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Medical management of pancreatic cancer: from personalization to broadening treatment strategies

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the most heterogeneous and deadly cancers. This review examines recently implemented strategies to integrate predictive tools and targeted therapies to improve treatments personalization and patient outcomes. Predictive transcriptomic signatures based on machine learning should optimize first-line chemotherapy selection, while organoid-based chemo-profiling could help late-line or non-standard treatments, particularly when transcriptomic signatures are unavailable to guide therapeutic decisions. Liquid biopsies enable real-time, non-invasive monitoring of tumour progression and resistance. Targeted therapies, even limited to a small subset of PDAC patients, exploit specific molecular vulnerabilities and several of those are under clinical evaluation to join PDAC armamentarium. Given PDAC's biological complexity, a multimodal approach combining predictive tools, functional testing, and molecularly-guided therapies is required to progress. Implementing those strategies in routine practice, combined with technological and clinical advances should enhance the precision, accessibility, and effectiveness of personalized PDAC treatment, as well as expand therapeutic options with new targets.

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Current therapeutic landscape of pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) remains one of the leading causes of cancer-related mortality worldwide, with a five-year survival rate of only 11 %.[1] Its poor prognosis is primarily due to diagnosis at advanced, often unresectable stages, with limited and poorly effective therapeutic options. PDAC is also markedly heterogeneous across patients (intertumoral) and within individual tumours (intratumoral) resulting in highly variable therapeutic responses. While standard regimens are evidence-based, they fail to adequately address the molecular and clinical diversity of this disease.

One cause of the limited efficacy of treatment is the absence of robust predictive biomarkers to guide selection of the most common treatments, and also the limited number of options to match therapy to tumour biology. Existing treatments are also unable to eliminate resistant intratumor subclones that drive disease progression.[2,3] It is therefore essential to develop reliable tools to guide personalized treatment selection and to expand the therapeutic options by designing strategies to more precisely and effectively target each tumour and adapt treatment to patient-specific factors (Fig. 1).

Gemcitabine monotherapy became the first standard treatment for advanced PDAC more than two decades ago, and only three combination chemotherapy regimens have been found to be superior since: 5-fluorouracil (5FU), (liposomal) irinotecan, and oxaliplatin (FOLFIRINOX and NALIRIFOX)[4,5], and the gemcitabine plus nab-paclitaxel regimen.[6] While combination regimens are more effective than monotherapy, this is often associated with increased toxicity and reduced tolerability. These polychemotherapy protocols are designed to address intratumoral heterogeneity, as PDAC frequently includes diverse cellular subpopulations with different therapeutic sensitivities, contributing to disease progression and relapse[3].

Unlike in other types of cancers, only about half of PDAC patients are eligible for second-line therapy due to rapid clinical deterioration or treatment-related complications. Moreover, only approximately 25 % receive third-line therapy whose options are scarce and poorly defined.[7] Therefore, achieving effective first-line therapy is essential in patients with PDAC. Therapeutic decisions are still primarily guided by clinical parameters such as performance status, age, and comorbidities, which do not take into account the molecular characteristics of the tumour.[7].

Another strategy under evaluation involves sequential chemotherapy regimens designed to expose intratumor subclones to multiple agents within a short time frame. This approach is based on the rationale that subclonal populations within the tumour may differ in their sensitivity to specific drugs, and that the use of multiple agents may produce synergistic antitumor effects. For instance, nab-paclitaxel has been shown to remodel the tumour microenvironment, thereby facilitating the intratumoral penetration and efficacy of FOLFIRINOX. [8] In the GABRINOX phase Ib/II trial, alternating nab-paclitaxel/gemcitabine with FOLFIRINOX resulted in a 65 % response rate, including two complete responses (n = 58). Similarly, the SEQUENCE phase II trial (n = 78) reported a response rate of 40 %.[9] However, these strategies have certain limitations. First, the cumulative toxicity of combination therapies is a major issue, with severe side effects that can limit the patient tolerance and duration of treatment. Moreover, no comparison versus standard FOLFIRINOX or NALIRIFOX is available.

Efforts have also been made to target the abundant and dynamic tumour microenvironment, which plays a central role in drug accessibility, in modulating epithelial cell states and sustaining plasticity. However, randomized trials aiming to modulate stromal components such as the Hedgehog signalling pathway, hyaluronic acid content, and more recently connective tissue growth factor (CTGF), in combination with chemotherapy, have shown no clinical benefit.[10,11] Targeting the stroma is complicated by cancer-associated fibroblasts (CAFs) heterogeneity and unexpectedly deleterious effects of the ablation of certain antitumoral CAF subpopulations or matrix depletion.[12,13].

Personalized therapeutic strategies for PDAC are rapidly evolving, driven by deeper biological understanding and a renewed focus on addressing systemic barriers through smarter, biology-guided clinical trial designs. [14].

Transcriptomic signatures

Transcriptomic signatures are panels of transcripts that provide biological insight into disease behaviour. There are two main categories: *prognostic* signatures, which accurately define patient survival but cannot guide treatment decisions,[15] and *predictive* signatures, which predict the response to a specific therapy.

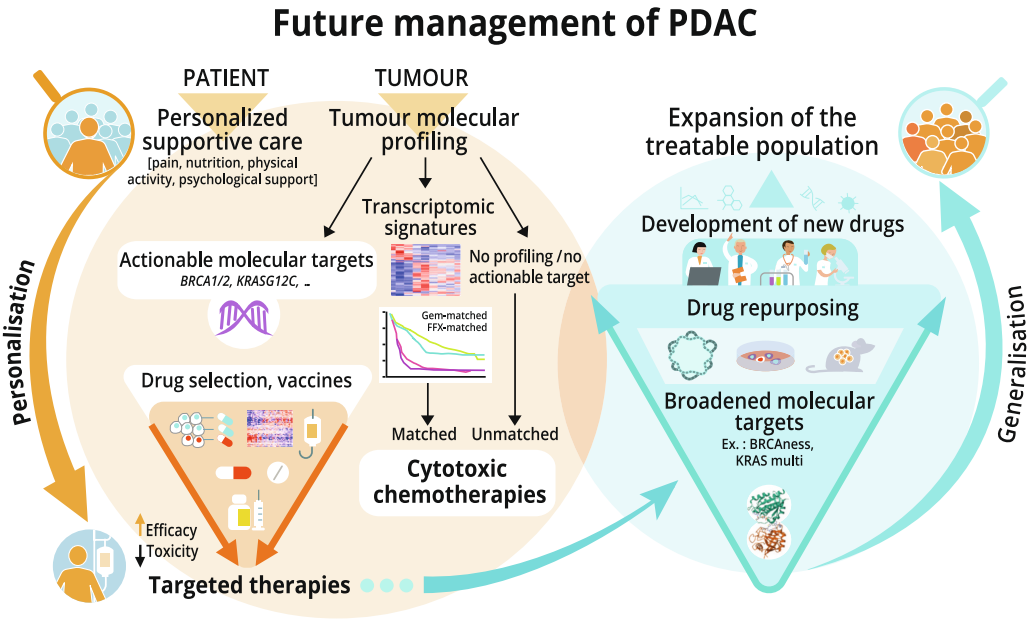

Fig. 1. Future Management of Pancreatic Ductal Adenocarcinoma. Schema of a comprehensive approach of future PDAC management, integrating personalized therapeutic strategies and extending treated populations with new targets and multimodal options.

1-Prognostic transcriptomic signatures

Advances in molecular classification, particularly through transcriptomic analyses, have identified distinct pancreatic tumour subtypes. The landmark studies by Moffitt,[16] Bailey,[17] Collisson,[18] Puleo [19] and Chan-Seng-Yue [2] have defined two major transcriptomic subtypes: *classical* and *basal-like* subtypes. The former are associated with a better prognosis and increased sensitivity to standard therapies while the latter is characterized by increased tumour aggressiveness and general resistance to conventional therapies and is associated with a worse prognosis. Based on these classifications, Rashid et al. [20] developed the Purity Independent Subtyping of Tumours (PurIST) classifier, which robustly distinguishes classical and basal-like subtypes in PDAC, independent from tumour purity and increases the precision of molecular subtyping for clinical applications. The Pancreatic Adenocarcinoma Molecular Gradient (PAMG) was also developed. This more nuanced classification expresses tumour heterogeneity on a continuous gradient with more precise prognoses accommodating the complexities of PDAC.[21,22].

Besides RNA profiling-based molecular classifications, artificial intelligence-based tools provide complementary approaches. With the PACpAInt deep learning model, for example, rapid PDAC subtyping from histopathological images bypasses the need for costly and complex RNA sequencing.[23] Trained on a large multicentre dataset combining digital slides and transcriptomic data from 202 patients and validated by pathologists, this model identifies intratumoral microheterogeneity by identifying multiple coexisting cellular subtypes within a single tumour. While PACpAInt provides a resource-efficient and scalable solution to expand precision medicine, it can only be used for prognosis in resected tumours because it requires structured tissue architecture that is difficult to obtain.

While significant progress has been made in classifying epithelial cells, there is no validated molecular classification for the tumour microenvironment, in particular the stroma and CAFs. Nevertheless, several classifications have been proposed following the description of the iCAF/myCAF model,[24], some associated with specific immune tumour microenvironments (such as periostin-positive CAFs associated with M2 macrophages infiltration).[25,26] Based on multiomic analysis, consensual CAFs subtypes that are conserved across tumours were recently proposed [27]. Studies show that distinct stromal phenotypes including inflammatory, desmoplastic, and immune-excluded subtypes, influence disease progression and treatment response. This is further complicated by heterogeneity of CAFs because different CAF subtypes can either promote or restrain tumour growth. These stromal contributions must be understood to refine prognostic models and identify therapeutic strategies that target both the tumour and microenvironment.

2-Predictive transcriptomic signatures

GemPred,[28], one of the first predictive transcriptomic signature developed for PDAC, predicts sensitivity to adjuvant gemcitabine in patients with resected tumours. The *GemCore* signature was developed as an advancement of *GemPred*, extending its predictive use beyond resected tumors to include metastatic PDAC. It incorporates biopsies from both primary tumors and metastatic sites, such as the liver, thereby enabling gemcitabine response prediction across the full spectrum of disease stages.[29] Finally *Pancreas-View*, a comprehensive tool that provides theragnostic insights on gemcitabine and the mFOLFIRINOX regimen, integrates data from both resected[30] and metastatic[31] PDAC. *Pancreas-View* uses machine-learning algorithms to analyse transcriptomic features from the neoplastic cells and its microenvironment. Retrospective clinical validation in the PRODIGE-24/CCTG PA6 trial showed that patients found to be sensitive to the administered chemotherapy had significantly longer disease-free survival (DFS). In fact, median DFS was 50.0 months in the mFOLFIRINOX-sensitive group treated with mFOLFIRINOX, and 33.7 months in the gemcitabine-sensitive group treated with gemcitabine. In contrast, patients who were not sensitive to the received treatment had a median DFS of 10.6 months, while those who were resistant to all drugs had a median DFS of 10.8 months.[30].

The evolution from *GemPred* to *GemCore* to *Pancreas-View* illustrates the ongoing progress in predictive transcriptomic signatures in PDAC. A key advantage of these signatures is their rapid clinical applicability to a broad patient population with reduced treatment toxicity. For example, Fraunhoffer et al[30]. showed that if patients were found to be highly sensitive to gemcitabine by transcriptomic signatures, this drug could be used rather than the more toxic mFOLFIRINOX regimen with the same efficacy. Two prospective ongoing clinical trials: PACsign (NCT05475366) and GemSign-01 (NCT06046794) are evaluating *Pancreas-View* for transcriptomic signature-guided first-line chemotherapy in patients with metastatic pancreatic cancer. The randomized phase II trial PRODIGE104-NeoPREDICT, will also test predictive signatures in patients with borderline resectable PDAC in the neoadjuvant setting.

Another transcriptomic signature is being used to predict the treatment response in the experimental arms of two randomized trials. It is included in ESPAC6 (EudraCT 2020–004906-79) adjuvant trial in resectable patients and in the ESPAC7 induction therapy trial for locally advanced disease. To further our understanding of tumour plasticity during therapy, genomic and transcriptomic profiling at baseline and over time is an integral part of these trials. This includes identifying both intrinsic and acquired tumour plasticity that evolves over time and in reaction to different therapies to improve the scientific approach to overcoming clonal resistance.[32].

Despite the promise of predictive transcriptomic signatures there are several limitations. Because they are based on bulk RNA sequencing, they may fail to detect minor resistant subclones in a globally sensitive tumour, which could drive relapse. Inferential approaches for cell populations, such as transcriptomic deconvolution, must be incorporated to resolve cellular heterogeneity and enhance predictive accuracy. Performance may be influenced by sample contamination with stromal or inflammatory cells and low percentage neoplastic components, especially in fine-needle aspiration (FNA) biopsies. Thus, sample quality must be improved for comprehensive tumour characterization. Also, analysis is performed on a tumour fragment which may reflect the characteristics of the sampled region rather than the full molecular landscape. Finally, prospective clinical validation is needed for most of these signatures before they may be applied for routine use.

Treatment personalization through chemoprofiling with organoids

Ex vivo chemoprofiling using patient-derived PDAC organoids is also an important advancement in personalized oncology. By replicating the genetic characteristics of the original tumour, organoids can be used as tumour avatars to directly test therapeutic options on patient-specific samples.[33] Although it does not fully replicate the tumour microenvironment (no stroma and no immune cells) this method provides a highly accurate assessment of drug sensitivity or resistance using three-dimensional tumour-derived structures. Moreover, they grow under differentiation-promoting conditions that more closely resemble *in vivo* tumour biology than conventional two-dimensional cell cultures, where glandular organization and cellular heterogeneity are almost absent.

Organoid-based chemoprofiling has demonstrated strong predictive value in late-line settings and in resected patients with resistance to standard therapies, with recent studies reporting 83 % sensitivity and 93 % specificity in anticipating treatment response.[34] This approach is especially useful for evaluating sensitivity to non-standard or emerging therapies that have no predictive factors (including predictive transcriptomic signatures), mainly because the large retrospective cohorts required for their development are lacking. In these cases, it is a

complementary tool to identify personalized treatments and expand therapeutic options, especially in late-line settings when transcriptomic-guided strategies are no longer effective. Organoids may also be a preclinical platform to test new drugs or combinations, including drug repositioning (Fig. 1).

Chemoprofiling shows potential in the search for more personalized and effective PDAC treatments, but with certain limitations.[35] For example, culture success rates rarely exceed 50 %, and organoid-based chemoprofiling results usually take 6–8 weeks, which limits their use in first-line therapeutic decision-making. During this interval, patients often receive an initial treatment which can alter tumour biology, raising concerns that organoid-based predictions made prior to treatment may not be valid for subsequent therapy selection. Chemoprofiling requires specialized culture media enriched with Wnt and R-spondin agonists to support 3D growth and differentiation, and sustained activation of these pathways induces phenotypic and molecular convergence across organoids, reducing their ability to reflect the true heterogeneity of clinical tumours.[35] This limitation is being actively investigated and should be overcome with the optimization of culture conditions.[36] Although preclinical data are supportive, organoid-based profiling remains limited to specialized centres with the necessary infrastructure and expertise. Current challenges related to reproducibility and scalability still limit its integration into routine clinical practices. In addition, broader implementation is limited by cost-effectiveness concerns, lack of standardized protocols, and the fact that these technologies remain largely confined to expert centers, limiting their availability in community settings.

Dynamic monitoring of treatments with liquid biopsy and tumour biomarkers

Biomarkers must be dynamically monitored to track postsurgical PDAC disease progression or relapse. While CA19-9 remains the standard biomarker, its clinical value is limited due to low sensitivity and specificity.[37] Emerging biomarkers such as circulating tumour DNA (ctDNA)[38] and circulating tumour cells (CTCs) provide more accurate, real-time assessments of tumour burden for dynamic monitoring of tumour progression, especially for the follow-up of patients with potentially resectable tumours.[39] ctDNA is a prognostic biomarker for all stages of PDAC, including during follow-up after curative intent surgery.[40] However, the rate of ctDNA detection varies greatly depending on the methodology, from 10 %-30 % in localized PDAC to 60 %-70 % in metastatic PDAC. The detection of ctDNA is associated with a metastatic course, most often by hematogenous route. In localized PDAC, the low sensitivity of ctDNA detection, along with a lack of assay standardization, limits its widespread clinical use. Beyond technical performance, the cost of advanced ctDNA assays and their limited standardization across laboratories also hamper accessibility in non-academic or community settings. It is therefore more effective in guiding locoregional treatment strategies (surgery, radiotherapy) than in predicting the efficacy of systemic chemotherapy.[41–43].

Exosome analysis in blood samples is another possible diagnostic method. Exosome's shuttle molecular cargoes between cells for intercellular communication. Nakamura et al.[44] have identified eight non-coding microRNAs specific to PDAC exosomes. The definition of a small panel of five blood cell-free DNA markers has generated a pertinent signature. The diagnostic accuracy of the combination of this RNA signature with CA19-9 was 97 % for early stages of PDAC.[44].

Recent results of an innovative non-invasive blood-based assay, PAC-MANN, were encouraging in identifying all stages of PDAC by detecting cancer-associated protease activity with high specificity. Combined with CA19-9, PAC-MANN reached 85 % sensitivity and 96 % specificity for stage I PDAC, suggesting that it could significantly improve early detection and monitoring in high-risk individuals.[45] Repeat testing could be used to rapidly adapt treatment and prevent invasive (re)biopsy of the primary tumour or metastases.[46] However, more studies are needed to evaluate whether it is suitable for widespread use for the assessment of minimal/undetectable residual PDAC as well as for treatment monitoring and surveillance.[47].

Genomic alterations and targeted therapies in pancreatic cancer

Although the frequent mutations in PDAC, such as *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* must be identified to understand carcinogenesis, this does not help stratify patients or make therapeutic decisions.[48,49] *KRAS* mutant allele-specific imbalances were evaluated to assess whether the ratio of mutant to wild-type alleles could serve as a prognostic marker, but this could not be used to stratify tumours into distinct classes with differential treatment responses.[50] Other studies, such as the work by Mueller et al.,[51] highlighted that *KRAS* dosage, influenced by allelic imbalance, not only drives oncogenic signalling but also shapes the evolutionary trajectories of PDAC, reinforcing the complexity of their heterogeneity. Comprehensive genomic studies revealed a wide array of less frequent genetic alterations.[52] This contributes to tumour heterogeneity but still cannot be translated into clear subtypes applicable to targeted therapies.

Nevertheless, the emergence of targeted therapies has provided promising options that exploit specific molecular vulnerabilities such as DNA repair deficiencies (*BRCA1/2* mutations), *KRAS* mutations, and immune evasion pathways. These strategies are a growing aspect of personalized medicine, as summarized in Table I. However, the clinical efficacy is often limited or transient again due to tumour heterogeneity and resistance. Pischvaian have reported that 25 % of PDAC patients harbour potentially actionable genomic alterations but only about 2 % receive matched therapies, that improve survival.[53] This confirms the importance of early, systematic genomic testing to maximize the window for targeted treatment before clinical deterioration prevents these options.

1-PARP inhibitors for BRCA germline mutations

PARP inhibitors exploit synthetic lethality by selectively targeting HRR-deficient cancer cells that require the PARP enzyme to repair DNA breaks, thus enhancing specificity while sparing normal cells. The POLO study[54] showed that maintenance therapy with olaparib significantly improved PFS in patients with metastatic PDAC and germline *BRCA1/2* mutations that were controlled by first-line platinum-based systemic chemotherapy. Of the 7 % of patients harbouring germline *BRCA1/2* mutations, 5 % achieve sufficient disease control to become eligible for olaparib maintenance therapy. Despite this hyper-selection, olaparib treatment is not beneficial in nearly 40 % of patients due to primary resistance to PARP inhibition, while secondary resistance mainly occurs from secondary mutations that restore HRR proficiency or activate compensatory repair pathways.[55] Finally, about 25 % of patients have a prolonged PFS with olaparib. Strategies to overcome resistance are being tested including a combination of PARP inhibitors with other agents, such as platinum-based chemotherapy or immune checkpoint inhibitors.

Maintenance therapies combining PARP inhibitors and checkpoint inhibitors are being explored for their potential role in prolonging disease control. In the study by Reiss et al.,[56] the 6-month PFS was 59.6 % with niraparib plus ipilimumab (anti-CTLA4) compared to 20.6 % with niraparib plus nivolumab (anti-PD-1), although this resulted in greater toxicity. Finally, there are still barriers to routine *BRCA1/2* mutation testing, such as low referral and management rates, delayed referral and results, cost, and biopsy or assay limitations in the case of somatic testing, often necessitating subsequent germline testing. [57] Gene mutations beyond germline *BRCA1/2* (non-core HRD), as well as patients with very good responses to platinum, should be considered candidates for the olaparib plus pembrolizumab combination. [58].

2-Targeting KRAS mutations

KRAS mutations are a hallmark of PDAC, occurring in up to 85 % of cases. These mutations drive oncogenesis through the continuous activation of downstream signalling pathways such as MAPK and PI3K-AKT. They are the main reason for the rapid deterioration in general status as well as the unique therapeutic resistance of PDAC. Targeting KRAS has been challenging due to its high affinity for GTP and lack of suitable binding pockets.[59] Previous attempts (farnesyl transferase inhibitors, targeting of downstream MAPK/mTOR pathway) were negative.[60,61] Recent advances in KRAS-targeted therapies have led to the development of allele-specific inhibitors. Sotorasib and adagrasib both target *KRAS-G12C* mutations and have demonstrated clinical activity in non-small cell lung cancer (NSCLC), and are under investigation for their potential utility in PDAC, although these mutations are less frequent in the latter (<1%). These agents provide objective response rates (ORRs) of 21 % to 46 %, with a median PFS of 4.0–5.5 months in heavily pre-treated PDAC patients.[62–66].

MRTX1133 is a non-covalent inhibitor specifically targeting KRAS-G12D, and a breakthrough in KRAS-directed therapies.[67] This inhibitor has been found to be effective in preclinical studies with significant tumour regression in patient-derived xenografts and immunocompetent mouse models. The first-in-human trials (NCT05737706) were initiated to evaluate its safety and clinical efficacy in advanced solid tumours harbouring the *KRAS*-G12D mutation. Strategies involving MRTX1133 and upstream tyrosine kinase receptor (RTK) or downstream pathway inhibitors show synergistic effects in overcoming adaptive resistance mechanisms. These approaches include dual inhibition of KRAS and pan-ERBB, which have been shown to have enhanced therapeutic efficacy in preclinical PDAC models[68] and RMC-9805, a tri-complex inhibitor targeting the KRAS-G12D active state.[69].

The pan-KRAS inhibitor RMC-6236 is an oral RAS(ON) multi-selective noncovalent inhibitor of the active, GTP-bound state of both mutant and wild-type variants of canonical RAS isoforms including KRAS, NRAS, and HRAS. A phase I/Ib trial in heavily pre-treated patients with *KRAS*-mutated PDAC has shown a disease control rate (DCR) of 87 % and good tolerance (NCT05379985).[70,71] A phase III study RASolute 302 randomize RMC-6236 monotherapy versus a second-line standard of care chemotherapy is recruiting (NCT06625320). This approach could overcome the adaptative resistance mechanisms of allele-specific therapies by inhibiting wild-type RAS isoforms and secondary mutations. Several combination therapies are also being explored to counteract resistance mechanisms. Strategies include co-targeting RTKs, MEK inhibitors, or using SHP2 inhibitors to mitigate feedback activation of the MAPK pathway. For example, adagrasib combined with EGFR inhibitors such as cetuximab was found to be more effective in *KRAS*-mutant colorectal cancer.[72] While these advances are promising, resistance is still critical often occurring from secondary mutations, compensatory pathway activation, or tumour heterogeneity. Future research must focus on optimizing combination strategies, early-line interventions, and patient stratification to enhance clinical applications of KRAS-directed therapies.

Finally, *KRAS* wild-type PDAC constitute a biologically and clinically distinct, but infrequent (<10 %), subgroup. They are more common in acinar cell carcinomas (>90 %)[73] and potentially sensitive to matched targeted therapies (Table I)[74] This group can be sensitive to specific drugs such as nimotuzumab.[75,76] They have also potentially actionable molecular events such as *BRAF* mutations [77] (13.0 %) and fusions (6.6 %), *NTRK*[78], *NRG1*[79] *ALK*[80], *RET*[81] rearrangements, and MSI-high status (4.7 % vs 0.7 %). These findings support the need for systematic molecular profiling in *KRAS* wild-type PDAC.

Targeting PDAC metabolism or its tumour microenvironment

PDAC is characterized by extensive reprogramming of the cell metabolism enabling tumour cells to proliferate in a nutrient-poor, hypoxic microenvironment.[82,83] *KRAS* gene alterations play a key role in this process and cause dysregulation of metabolic pathways leading to addictions to metabolites such as glutamine and asparagine.[84] To exploit this potential vulnerability in PDAC by administering asparaginase encapsulated in allogeneic red blood cells (eryaspase) to degrade asparagine and glutamine in the circulation and deprive tumour cells of these key aminoacids, have shown potential relevance. However, OS in the phase 3 TRYBECA-1 study (NCT03665441) testing eryaspase in combination with chemotherapy as second-line treatment in advanced PDAC did not improve compared to control arm.[85] The AVENGER study (NCT03504423) combining the dual tumoral mitochondrial metabolism inhibitor devimistat with FOLFIRINOX as first-line treatment in advanced PDAC also failed to improve OS compared to chemotherapy alone.[86].

It is still difficult to target PDAC metabolism and the tumour microenvironment. New strategies may be found at the biochemical level. A metabolic vulnerability exists in approximately 20 %-30 % of pancreatic cancers harbouring MTAP deletions, which create dependency on protein arginine methyltransferase 5 (PRMT5). This synthetic lethality offers a therapeutic opportunity as PRMT5 inhibitors selectively target these MTAP-deleted tumours while sparing normal cells, representing a potential precision medicine approach in these patients. [87] PRMT5/MTA interaction inhibitors such as AMG193, BMS-986504, TNG462, and TNG456 are being tested alone or in combination with chemotherapy in MTAP-deficient tumors, which accumulate MTA and are therefore selectively vulnerable to PRMT5 inhibition (NCT05094336, NCT06360354) (Table 1).[87].

Alternative metabolic pathways are also being explored. For example, iron catalyses the oxidation of lipids in biological membranes promoting a form of cell death called ferroptosis. Whereas genetic approaches have identified ferroptosis suppressors, small molecules can provide spatiotemporal control of the chemistry of this process. The ferroptosis inhibitor liproxstatin-1 exerts protective activity by interfering with iron in lysosomes. A compound called fentomycin-1 targets phospholipids at the plasma membrane and activates iron in lysosomes upon endocytosis, inducing oxidative degradation of phospholipids and ferroptosis.[88] This drug appeared to be highly active against PDAC cells, selectively targeting iron-rich CD44 high cells associated with metastases and drug tolerance. Since iron regulates epigenetic cell adaptation, fentomycin-1 renders these cells more vulnerable to ferroptosis. This phospholipid degrader could eradicate drug-tolerant persister cancer cells and is therefore a potential therapeutic candidate. [89] NUPR1, a key regulator of cellular stress response in PDAC, is also involved in ferroptosis resistance. Its pharmacological inhibition with ZZW-115 could further sensitize tumour cells to ferroptosis, representing another interesting combination approach.[90,91] However, these results remain limited to preclinical models, and no clinical validation has been achieved to date. The translational potential of ferroptosis-inducing strategies in PDAC will depend on further studies assessing delivery, safety, and efficacy *in vivo*, particularly in patients. While still preliminary, these approaches are conceptually attractive and reflect a growing interest in exploiting alternative vulnerabilities to overcome treatment resistance.

Another approach in locally advanced PDAC is the use of Tumor Treating Fields (TTFields); the electric fields that exert physical forces able to destroy tumor cells of PDAC. The recently announced results of the phase III PANOVA-3 trial (NCT03377491) showed a significant OS benefit when TTFields were combined with gemcitabine and nab-paclitaxel, with good tolerability. This non-invasive modality could represent a meaningful addition to standard regimens in unresectable disease, and preclinical evidence also supports synergistic effects with immunotherapy, PARP inhibitors, and radiation therapy. In parallel, other emerging therapies are being evaluated in first-line settings, such as elraglusib (9-ING-41), a glycogen synthase kinase-3 βinhibitor currently under investigation in combination with gemcitabine and nab-paclitaxel (NCT03678883). These innovative approaches illustrate the

Table 1
Summary of targeted therapies under clinical evaluation in PDAC.

Molecular Target	Study	Drug(s)	Trial (NCT)	Phase	Key Outcomes
MSI-H/dMMR	KEYNOTE158 [100]	Pembrolizumab	NCT02628067	II	ORR: 18.2 %, PFS: 2.4 mo OS: 4 mo
	Taïeb et al [101]	Various CPI +/− chemo	–	II	ORR: 48 %, PFS 26.7 mo
BRCA1/2	POLO Golan et al [54]	Olaparib vs.placebo (maintenance)	NCT02184195	III	PFS: 7.4 mo (vs 3.8)
KRAS G12C	CODEBREAK-100 Strickler et al [62]	Sotorasib	NCT03600883	Ib/II	ORR: 21 %, PFS: 4 mo, OS: 6.9 mo
	KRYSTAL-1 Bekaii-Saab et al [63]	Adagrasib	NCT03785249	II	ORR: 33.3 %, PFS: 5.4 mo, OS: 8 mo
	Sacher et al [64]	Divarasib	NCT04449874	I	ORR: 43 %
	Suk Heist et al [65]	Olomorasib	NCT06119581	I/II	ORR: 33 %
	Hollebecque et al [66]	Glecirasib	NCT04956640	I/II	ORR: 46.4 %, PFS: 5.5 mo
KRAS wild-type (anti-EGFR)	Schultheis et al [75]	Nimotuzumab	NCT00561990	IIb	OS: 11.6 mo vs. 5.6 mo in KAS mutated (p = 0.03)
					PFS: 4.2 mo vs. 3.6 mo, OS:10.9 vs. 8.5 mo (ns)
	Qin et al [76]		NCT02399516	III	
BRAF V600E	Salama et al [77]	Dabrafenib + Trametinib	NCT04439292	I	ORR: 38 %, PFS: 11.4 mo
NTRK fusions	Qi et al [78]	Larotrectinib	NCT02576431	II	ORR: 15 %
NRG1 fusions	Schram et al [79]	Zenocutuzumab	NCT02912949	II	ORR: 42 %, PFS: 7.4 mo
ALK	Singhi et al [80]	Crizotinib, Ceritinib, Alectinib	Case reports	–	OS:> 5 mo-52 mo
RET fusions	Subbiah et al 8[81]	Selpercatinib	NCT03157128	I/II	ORR: 54 %, PFS: 5 mo
Asparagine/ glutamine	Hammel et al [85]	Eryaspase	NCT03665441	III	PFS: 3.7 mo (eryaspase) 3.4 mo (control); OS: 7.5 mo (eryaspase) vs 6.7 mo (control) (ns)
Pyruvate/a-ketoglutarate deshydrogenases	Philip et al [86]	Devimistat	NCT03504423	III	PFS: 7.8 mo (devimistat + FFX) vs. 8.0 mo (FFX), OS: 11,1 mo vs. 11,7 mo (ns)
MTAP deletion	Rodon et al [87]	AMG193	NCT05094336	I	ORR: 21.4 %, (all tumours)
Connective tissue growth factor (CTGF)	Picozzi et al [92]	Pamrevlumab	NCT03941093	III	PFS: 9.36 mo vs. 9.4 mo; OS:17 0.2 mo vs. 17.9 mo (ns)
Claudin1 8.2	Jin et al [94]	Zolbetuximab	NCT06396091	I/Ib	ORR: 50 %, Combined with gemcitabine and nab-paclitaxel: DCR disease control rate 100 %
	Yu et al [95]	IBI343	NCT05458219	I	ORR: 40 %, CLDN18.2 Drug conjugate (with exatecan)
	Hao et al. [96]	IBI389	NCT05164458	I	ORR: 30.4 %, Anti-CLDN18.2/CD3 bispecific antibody DCR 69.6 %

Abbreviations: mo, month; ICI, immune checkpoint inhibitor; ORR, overall response rate; DCR, disease control rate; IHC, immunohistochemistry; PFS, progression-free survival; OS, overall survival; PR, partial response; CR, complete response; mPFS/mOS, median PFS/OS; FFX; Folfirinox; ns, non-significant difference; NCT, National Clinical Trial identifier.

growing effort to broaden treatment options beyond conventional chemotherapy, particularly in patients who are not fit enough to receive aggressive regimens like FOLFIRINOX.

Efforts to target the tumour microenvironment, a defining feature of PDAC, have also been explored. Although pamrevlumab, an antibody directed against CTGF, inhibits fibrosis and stromal remodelling, thus targeting the desmoplastic stroma characteristic of PDAC,[92] clinical results in locally advanced PDAC have been disappointing. Another stromal target is claudin18.2. This epithelial tight-junction protein, abnormally expressed in several gastrointestinal tumours, is being evaluated in PDAC through antibody-based approaches including zolbetuximab and the bispecific antibody anti-claudin18.2 /CD3 ASP2138 (NCT05365581).[93–96].

Immunotherapy and MSI-H/dMMR biomarkers

Although immune checkpoint inhibitors (ICI) have little or no efficacy in unselected PDAC patients,[97,98] based on excellent results in patients with microsatellite instability (MSI) colorectal cancer[99] the same treatment was applied to PDAC with MSI, with fewer benefits.[100] Real-life data in this subgroup have suggested a more favourable response to ICI with anti-PD1 antibodies, alone or in combination.[101] ICI in combination with other ICI or chemotherapy was not found to be effective except in MSI patients.[98,102] The goal of clinical trials is to enhance the efficacy of immunotherapy by exploring new combinations to boost T-cell infiltration and amplify immune responses. Another major challenge is to improve identification of PDAC susceptible to respond to ICI and good potential candidates with DNA damage repair alterations.[58] The CD40 antibody agonist, mitazalimab, which recruits the myeloid-cell compartment, was recently found to induce a notable 40 % tumour response rate when combined with FOLFIRINOX as first-line treatment for metastatic PDAC.[103] Emerging data suggest a potential role for ICI in specific patient subpopulations with tumour microenvironments more favourable to immunotherapy, such as those with germline *BRCA1/2* mutations[104] or combined with treatments such as CD40 agonists that can remodel the immunosuppressive tumour environment. CAR-T cell therapies are currently being evaluated as a strategy for PDAC in clinical trials. However, due to the low mutational burden and limited specificity of tumour-associated antigens in PDAC, combined with its highly immunosuppressive microenvironment, adoptively transferred lymphocytes often fail to efficiently infiltrate the tumour and exert their activity. [105] Nonetheless, a proof of concept was reported by Leidner et al.,[106] who successfully treated a patient with metastatic PDAC using a single infusion of autologous T cells genetically engineered to clonally express two allogeneic HLA-C*08:02-restricted T-cell receptors targeting the KRAS G12D mutation expressed by the tumour.

Vaccines

The goal of cancer vaccination is to train a patient's immune system to recognize and eliminate tumour cells or prevent recurrence during

adjuvant therapy after surgical resection. Unlike initial beliefs, PDAC tumours do express neoantigens that stimulate cellular immune responses allowing the development of vaccines based on somatic mutation-derived neoantigens using RNA technologies. These anti-tumour vaccines are being investigated as potential tools for personalized treatment in PDAC. Various platforms, including peptide-based, dendritic cell-based, and viral vector-based vaccines, have been explored in both preclinical and clinical settings.

The off-the-shelf vaccine ELI-002 2P increases lymph node delivery and immune response using an amphiphile change in G12D and G12R mutant KRAS peptides together with the CpG oligonucleotide adjuvant (Amph-CpG-7909) in patients with PDAC or colorectal cancer. This vaccine induced high T cell responses (both CD4 + CD8 +).[107] In another study, Rojas et al.[108] administered a single dose of the anti-PD-L1 antibody atezolizumab as adjuvant treatment, followed by priming doses of an individualized vaccine containing 20 neoantigens, based on uridine mRNA-lipoplex nanoparticles (autogene cevumeran), prepared from resected PDAC tumours. A booster dose was administered after completion of a six-month mFOLFIRINOX course. A phase II adjuvant vaccine trial with the same administration schedule is currently ongoing (NCT05968326). Clinical vaccine efficacy was suggested by the absence of relapse in patients who developed strong T cell responses after vaccination, observed in 50 % of treated patients.[109] Vaccines for patients with PDAC must overcome major limitations. Neoantigen-based mRNA vaccines must be personalized, requiring cost-effective technologies to identify tumour-specific antigens (vs off-the-shelf vaccines, an alternative approach requiring the identification of shared epitopes) and characterize immune subtypes. The specific, highly heterogenous characteristics of PDACs contain an unfavourable microenvironment, thus knowledge of the precise mechanisms allowing tumour cells to escape immune control must be improved.[110].

Future perspectives

The challenges of PDAC may only be overcome by a comprehensive approach integrating predictive, dynamic treatment adjusted to tumour progression and targeted strategies (Table I). Predictive transcriptomic signatures such as *Pancreas-View* provide a companion to tailor first-line chemotherapy, using routine diagnostic biopsies for rapid and precise guidance. Chemoprofiling using patient-derived organoids can fill the gap for subsequent lines of treatment with personalized drug testing, especially for late-line experimental therapies. Despite the technical limitations, longer processing times, and a moderate culture success rate, it is an important option in patients without available transcriptomic signatures. The dynamic, non-invasive monitoring of treatment responses with liquid biopsies improves personalized care by allowing adjustments based on tumour progression and resistance mechanisms. Future trials are needed to identify the best treatment according to individual tumour and clinical characteristics. Meanwhile, targeted therapies, exploiting specific molecular vulnerabilities, such as germline *BRCA1/2* mutations, *KRAS* mutations, or immune checkpoint deficiencies, offer highly tailored interventions. Resistance remains a significant obstacle, emphasizing the need for integration with predictive and monitoring methods. Nevertheless, targeted therapies have not yet changed the natural course of PDAC for most patients, and their overall impact remains limited. The development of combination strategies is necessary to enhance their efficacy and broaden their clinical scope.

While efforts to personalize treatment should be applied to all existing and emerging therapeutic strategies, it should not be the sole focus. New treatments are still needed to overcome the limited efficacy of current options and provide coverage across patient populations. For instance, FOLFIRINOX, a multi-drug regimen that improves outcomes in a significant proportion of patients is probably successful because it simultaneously targets multiple tumour vulnerabilities rather than specific molecular alterations (Fig. 1). Thus, the development of pan-KRAS inhibitors, which target a key oncogenic driver of most PDAC, could reshape the therapeutic landscape and reduce the reliance on narrowly targeted approaches for less frequent molecular alterations.[70] To optimize treatment, PDAC must also be approached as a systemic disease. Patient-related factors such as pain, sarcopenia or cachexia, which affect overall health status and treatment efficacy, should be considered therapeutic targets. Supportive care should also play a major role, including pain management, nutritional support, physical exercise,[111] psychological support and microbiota modulation.[112].

Additional strategies under early clinical or preclinical investigation include the pharmacogenomic adaptation of chemotherapy dosing (e.g., DPD and UGT1A1 genotyping), GDF-15 inhibition to mitigate cachexia, and the induction of ferroptosis through disruption of redox homeostasis or iron metabolism. These exploratory approaches are part of a broader conceptual framework for personalized PDAC management. These future directions illustrate how the management of PDAC increasingly depends on the integration of clinical, anatomical, molecular and metabolic data to inform therapeutic decision-making (Fig. 2). This conceptual framework delineates the principal levels of intervention currently under investigation, including patient-centered supportive care, advanced imaging techniques, blood-based biomarkers, transcriptomic-driven drug selection and molecularly targeted therapies, together with their respective limitations and potential for clinical translation.

While significant progress has been made in identifying actionable molecular targets and predictive biomarkers in PDAC, translating these advances into routine clinical practice remains a major challenge. Access to comprehensive molecular diagnostics, organoid chemoprofiling, and transcriptomic signatures is largely restricted to expert centers with dedicated infrastructures, leaving most patients, particularly those treated in community settings, without the opportunity to benefit from personalized strategies. Moreover, trial recruitment is frequently hampered by the rapid clinical deterioration of patients and by the lack of integrated molecular screening platforms across institutions. Overcoming this translational bottleneck requires systemic efforts to harmonize biomarker testing workflows, improve funding models for precision diagnostics, and decentralize innovation to include non-academic oncology networks. Without addressing these structural barriers, the impact of personalization in PDAC will remain limited to a small subset of patients.

In the future, integrating multiple complementary tools into a unified clinical workflow will likely be essential to personalize treatment decisions in PDAC. Transcriptomic signatures can inform on intrinsic tumor biology and drug sensitivity, while ctDNA can provide dynamic, real-time information on residual disease and emerging resistance. Functional profiling using organoids adds a layer of phenotypic validation that may refine or challenge molecular predictions. Incorporating these elements alongside genomic data and classical clinical parameters may enable the design of adaptive, multimodal treatment algorithms. Such integrated approaches will require coordinated efforts in data harmonization, turnaround optimization, and prospective validation, but they hold promise for delivering truly individualized care in pancreatic cancer.

Conclusions

The management of PDAC may be improved by tailoring existing therapies to individual tumour and patient characteristics through predictive tools and by broadening the therapeutic landscape with novel agents, drug combinations, and innovative strategies. This dual approach of personalization and expansion offers the best chance to overcome the biological complexity and therapeutic resistance that define this aggressive disease.

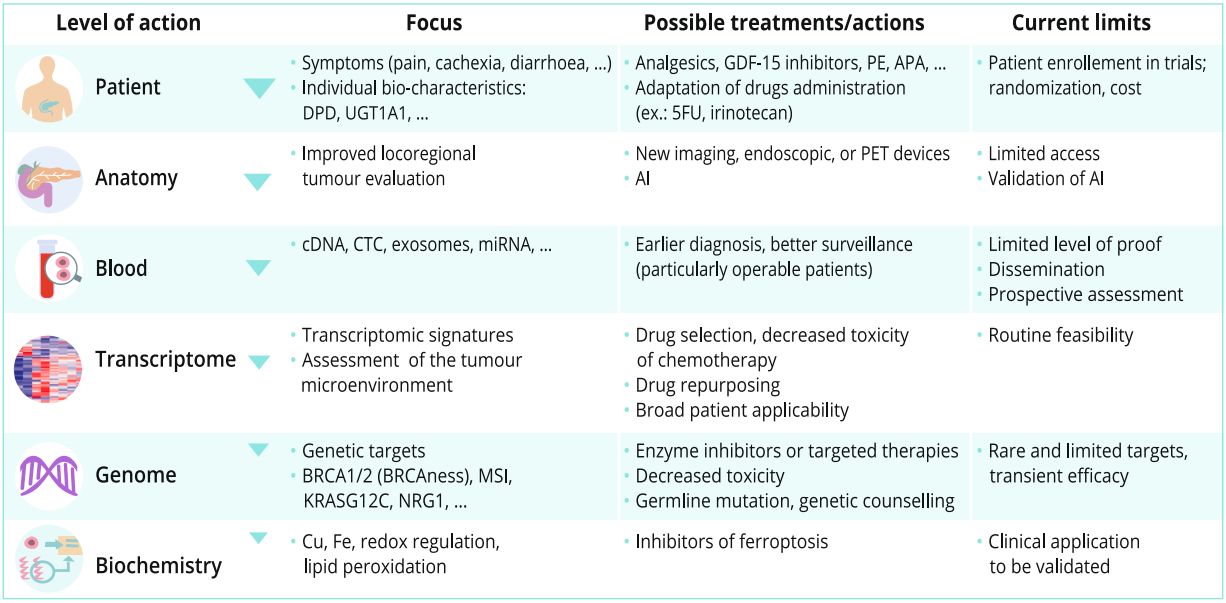

Fig. 2. Multiscale Approach to Personalized Treatment in Pancreatic Cancer. Hierarchical and synoptic framework for PDAC treatment approaches, integrating strategies from the patient to molecular levels. This figure illustrates a multiscale model integrating six levels of information used to personalize treatment in pancreatic cancer: patient-level clinical and pharmacogenetic factors; anatomical data from imaging and endoscopy; circulating biomarkers such as ctDNA and CTCs; transcriptomic signatures predicting chemotherapy response; actionable genomic alterations; and biochemical features such as redox status and ferroptosis sensitivity. These interconnected levels reflect the complexity of PDAC and provide complementary entry points for precision oncology. DDPD: Dihydropyrimidine dehydrogenase; UGT1A1: UDP-glucuronosyltransferase family 1 member A1; GDF-15: Growth differentiation factor-15; PE: Pancreatic enzymes; APA: Adapted physical activity; AI: Artificial intelligence; BRCA: Breast cancer gene; MSI: Microsatellite instability; NRG1: Neuregulin 1.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed using the terms "pancreatic ductal adenocarcinoma," "personalized treatment," "transcriptomic signatures," "targeted therapy," "liquid biopsy," and "KRAS inhibitors" from 2011 to 2025. Additional articles were selected from the authors' own archives. The final reference list was based on relevance to recent advances in PDAC management, with key earlier studies included for context. Only articles published in peer-reviewed journals were considered.

CRediT authorship contribution statement

Conceptualization and writing of original draft: ND and PH. Review, and editing the first version: JBB and JLI. Critical revision of the manuscript for important intellectual content: BC, CN, LDM, NW, NF, RN, AT, AB, RR, JC. All authors contributed significantly to this manuscript, and read and agreed to the submitted version of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ND and JI are co-founders of Predicting Med. ND, NF and JI are inventors for the patent PCT/EP2022/065222: Simple transcriptomic signatures to determine chemosensitivity for pancreatic ductal adenocarcinoma. SATT Sud-Est.: 2021. Licensing to Predicting Med. PH is consultant and trial investigator for Revolution Medicines. AB: Merck Serono, Servier, Takeda, Ipsen, MSD CN : Honorary/consulting: Amgen, AstraZeneca, Baxter, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences, Jazz, Merck, MSD, Mundipharma, Nestlé Health Science, Novartis, Nutricia, OncoSil, OSE Immunotherapeutics, Pierre Fabre, Roche, Sanofi, Servier, Tahio, Théradial, Viatris. Research funding/clinical trials: AstraZeneca, Bristol-Myers Squibb, Fresenius Kabi, Nutricia, OSE Immunotherapeutics, Roche, Servier, Viatris. Funding member of Cereus bioscience. LdM : Honorary/consulting : AAA/Novartis, Boehringer-Ingelheim, Esteve, Ipsen, Mayoly, Servier, Viatris ; Research funding : Boehringer-Ingelheim, Esteve, Ipsen. All other authors have declared no conflicts of interest. AT: Honorary/consulting : AstraZeneca, MSD, Norgine, Servier, Pierre-Fabre, Merck, Incyte Bioscience. Research Funding: Beigene. Congress grant for travel: AstraZeneca, Pierre Fabre, Merck.

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Data availability

Data will be made available on request.

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