % for grade 3 events [43]. This appears to be more frequent than the neurotoxicity observed with oxaliplatin. Central neurotoxicity is extremely rare (5 %), although slightly more common than that associated with oxaliplatin. Therefore, nab-paclitaxel should be avoided in patients with pre-existing peripheral neuropathy or underlying central nervous system disorders.

Chest pain, coronary vasospasm, and myocardial infarction are well-recognized AEs associated with fluoropyrimidines, with 5-FU demonstrating a higher incidence of cardiotoxicity compared with capecitabine [44]. Conversely, diarrhoea, both in frequency and severity, is more common with capecitabine, with grade 3–4 diarrhoea reported in up to 20 %, versus 10 % with 5-FU. These data derived from retrospective analyses including various tumour types; in pancreatic cancer, fluoropyrimidines are frequently administered as part of combination regimens and with different concentrations, and the observed incidence of both cardiotoxicity and diarrhoea is generally lower. Overall, patients with a history of heart disease or chronic diarrhoea are not candidates for these treatments.

Gemcitabine-related pulmonary toxicity, including interstitial pneumonitis and exacerbation of pre-existing pulmonary diseases, is rare (2–5 %) [45]. However, this chemotherapeutic agent should be avoided in patients with a history of severe lung disease.

Irinotecan and nal-irinotecan are both associated with diarrhoea (acute diarrhoea is more typical of irinotecan, whereas delayed-onset one is more common with nal-irinotecan) [46]. Consequently, their use should be approached with caution in patients with pre-existing gastrointestinal disorders involving diarrhoea.

Finally, to further minimize treatment discontinuation, personalized schedules can also be adopted: The AG regimen may be administered every two weeks with a one-week break [47] or on a biweekly schedule [48] to reduce hematologic toxicity without compromising treatment efficacy.

4. Molecular biomarkers for personalization

Compared with other solid tumours, only a small proportion of PDAC patients currently benefit from molecularly targeted therapies. Clinically actionable genomic alterations include defects in DNA damage repair (DDR) genes, microsatellite instability, rare oncogenic fusions such as NTRK or NRG1, and the recently identified druggable KRAS G12C mutation. Although these biomarkers are present in only a minority of cases, they represent an important step toward precision oncology and the incorporation of comprehensive molecular profiling into routine PDAC management strategies. The main established molecular predictive biomarkers and their corresponding targeted therapeutic implications in PDAC are summarized in Table 1.

4.1. BRCA1/2, PALB2 and other HRR gene mutations

Homologous recombination repair (HRR) deficiency is one of the best-characterized molecular vulnerabilities in PDAC. In a large systematic review encompassing more than 21,000 cases, Casolino et al. reported germline and somatic mutation rates of 0.9 % for BRCA1, 3.5 % for BRCA2, 0.2 % for PALB2, and 2.2 % for ATM [49]. When genomic scars and mutational signatures were used to define homologous recombination deficiency (HRD), its prevalence increased markedly to 24–44 % of PDACs, suggesting that functional HRD can exist even in the absence of canonical HRR gene mutations.

These mutations lead to increased sensitivity to DNA damaging agents [50,51], such as platinum salts [52]. Retrospective studies have reported the antitumor activity of platinum agents in patients with HR deficiency (HRD), showing improved outcomes, including overall survival (OS), compared to wild-type patients [53]. However, these studies were limited by their small sample size, non-randomized design, inclusion of mixed disease stages, and restriction of HRD assessment only to BRCA and PALB2.

In another retrospective Italian survey enrolling patients at various disease stages who had completed a first course of systemic therapy, germline BRCA1–2 (gBRCA1–2) was analyzed [54]. Platinum-based triplet (81 %) and quadruplet (73 %) regimens yielded higher RECIST response rates than the nab-paclitaxel plus gemcitabine (AG) regimen (41 %). A similar trend was observed for Carbohydrate Antigen 19.9 (CA 19.9) reduction: two-thirds of metastatic patients treated with triplet or quadruplet regimens achieved a >89 % reduction at nadir, compared with 33 % and 45 % in those receiving oxaliplatin-based doublets or AG, respectively. Median progression-free survival (mPFS) was also longer with triplet/quadruplet therapy (>10.8 months) than with AG (6.4 months) therapy.

Another recent study analyzed the second-line chemotherapy setting in gBRCA1–2 patients [55]. The results showed a significant improvement in mPFS (8.8 vs. 3.7 months) and a doubled objective response rate (ORR, 48 % vs. 24 %) in the platinum-based second-line subgroup compared to the platinum-free group, suggesting the benefit of platinum salts in the second line.

Similarly, these tumours display sensitivity to platinum compounds and PARP inhibition. The phase III POLO trial provided prospective validation of this concept: among patients with metastatic germline BRCA1/2-mutated PDAC who had not progressed after at least 16 weeks of platinum-based chemotherapy, maintenance olaparib significantly prolonged PFS (7.4 vs. 3.8

Table 1
Established Predictive Biomarkers and Corresponding Targeted Therapeutic Implications in Pancreatic Ductal Adenocarcinoma.

Biomarker	Involved gene(s)	Alteration type	Prevalence in PDAC	Therapeutic implication	Drug	Key references
HRR	*BRCA1*	Germline/somatic mutations	0.9 %	Predicts sensitivity to platinum and PARP inhibitors	*Platinum-based* regimens, olaparib, rucaparib	48, 55
HRR	*BRCA2*	Germline/somatic mutations	3,5 %	Predicts sensitivity to platinum and PARP inhibitors	*Platinum-based* regimens, olaparib, rucaparib	48, 55
HRR	*PALB2*	Germline/somatic mutations	0,2 %	Predicts sensitivity to platinum and PARP inhibitors	*Platinum-based* regimens, rucaparib	48, 57
HRR	*ATM*	Germline/somatic mutations	2,2 %	Predicts sensitivity to platinum	*Platinum-based* regimens	48
KRAS	*KRAS*	Somatic mutations (mostly at codon 12)	≈90 % (G12D ~40 %, G12V ~30 %, G12C 1–2 %)	Direct therapeutic targeting possible	Sotorasib and adagrasib (G12C), MRTX1133 and RMC-6236 (non-G12C variants)	58, 59. 60
NTRK	*NTRK1/2/3*	Gene fusions	<0.5 %	Highly responsive to TRK inhibitors	Larotrectinib, entrectinib	62
NRG1	*NRG1*	Gene fusions	0.2–0.5 %, enriched in KRAS wild-type PDAC	Responsive to bispecific HER2xHER3 antibody	Zenocutuzumab	64
Microsatellite instability	MMR genes	Mismatch Repair Deficiency (dMMR)	<1 %	Predicts benefit from immunotherapy	Pembrolizumab	98

Abbreviations: ATM, ataxia telangiectasia mutated; BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; HRR, homologous recombination repair; KRAS, Kirsten rat sarcoma viral oncogene homolog; MMR, mismatch repair; NRG1, neuregulin 1; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PDAC, pancreatic ductal adenocarcinoma.

months; HR 0.53) [56]. Real-world data from Italian cohorts further confirmed improved OS with olaparib in patients with BRCA-mutated cases [57]. Other PARP inhibitors have also shown similar results. In a single-arm phase II study, Reiss et al. evaluated rucaparib maintenance in platinum-sensitive PDAC harbouring germline or somatic BRCA1/2 or PALB2 variants, reporting a disease control rate of 59 %, median PFS of 13.1 months, and median OS of 23.5 months [58]. Notably, durable responses were also observed in tumours with somatic, rather than germline mutations, underscoring the broader relevance of HRD biology. Collectively, these findings define a molecularly distinct subset of PDAC with enhanced sensitivity to DNA-damaging agents and PARP inhibitors and support the need for comprehensive germline BRCA testing in all patients with PDAC, irrespective of disease stage, to inform and guide appropriate therapeutic decision-making.

4.2. KRAS mutations

Activating mutations in KRAS are a molecular hallmark of PDAC, present in approximately 90 % of tumours [59]. Most mutations involve codon 12 (G12D, G12V, G12R, or G12C), resulting in the constitutive activation of downstream signalling pathways. For decades, KRAS was considered “undruggable.” However, this perception changed with the development of inhibitors targeting KRAS G12C, such as sotorasib and adagrasib. In PDAC, KRAS G12C mutations occur in only 1–2 % of cases. Early clinical trials reported the modest efficacy of KRAS 12C inhibitors (objective response rates of approximately 20 %, PFS 4–5 months) [60,61]. In contrast, KRAS G12D (≈40 %) and KRAS G12V (~30 %) variants are much more prevalent. Next-generation inhibitors, including MRTX1133 and RMC-6236, have demonstrated encouraging preclinical activity and early clinical responses, renewing optimism that direct KRAS targeting may soon become feasible for a broader proportion of PDAC patients [62].

4.3. NTRK and NRG1 fusions

Gene fusions involving NTRK1/2/3 occur in fewer than 0.5 % of PDACs cases but represent highly actionable oncogenic drivers. The TRK inhibitors larotrectinib and entrectinib have yielded exceptional and durable responses across multiple tumour types, with overall response rates exceeding 75 %, although PDAC-specific experience remains limited [63,64]. In parallel, NRG1 fusions, detected in approximately 0.2–0.5 % of cases, define a distinct subgroup of KRAS wild-type PDAC characterized by aberrant HER2/HER3 signalling. These tumours have shown meaningful and sustained responses to the bispecific antibody zenocutuzumab, as observed in the phase I/II eNRGy trial [65].

4.4. Microsatellite instability (MSI) and mismatch repair deficiency (dMMR)

MSI results from dMMR and produces a hypermutated, immunogenic phenotype that is susceptible to immune checkpoint blockade therapy. The phase II KEYNOTE-158 trial demonstrated the efficacy of pembrolizumab in MSI-H/dMMR solid tumors, including PDAC, achieving an overall response rate of approximately 18 % [66]. Although the frequency of MSI-H/dMMR in PDAC is low (<1 %), routine testing might identify the rare subset of PDAC patients who are eligible for immunotherapy.

Taken together, these biomarkers exemplify the ongoing transition of PDAC management from a purely histology-based paradigm to a more individualized, molecularly driven approach. While most patients still lack actionable targets, expanding access to high-quality molecular profiling and precision oncology trials offers a tangible opportunity to improve outcomes in this highly lethal malignancy.

5. Novel biomarkers for personalization

Beyond established biomarkers, which currently guide treatment decisions in only a small subset of patients, there is an urgent need for novel predictive and prognostic tools applicable to a broader PDAC population. Therapeutic personalization requires biomarkers capable of capturing tumor heterogeneity and dynamic evolution under treatment pressure. Complementary approaches have emerged along four major axes: liquid biopsies, predictive transcriptomic signatures, proteomic and metabolomic markers, and tumor microenvironment-derived indicators. Together, these modalities have the potential to refine initial treatment selection, enable de-escalation strategies, anticipate resistance, and prioritize enrolment in innovative clinical trials.

Table 2
Clinically Relevant Transcriptomic Signatures Predicting Chemotherapy Sensitivity in Pancreatic Ductal Adenocarcinoma.

Entity name	Category	Biological rationale	Predicted treatment sensitivity	Clinical setting	Sample type	Level of clinical validation	Key references
Transcriptomic subtypes (*classical* vs *basal-like*)	Transcriptomic signature	Tumor differentiation state and transcriptional programs influencing global chemosensitivity	Relative chemosensitivity (non drug-specific)	All disease stages	Resected tumors and diagnostic biopsies	Multiple retrospective cohorts	72. 73
GemPred	Transcriptomic signature	Baseline transcriptional programs associated with intrinsic sensitivity to gemcitabine	Gemcitabine	Mainly adjuvant	Resected tumor tissue	Retrospective validation in multiple cohorts, including PRODIGE-24	26, 81
GemCore	Transcriptomic signature	Transcriptomic determinants of gemcitabine response in advanced PDAC	Gemcitabine	Metastatic PDAC	Resected tumor tissue and EUS-guided FNA biopsies	Retrospective validation in advanced PDAC cohorts	83
Pancreas-View	Integrated transcriptomic signature	Integration of multiple drug-specific transcriptomic predictors with stromal and immune correction	Gemcitabine and FOLFIRINOX components	Adjuvant and metastatic PDAC	Resected tumor tissue and EUS-guided FNA biopsies	Retrospective validation and ongoing prospective trials	84. Ongoing clinical trials: PACSign-01, GemSign-01, NeoPREDICT

Abbreviations: EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; PDAC, pancreatic ductal adenocarcinoma.

5.1. Liquid biopsies

Liquid biopsies represent a rapidly evolving field that provides minimally invasive access to tumor-derived material and enables longitudinal monitoring of disease biology. They have been investigated in pancreatic ductal adenocarcinoma (PDAC) to overcome the limitations of tissue biopsies, which are invasive, prone to sampling bias, and often insufficient in quantity/quality for comprehensive molecular analyses. Among liquid biopsy markers, circulating tumour DNA (ctDNA) is the most advanced. Detection rates vary depending on the disease stage, with ctDNA identifiable in approximately 10–30 % of patients with localized PDAC and only 60–70 % of advanced cases. Quantitative ctDNA levels correlate with tumour burden and are consistently associated with prognosis across stages [67,68]. Importantly, ctDNA positivity after surgical resection can precede radiological evidence of recurrence by several months, providing a window for earlier therapeutic interventions or tailoring surveillance strategies [69]. These data support ctDNA as a marker of minimal residual disease and an early indicator of treatment failure. However, several barriers to clinical implementation remain, including inter-assay variability, relatively low sensitivity in early disease due to limited tumour shedding, hepatic filtration through portal venous drainage of the tumour, lack of standardized workflows, and issues of cost and accessibility. The limited sensitivity of circulating tumour cells (CTCs) in PDAC arises from the same factors.

Exosomes provide an additional dimension. These extracellular vescicles (EVs) encapsulate nucleic acids, proteins, and metabolites that reflect tumour-specific processes. In PDAC, exosome-derived RNA signatures have been shown to enhance tumour detection. For instance, a panel of eight microRNAs enriched in PDAC EVs achieved a diagnostic accuracy of 97 % when combined with CA19–9 in early-stage disease, significantly outperforming CA19–9 alone [70]. These results suggest that exosomal markers can complement conventional biomarkers for early detection and stratification. In addition, analysis of EV-bound DNA markedly enhances the detection sensitivity of tumour mutations compared to free ctDNA [71].

Other innovative approaches such as PAC-MANN, which detects protease activity in plasma, further extend the scope of liquid biopsies. When combined with CA19–9, PAC-MANN achieved 85 % sensitivity and 96 % specificity for stage I PDAC, indicating its potential for early diagnosis and real-time treatment monitoring [72]. Circulating proteomic panels are under active investigation for non-invasive diagnosis and dynamic monitoring.

Collectively, while tumour tissue biopsies remain indispensable for establishing a definitive cancer diagnosis, liquid biopsies are powerful tools that provide dynamic and non-invasive insights into tumour biology. Application of these liquid biopsy elements is particularly promising for PDAC screening, early detection, and determination of KRAS status. Although they are not yet the standard of care, their integration into multimodal predictive frameworks could reduce the reliance on invasive tissue sampling and enhance treatment personalization in PDAC.

5.2. Transcriptomic signatures

Transcriptomic profiling has evolved from early molecular subtype classification to clinically actionable predictive tools. This trajectory reflects the need to stratify patients more effectively in a setting where cytotoxic chemotherapy remains the cornerstone of treatment, although outcomes vary widely. Early transcriptomic classifiers have distinguished classical and basal-like subtypes [73–75]. Classical tumours are characterized by expression of adhesion and epithelial differentiation genes, better prognosis, and relatively higher sensitivity to fluoropyrimidine-based regimens. Basal-like tumours, enriched for squamous programs, are associated with poor prognosis and chemotherapy resistance.

The COMPASS trial prospectively analyzed patients with advanced PDAC who underwent first-line combination chemotherapy, demonstrating improved RECIST response (34 % vs. 8 %) with better PFS (6.2 vs. 2.3 months) and OS (10 vs. 6.3 months) in the classical subtypes compared to the basal-like ones; the best PFS was reached in the classical subtypes treated with mFOLFIRINOX, the worst in the basal-like group treated with the same regimen (8.5 vs. 2.7 months, respectively) [76]. Basal-like patients do not benefit from triplets in the neoadjuvant setting [77]. The PurIST classifier enabled robust single-sample subtype assignment across cohorts, whereas GATA6 immunohistochemistry was proposed as a pragmatic surrogate [78–80]. These classifiers improved biological understanding but were not designed to provide drug-specific predictions, limiting their clinical impact on treatment selection.

Functional models, such as patient-derived organoids (PDOs), have provided additional insights into chemosensitivity. PDOs can reproduce patterns of drug response observed clinically and have been useful for late-line testing and drug repurposing efforts. However, their limitations, such as long establishment times, modest success rates, and lack of applicability for first-line therapy, reduce their clinical utility [81]. Newer approaches, including tumor-on-chip platforms and 3D bioprinting, may accelerate phenotypic testing, but they remain experimental.

Predictive transcriptomic signatures have progressively evolved from single-drug predictors to integrated multi-drug platforms designed to provide clinically actionable guidance. These tools integrate baseline expression data from preclinical models and clinical samples with outcomes using multivariate statistics and machine learning to predict drug sensitivity. *GemPred* was the first predictive transcriptomic signature in PDAC, designed to identify patients likely to benefit from adjuvant gemcitabine. Developed from patient-derived cultures and xenografts, *GemPred* was retrospectively validated in multiple cohorts, including analyses from the pivotal PRODIGE-24/CCTG PA6 trial. It consistently identified patients who derived survival benefits from gemcitabine while showing no prognostic effect in untreated cases, confirming its predictive nature [82,83]. The *GemCore* signature was developed to guide gemcitabine use across both advanced and resected PDAC, with demonstrated robustness in small biopsy specimens including fine-needle aspirates, it stratified patients into responders and non-responders with a clinically meaningful separation [84]. By addressing the practicalities of metastatic sampling, *GemCore* has brought predictive transcriptomics closer to clinical applicability. The most comprehensive effort is the *Pancreas-View* tool, which integrates *GemCore* with additional drug-specific signatures such as *5FUCore, OxaCore*, and *IriCore*, allowing prediction of sensitivity to all components of FOLFIRINOX as well as gemcitabine. The incorporation of AI-based refinement enabled the correction of stromal and immune contributions within bulk transcriptomes [85–87]. Retrospective validation demonstrated that patients treated in line with predicted sensitivity had significantly better survival, while ~27 % of patients were classified as multidrug resistant with particularly poor outcomes [85].

From a practical perspective, *GemPred* represents the first generation of predictive transcriptomic tools and provided proof-of-concept in the adjuvant setting. *GemCore* subsequently demonstrated robustness across both resected and metastatic tumours and compatibility with small biopsy specimens, effectively extending predictive applicability beyond surgical cohorts. *Pancreas-View* currently constitutes the most comprehensive and clinically versatile platform, integrating multi-drug sensitivity prediction and AI-assisted refinement, and is progressively emerging as the most actionable transcriptomic framework across disease stages. Importantly, while *GemCore* and *Pancreas-View* have accumulated extensive retrospective validation across independent cohorts and clinical trial datasets, their broad implementation still depends on prospective confirmation and the availability of standardized analytical infrastructures. The most clinically relevant and currently translatable predictive transcriptomic signatures for chemotherapy sensitivity in PDAC are summarized in Table 2.

The clinical implications of transcriptomic signatures include supporting first-line optimization, which is critical given that fewer than half of patients with advanced PDAC receive second-line therapy [85], and enabling de-escalation strategies by allowing patients predicted to be gemcitabine-sensitive to avoid the toxicity of FOLFIRINOX without compromising efficacy [82]. They also allow for the early identification of multidrug chemoresistant profiles, guiding patients toward experimental or targeted therapies [85]. In real-world clinical practice, additional implementation barriers must be considered. Turnaround time for transcriptomic assays may conflict with the need for rapid therapeutic decisions, particularly in advanced disease. Moreover, the quality and quantity of RNA obtained from EUS-guided biopsies can be variable and sometimes insufficient for robust analysis. The feasibility of performing serial re-biopsies during treatment is also limited by procedural risks, patient condition, and logistical constraints. These factors contribute to the current gap between promising transcriptomic evidence and routine clinical integration [88]. Several prospective trials, such as PACSign-01 (NCT05475366), GemSign-01 (NCT06046794), and NeoPREDICT, are underway to validate their feasibility and clinical benefits [89]. From a clinical standpoint, predictive transcriptomic signatures are progressively transitioning from exploratory tools to decision-support instruments. Among available tools, integrated multi-drug platforms are increasingly positioned to inform multidisciplinary therapeutic decisions across both resectable and advanced PDAC. However, they are still under clinical evaluation and are not validated for routine use.

5.3. Proteomic and metabolomic markers

Beyond transcriptomics, proteomics, and metabolomics, which capture functional states and adaptive rewiring that influence therapy response in PDAC. These approaches probe the biochemical tumour phenotype, complementing genetic and transcriptomic analyses. Proteomic studies of tumour tissue, plasma, and secretomes have identified markers of tumour progression, metastatic potential, and chemoresistance. Secretome profiling highlights proteins that are actively released into the extracellular space. Analyses of PDAC secretomes revealed recurrent enrichment of extracellular matrix components, growth factors, and vesicle-associated proteins, nominating them as biomarkers of aggressiveness and mediators of treatment response.

Metabolomic profiling has revealed profound metabolic reprogramming in PDAC. Two levels of metabolic reprogramming can be distinguished: tumour cell-intrinsic alterations and systemic cachexia driven by the tumour, characterized by hypercatabolism, muscle wasting, and adipose tissue depletion. In metabolomics, this can also encompass the gut microbiota and microbially derived metabolites, adding an additional layer of biologic information at the host–tumour interface. Tumours exhibit altered glutamine metabolism, lipid synthesis and oxidation, and redox adaptation [90–92]. The integration of metabolomic data with genomic features has identified vulnerabilities, including the deletion of MTAP, which creates synthetic lethality with PRMT5 inhibition. Pharmacological inhibition of PRMT5 is currently being clinically evaluated in MTAP-deficient tumors, providing a paradigm for genomically guided metabolic targeting [93]. Although still largely investigational, proteomic and metabolomic markers have the potential to enrich the multimodal predictive frameworks. By combining genomic, transcriptomic, proteomic, and metabolomic information, it may be possible to achieve more precise patient stratification, refine prognosis, and identify metabolic or signalling dependencies suitable for targeted therapy.

5.4. Tumor microenvironment indicators (stroma, immune cells)

The tumor microenvironment (TME) in PDAC is a defining feature of the disease and a major determinant of treatment outcome. It is characterized by dense desmoplasia and profound immune suppression, both contributing to therapeutic resistance.

Attempts to directly target stromal components have largely failed. Early strategies aimed to deplete desmoplasia to improve drug delivery; however, randomized trials combining Hedgehog pathway inhibition (vismodegib [94]) or hyaluronan degradation with pegvorhyaluronidase alfa (PEGPH20) [95] with chemotherapy

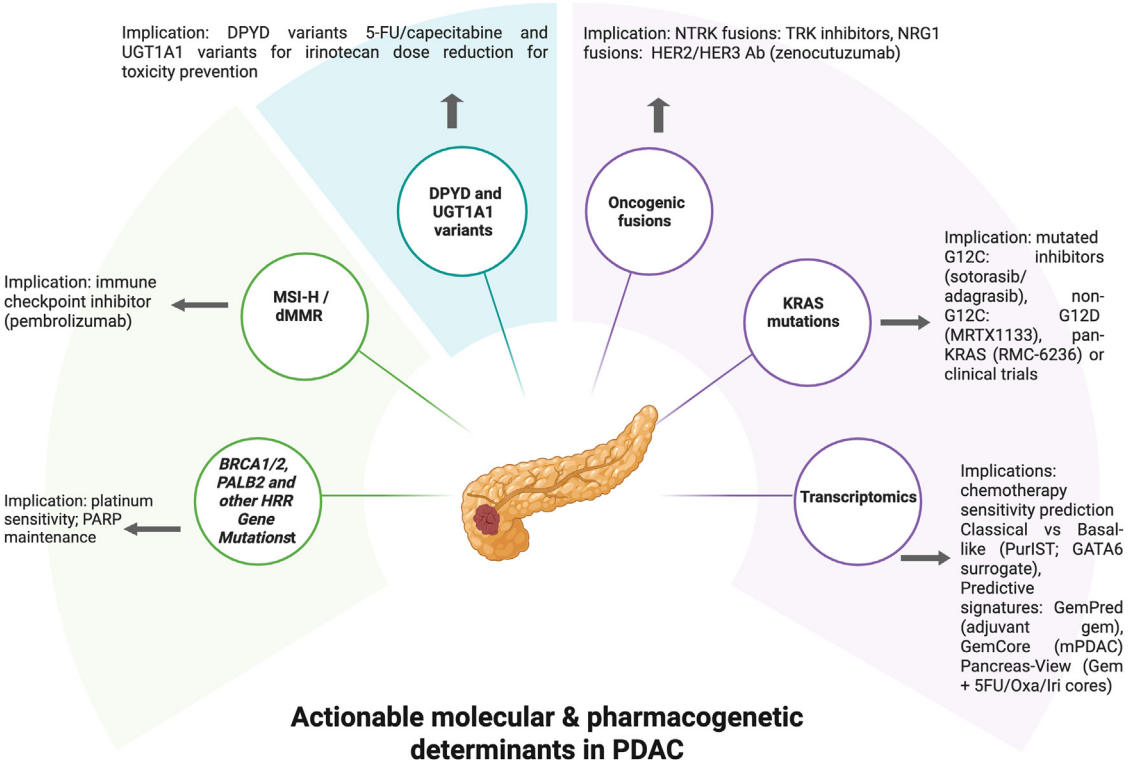

Fig. 1. Actionable molecular and pharmacogenetic determinants in PDAC. Key biomarker classes that can inform precision or tailored treatment are summarised. Homologous recombination repair deficiency (HRR/HRD; e.g., BRCA1/2, PALB2 and other HRR gene alterations) is associated with platinum sensitivity and supports consideration of PARP inhibitor maintenance in eligible patients. Microsatellite instability–high/deficient mismatch repair (MSI-H/dMMR) identifies the rare subgroup potentially benefiting from immune checkpoint inhibition. Rare oncogenic fusions (e.g., NTRK and NRG1) represent targets for TRK inhibitors and HER2/HER3-directed therapy (e.g., zenocutuzumab), respectively. In generally, KRAS mutations are prevalent in PDAC; rare KRAS G12C can be treated with G12C inhibitors, while non-G12C variants (including KRAS G12D and pan-KRAS strategies) are under clinical development. Transcriptomic subtypes (classical vs basal-like; PurIST and GATA6 surrogate) and predictive signatures (GemPred, GemCore, Pancreas-View) may refine chemotherapy sensitivity prediction. Host pharmacogenetic variants (DPYD for 5-FU/capecitabine; UGT1A1 for irinotecan) guide dose adaptation to reduce toxicity. Created in BioRender. Garajova, I. (2026) https://BioRender.com/5cjzmuj.

did not improve survival. These results underscored the functional complexity and context-dependent roles of the stroma.

Cancer-associated fibroblasts (CAFs), the predominant stromal population, are heterogeneous and functionally diverse. Beyond myCAF and iCAF subsets, single-cell and multiomic analyses have identified additional populations, including periostin-positive CAFs associated with M2 macrophage recruitment and immunosuppression [96,97]. Notably, preclinical studies demonstrated that depletion of specific CAF subsets or reduction of collagen content can paradoxically accelerate tumor progression, indicating tumor-restraining roles for certain stromal components [98,99]. These findings argue against indiscriminate stromal ablation and support selective stromal reprogramming as a more rational therapeutic strategy.

From an immunological perspective, PDAC is dominated by immunosuppressive populations, including regulatory T cells, M2-polarized macrophages, and myeloid-derived suppressor cells, with limited effector T-cell infiltration [100]. This “cold” microenvironment, characterized by low tumor mutational burden, impaired antigen presentation, and stromal barriers to T-cell trafficking, explains the limited efficacy of immune checkpoint inhibitors (ICIs) in unselected patients. Multiple trials evaluating PD-1, PD-L1, or CTLA-4 blockade, alone or in combination, have failed to demonstrate meaningful survival benefit in the broader PDAC population [101–105].

In contrast, rare molecular subsets with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), representing approximately 1–2 % of cases, can achieve clinically relevant responses to PD-1 blockade [106]. These data emphasize the importance of molecular profiling while highlighting the intrinsic resistance of most PDACs to checkpoint inhibition alone. Accordingly, strategies aimed at remodeling the immune microenvironment are under active investigation.

CD40 agonists, which activate antigen-presenting cells and enhance T-cell priming, have shown encouraging activity in combination with chemotherapy, providing proof of concept that modulation of innate immunity may partially overcome immune resistance [107–109]. Additional approaches targeting innate immunity, including STING and Toll-like receptor agonists, aim to convert the immunologically “cold” TME into a more inflamed and responsive state.

Therapies targeting myeloid populations (e.g., CSF1/CSF1R and CCL2/CCR2 inhibition, CD47 blockade), stromal signaling pathways (TGF-β and FAK), and metabolic dependencies within the TME are also being explored to enhance immune infiltration and function. mRNA-based vaccines and other neoantigen-targeting platforms are under active investigation, particularly in the adjuvant setting where immunosuppression may be less pronounced [110]. Adoptive cell therapies, including CAR-T cells directed against PDAC-associated antigens, are also in clinical evaluation, though their efficacy remains limited by the hostile microenvironment.

Overall, these data highlight the multifaceted and context-dependent role of the TME in PDAC progression. Integration into biomarker-driven frameworks incorporating transcriptomic, proteomic, and metabolomic profiling will be essential to develop rational combination strategies and identify patients most likely to benefit. However, the limited fidelity of current preclinical models remains a major obstacle, and single-target approaches,

particularly when simply added to first-line chemotherapy, are unlikely to yield meaningful clinical benefit.

6. Challenges and limitations and future perspectives

Chemotherapy remains the only validated standard treatment for PDAC; however, the limited repertoire of available agents underscores the need for potential biomarkers to guide the selection of a tailored chemotherapeutic regimen.

BRCA and KRAS are among the most extensively investigated biomarkers. However, to date, no specific evidence indicates that any mutation in these genes confers increased responsiveness to specific chemotherapeutic agents, except for the well-recognized platinum sensitivity in gBRCA patients.

In line with the growing interest in identifying factors that may predict treatment response, two clinical trials warrant mention: PASS-01 [111] and PRIMUS-001 [112]. Both are multicenter phase II studies enrolling treatment-naïve patients with metastatic pancreatic cancer, requiring the availability of baseline biopsy tissue for comprehensive genomic and transcriptomic profiling. The aim of both studies is to enable future upfront multi-omic profiling to improve the identification of patients who could benefit from specific chemotherapeutic regimens.

In the PASS-01 study, patients were randomized to receive mFOLFIRINOX or AG treatment. The primary endpoint was to assess the differences in PFS between the two treatment arms. The secondary objectives included evaluation of OS, assessment of GATA6 as a predictive response biomarker, examination of chemotherapy sensitivity signatures, and analysis of circulating tumour DNA. At disease progression, patients were additionally reviewed by a molecular tumour board to guide the selection of the most appropriate second-line therapy. Preliminary results indicate comparable PFS between the two arms, whereas OS and safety trends appear to favour the AG regimen. However, the second-line setting seems inadequate to provide meaningful precision-based treatment choices, given the short survival observed [113].

In the PRIMUS-001 study, patients were randomized to receive FOLFOX plus nab-paclitaxel (FOLFOX-A) or AG. The primary objective was to assess the efficacy of FOLFOX-A compared with AG in an all-comers population and in a biomarker-positive subgroup using PFS as the primary endpoint. The secondary endpoints included overall survival (OS), objective response rate (ORR), safety and tolerability of FOLFOX-A, and biomarker discovery and development. Recruitment is still ongoing.

In conclusion, in PDAC, chemotherapy remains the backbone of systemic treatment; however, its selection is progressively shifting from an empirical approach to biology-informed decision-making that integrates tumour characteristics, patient fitness, and treatment-related risks. While currently actionable molecular subgroups, such as homologous recombination–deficient tumours, MSI-H/dMMR disease, and rare oncogenic fusions, apply to a limited proportion of patients, emerging strategies targeting the KRAS pathway have the potential to expand personalization to the majority of PDAC cases (see Fig. 1). The next phase of treatment individualization is likely to be dynamic rather than static, combining baseline patients' and molecular profiling with longitudinal reassessment of tumour biology over the disease course. In this context, the increasing feasibility of repeat endoscopic ultrasound–guided biopsies, together with circulating biomarkers such as ctDNA and extracellular vesicles, offers a practical means of capturing tumour heterogeneity, monitoring treatment-induced evolution, and anticipating resistance. Integrated with predictive transcriptomic signatures capable of guiding first-line choice and treatment de-escalation, these approaches may allow a more rational use of chemotherapy in a disease characterized by narrow therapeutic windows. Ultimately, embedding adaptive, biomarker-driven strategies into gastroenterology-centered care pathways will be essential to translate precision chemotherapy into meaningful clinical benefits for patients with PDAC.

Funding

Prof. Capurso received funding from Associazione Italiana Ricerca Cancro (AIRC project IG 26,201).

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2026.02.020.

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