REVIEW
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Molecular profiling and personalized targeting in PDAC: implications of KRAS, BRCA, SMAD4, and emerging biomarkers

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid tumors. This review synthesizes current understanding of the principal molecular drivers of PDAC, namely KRAS, BRCA1/2, and SMAD4 together with emerging biomarkers, and examines how this knowledge is being translated into personalized therapeutic strategies. A narrative review was conducted using the PubMed database to identify articles published between January 2016 and June 2026 relevant to molecular profiling and personalized targeting in PDAC. Articles were screened against predefined inclusion and exclusion criteria and synthesized thematically. KRAS, mutated in over 90% of cases (predominantly G12D), has shifted from an undruggable target to one addressed by mutation-selective and pan-RAS inhibitors, although adaptive resistance through receptor tyrosine kinase reactivation and YAP/TAZ signaling limits response durability. BRCA1/2 mutations (5–10%) confer homologous recombination deficiency and sensitivity to PARP inhibitors through synthetic lethality, with olaparib improving progression-free survival in the POLO trial. SMAD4 inactivation (50–55%), a late-stage event, functions as a prognostic biomarker associated with aggressive, metastatic disease and poorer survival. Emerging biomarkers, including circulating tumor DNA, exosomal GPC1, MSI-H/dMMR status, tumor mutational burden, rare fusions (NTRK, NRG1, FGFR2), and the Hippo-YAP/TAZ pathway, are broadening precision oncology options. KRAS, BRCA1/2, and SMAD4 each provide distinct therapeutic and prognostic information in PDAC.

Keywords: pancreatic ductal adenocarcinoma; KRAS; BRCA1/2; SMAD4; PARP inhibitors; synthetic lethality; precision oncology; liquid biopsy; molecular profiling.
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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid tumors, with a five-year survival rate that has only recently crept above 10% despite decades of incremental progress in oncology more broadly. Several features of the disease converge to explain this persistent lethality. Most patients present with locally advanced or metastatic disease at diagnosis, since the pancreas sits deep within the abdomen and early lesions rarely produce specific symptoms. Even among the minority of patients eligible for surgical resection, recurrence is common, and conventional chemotherapy regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel offer only modest survival benefits at the cost of substantial toxicity.[1,2]

Underlying this clinical picture is a genomic landscape that has become increasingly well characterized over the past two decades. PDAC is driven by a relatively small set of recurrent genetic alterations, most notably in KRAS, TP53, CDKN2A, and SMAD4, yet their functional consequences are far from straightforward. KRAS mutations alone are found in the vast majority of tumors and were long considered untreatable, while alterations in tumor suppressors such as SMAD4 and BRCA1/2 carry distinct implications for disease behavior, prognosis, and treatment selection. This genetic complexity, combined with a notoriously immunosuppressive and fibrotic tumor microenvironment, has made PDAC particularly resistant to therapies that have transformed outcomes in other cancer types.[3,5]

In recent years, however, this picture has begun to shift. The development of direct KRAS inhibitors, the clinical validation of synthetic lethality approaches for BRCA-mutated tumors, and growing recognition of SMAD4 as both a prognostic marker and a window into metastatic behavior have together enabled a more personalized approach to PDAC management. At the same time, emerging biomarkers, ranging from liquid biopsy components to rare actionable gene fusions and novel resistance pathways such as YAP/TAZ signaling, are expanding the scope of what precision oncology can offer patients with this disease.[3–5]

This review aims to synthesize current understanding of the molecular drivers of PDAC, with particular attention to KRAS, BRCA1/2, and SMAD4, and to examine

how this knowledge is being translated into personalized therapeutic strategies. We further explore emerging biomarkers that may refine diagnosis, prognosis, and treatment selection, and consider how the interplay between these molecular targets shapes both the promise and the limitations of precision medicine in pancreatic cancer.

MATERIALS AND METHODS

Search strategy

A literature search was conducted using the PubMed database to identify articles relevant to molecular profiling and personalized targeting in pancreatic ductal adenocarcinoma (PDAC), with particular focus on KRAS, BRCA1/2, SMAD4, and emerging biomarkers. The search covered articles published between January 2016 and June 2026.

Search terms were developed using a combination of Medical Subject Headings (MeSH) and free-text keywords, combined using Boolean operators (AND, OR). The core search terms included combinations of "pancreatic ductal adenocarcinoma" OR "PDAC" OR "pancreatic cancer" with target-specific terms such as "KRAS mutation", "KRAS inhibitor", "BRCA1" OR "BRCA2", "PARP inhibitor", "synthetic lethality", "SMAD4" OR "DPC4", "TGF-beta", "liquid biopsy", "circulating tumor DNA", "YAP" OR "TAZ", "TEAD inhibitor", "microsatellite instability", and "molecular profiling" OR "precision medicine" OR "targeted therapy".

Inclusion and Exclusion Criteria

Articles were included if they met the following criteria: published in English, full text available, focused on PDAC or pancreatic ductal adenocarcinoma specifically, and discussed molecular mechanisms, genetic alterations, biomarkers, or targeted therapeutic strategies relevant to KRAS, BRCA1/2, SMAD4, or other emerging molecular targets.

Articles were excluded if they were published in languages other than English, full text was not accessible, the primary focus was on pancreatic neuroendocrine tumors or other non-ductal pancreatic malignancies, or the content was limited to conference abstracts, editorials, or correspondence without substantive original or review data.

Study selection

Titles and abstracts retrieved from the initial search were screened for relevance based on the inclusion and exclusion criteria above. Articles deemed potentially relevant underwent full-text review to confirm eligibility. Reference lists of selected articles, including major review articles, were additionally screened to identify further relevant studies that may not have been captured through the primary database search.

Data extraction and synthesis

For each included article, relevant information was extracted regarding the molecular target or pathway discussed, mechanism of action, prevalence or epidemiological data where applicable, associated therapeutic agents and their clinical trial outcomes, and prognostic or diagnostic implications. Given the narrative nature of this review, data were synthesized thematically across four major sections: KRAS signaling and inhibitor development, BRCA1/2-related synthetic lethality and PARP inhibition, SMAD4 as a prognostic biomarker, and emerging biomarkers including liquid biopsy components, immunotherapy markers, rare actionable targets, and the YAP/TAZ signaling pathway.

RESULTS

Molecular profiling in PDAC

Unlike many solid tumors that accumulate mutations across a broad and heterogeneous set of genes, PDAC is characterized by a comparatively limited number of recurrently altered driver genes that function through a small number of core pathways. Yet this genomic simplicity has not translated into therapeutic simplicity. Each of the major drivers, KRAS, TP53, CDKN2A, and SMAD4, plays a distinct mechanistic role, and the combination and sequence in which these alterations occur shape both tumor biology and clinical behavior.[1,2,6–8]

KRAS mutations occur early in tumorigenesis and are present in more than 90% of PDAC cases, making KRAS the central oncogenic driver of the disease. Loss of CDKN2A and TP53 function typically follows, contributing to genomic instability and loss of cell cycle control, while SMAD4 inactivation tends to occur later and is closely tied to the transition toward an aggressive, metastatic phenotype. This sequence carries practical weight. It has direct implications for how molecular profiling results should be interpreted, since the presence or absence of a given alteration can indicate where a tumor sits along its evolutionary trajectory and what clinical behavior might be expected.[3–5]

Beyond these four canonical drivers, molecular profiling has also revealed that PDAC can be stratified into broader transcriptional subtypes, most notably classical and basal-like phenotypes, which differ substantially in differentiation status, chemotherapy responsiveness, and prognosis. While these subtypes are not the central focus of this review, they provide important context for understanding why tumors with seemingly similar driver mutation profiles can behave very differently, and why a purely mutation-based view of PDAC is insufficient on its own.[1,9,10]

Crucially, molecular profiling is no longer merely descriptive, but increasingly guides therapy. KRAS, once dismissed as undruggable, is now the target of several inhibitors in active clinical development. BRCA1/2 mutations, although present in only a small subset of patients, identify a group with a clear and actionable vulnerability to PARP inhibition. SMAD4 status offers prognostic information that can guide the intensity and focus of systemic therapy. And a growing list of rarer alterations, from BRAF V600E to NTRK and NRG1 fusions, define small but clinically meaningful subgroups for whom targeted agents already exist.[1,6,11–13]

Collectively, these data justify moving away from uniform treatment toward an approach in which molecular profiling actively informs clinical decision-making. The sections that follow examine in detail how three of the most clinically significant alterations, KRAS, BRCA1/2, and SMAD4, contribute to this evolving picture, before turning to emerging biomarkers that may further refine personalized targeting in the years ahead.

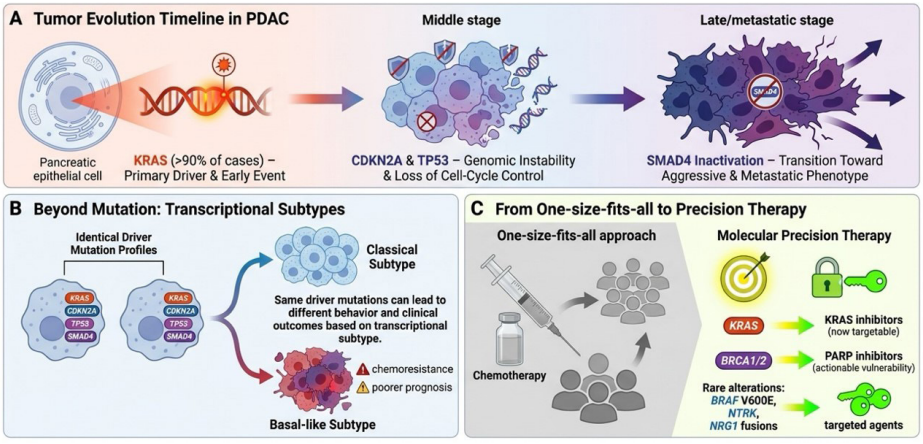

Figure 1. Molecular landscape and therapeutic progress in PDAC

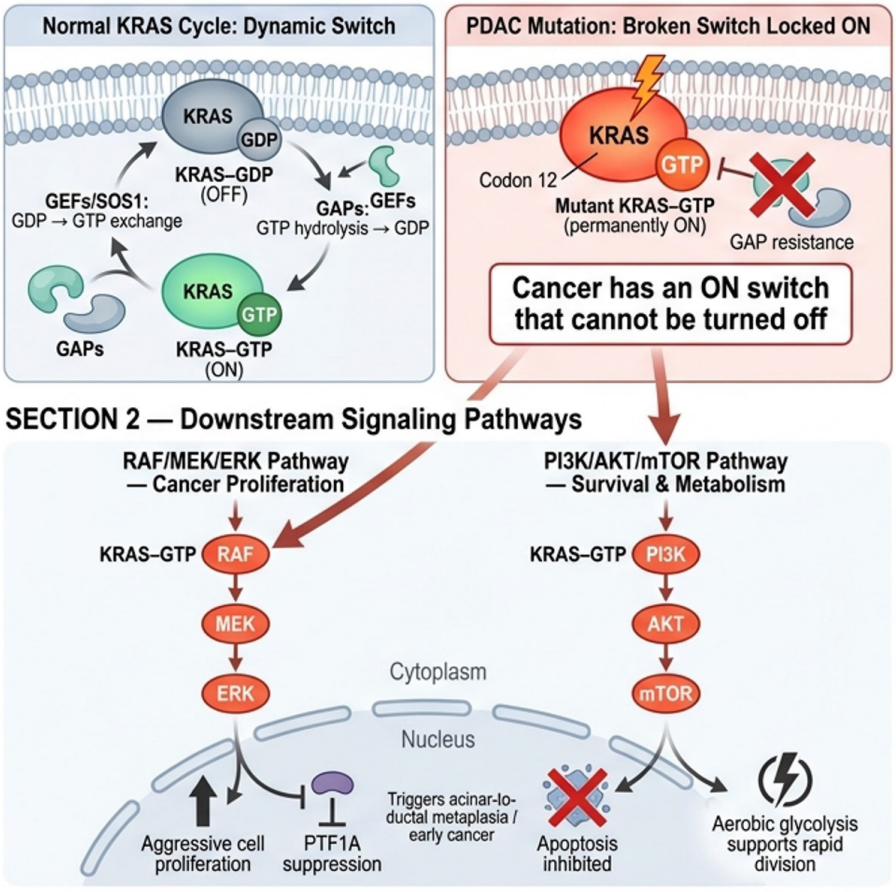

Figure 2. Binary KRAS switch mechanism

KRAS: key driver and therapeutic evolution

KRAS (Kirsten rat sarcoma viral oncogene homolog) functions as a binary molecular switch. Under normal conditions, this protein cycles between an inactive state bound to guanosine diphosphate (GDP) and an active state bound to guanosine triphosphate (GTP). The shift toward the active state is facilitated by guanine nucleotide exchange factors (GEFs) such as SOS1, while the return to the inactive state occurs through GTP hydrolysis, a process accelerated by GTPase-activating proteins (GAPs).[6,14,15]

In PDAC, point mutations at codon 12 of KRAS permanently disrupt this balance. These mutations render KRAS resistant to GAP activity, effectively locking the protein in its active conformation. As a result, pro-proliferative signals are continuously transmitted to downstream pathways without requiring stimulation from growth factor receptors. Cancer cells essentially possess an on switch that cannot be turned off.[6,16,17] This constitutive activation drives two major downstream signaling pathways. The first is the RAF/MEK/ERK cascade, which promotes aggressive cell proliferation and represses the transcription factor PTF1A, a process that contributes to acinar-to-ductal metaplasia, one of the earliest steps in pancreatic carcinogenesis. The second is the PI3K/AKT/mTOR pathway, which sustains cancer cell survival by inhibiting apoptosis while also reprogramming cellular metabolism through increased aerobic glycolysis to meet the energy demands of rapid cell division. The convergence of these two pathways explains why PDAC tends to be highly invasive and resistant to programmed cell death.[6,16,17]

The high activity of these pathways is closely tied to how frequently KRAS mutations occur in PDAC. KRAS mutations are found in more than 90% of cases, with a fairly distinctive pattern: G12D predominates (45%), followed by G12V (35%) and G12R (17%). Notably, G12C, the variant that has been the primary target of first-generation KRAS inhibitors, is rarely found in PDAC, accounting for only about 1-2% of cases. This stands in contrast to non-small cell lung cancer (NSCLC), where G12C represents around 13% of cases. This difference in mutational distribution is one of the key reasons why KRAS-targeted therapies successful in lung cancer cannot be directly translated to pancreatic cancer.[2,6,15,17]

Despite these advances, clinical responses to KRAS inhibitors are often not durable. One major reason is the reactivation of receptor tyrosine kinases (RTKs) such as EGFR, HER2, and FGFR. When KRAS is inhibited, the negative feedback mechanisms that normally suppress these RTKs are lost, prompting cancer cells to upregulate RTK expression and reroute proliferative signaling through alternative pathways. Another resistance mechanism that has drawn increasing attention is the activation of YAP1/TAZ through the Hippo pathway.

Cancer cells, particularly those of the basal-like subtype or those undergoing epithelial-mesenchymal transition (EMT), can exploit this pathway to sustain proliferation and metabolism even when KRAS is effectively inhibited.[1,17,18]

These findings on resistance mechanisms provide a strong rationale for combination therapy strategies. Two of the most widely explored approaches involve pairing KRAS inhibitors with RTK inhibitors, such as those targeting EGFR or pan-ERBB, to disrupt adaptive feedback loops, or combining them with YAP/TEAD pathway inhibitors to close off transcriptional bypass routes. Combinations with standard chemotherapy regimens such as gemcitabine/nab-paclitaxel have also shown synergy in preclinical models, which makes sense given that the cellular heterogeneity within a single PDAC tumor demands a multi-target approach. Moving forward, therapy combinations tailored to each patient's molecular profile appear to represent the most realistic direction for PDAC treatment.[17–19]

BRCA1/2: synthetic lethality and PARP inhibition

Genomic instability driven by deficient DNA repair mechanisms is one of the fundamental enabling characteristics that allows cancer cells to progress. Under normal physiological conditions, the tumor suppressor genes BRCA1 and BRCA2 play a critical role in the homologous recombination (HR) pathway, a high-fidelity DNA repair mechanism responsible for resolving double-strand breaks (DSBs). BRCA2 in particular acts as a key mediator that recruits the recombinase RAD51 to sites of DNA damage, facilitating strand invasion and accurate repair. Loss of function in either of these genes through mutation leads to homologous recombination deficiency (HRD), resulting in the accumulation of chromosomal rearrangements, copy-number alterations, and systemic genomic instability that drives malignant transformation.[19–21]

This deficiency has a clear epidemiological footprint in pancreatic cancer. BRCA1/2 mutations are found in approximately 5 to 10% of PDAC patients, placing PDAC among the malignancies in which this DNA-repair deficiency is clinically actionable. These mutations fall into two categories: germline and somatic. Germline BRCA1/2 mutations substantially increase lifetime PDAC risk, with a 2 to 4-fold increase for BRCA1 and a 3 to 8-fold increase for BRCA2. Somatic mutations, on the other hand, can arise during carcinogenesis without any inherited predisposition. Prevalence also varies considerably across ethnic backgrounds, with the Ashkenazi Jewish population showing markedly higher germline mutation rates, ranging from 5.5% to 21.6%.[15,19,20]

This HR deficiency provides the rationale for using poly(ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated cancers. PARP enzymes play a vital role in detecting and repairing single-strand breaks (SSBs) through the base excision repair pathway. When PARP is pharmacologically inhibited, unrepaired SSBs persist into the DNA replication phase, where the replication process converts them into far more damaging DSBs. In normal cells, these DSBs can be readily repaired through a functional HR pathway. However, in BRCA-deficient PDAC cells, the HR pathway is inactivated, leaving the cell unable to handle the resulting accumulation of DSBs. This double failure of two mutually compensatory DNA repair mechanisms causes replication fork collapse, extreme genomic instability, and ultimately triggers apoptosis.[15,20]

This mechanistic rationale has translated into real clinical progress for PARP inhibitors, particularly olaparib, rucaparib, and niraparib. Olaparib was the first PARP inhibitor to receive regulatory approval for PDAC, based on results from the phase III POLO trial (Pancreas Cancer Olaparib Ongoing). The trial evaluated olaparib as maintenance therapy for metastatic PDAC patients with germline BRCA mutations whose disease had not progressed after at least 16 weeks of platinum-based chemotherapy. Results showed a significant improvement in median progression-free survival (mPFS), 7.4 months in the olaparib group compared with 3.8 months in the placebo group (HR 0.53, $p = 0.004$). However, the final analysis showed no significant overall survival (OS) benefit, underscoring that the gain was confined to disease control rather than prolonged survival.[7,19,20]

Beyond olaparib, rucaparib and niraparib are also being explored intensively. Rucaparib demonstrated efficacy in the phase II RUCAPANC trial, with an objective response rate (ORR) of 16% in previously treated PDAC patients. More recent data on rucaparib as maintenance therapy show promising results, with mPFS reaching 13.[1] months and mOS of 23.5 months in platinum-sensitive patients with BRCA1/2 or PALB2 mutations. Meanwhile, niraparib is being tested in combination with immune checkpoint inhibitors such as ipilimumab or nivolumab. In a phase Ib/II study, the combination of niraparib and ipilimumab showed a favorable safety profile along with therapeutic potential, with mPFS of 8.1 months and mOS of 17.[3] months in the maintenance population.[6,19,20] Because these survival gains are clinically meaningful, identifying the right candidates through genetic testing, particularly germline testing, has become an urgent clinical need. Without adequate molecular profiling, patients carrying BRCA mutations risk missing out on treatment that could significantly extend their survival. That said, a major limitation remains: PARP inhibitor therapy currently applies only to a small subset of patients (5-10%) with functional BRCA mutations.[15]

Adaptive resistance also poses a significant clinical hurdle, as cancer cells can restore HR functionality through secondary mutations or other transcriptional bypass mechanisms. Future strategies are being directed toward expanding the reach of this therapy through the concept of "BRCAness", targeting tumors that exhibit an HRD phenotype even without germline BRCA mutations, alongside the development of combination therapies to address these complex resistance mechanisms. Integrating molecular profiling into routine clinical practice is expected to help bridge the gap between academic discovery and therapeutic reality.[20,22]

SMAD4: prognostic biomarker and therapeutic implications

SMAD4 (Small Mothers Against Decapentaplegic homolog 4), also known as DPC4 (Deleted in Pancreatic Cancer

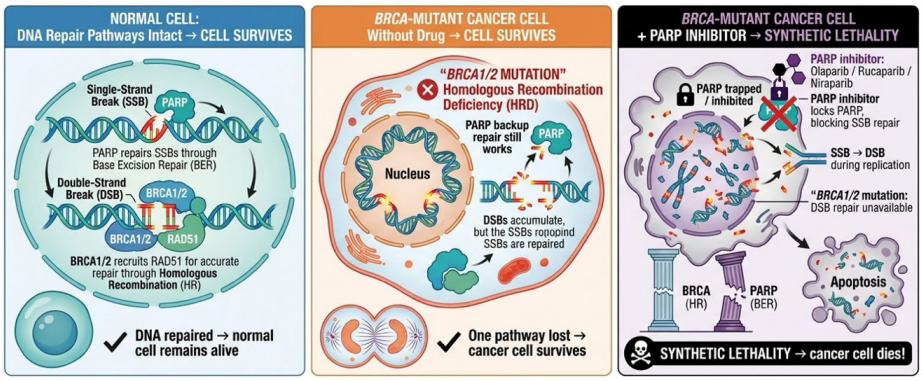

Figure 3. BRCA1/2 mutation & PARP inhibition in PDAC

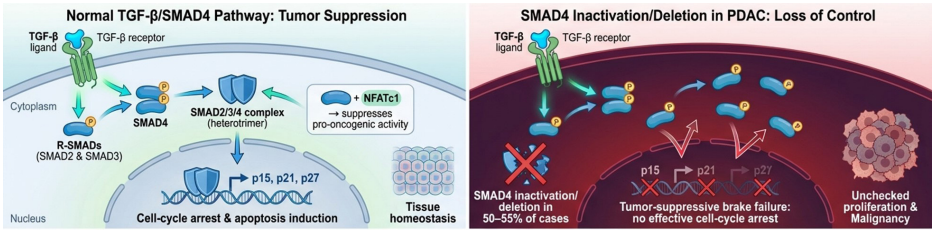

Figure 4. Normal and inactivated molecular SMAD4 signaling

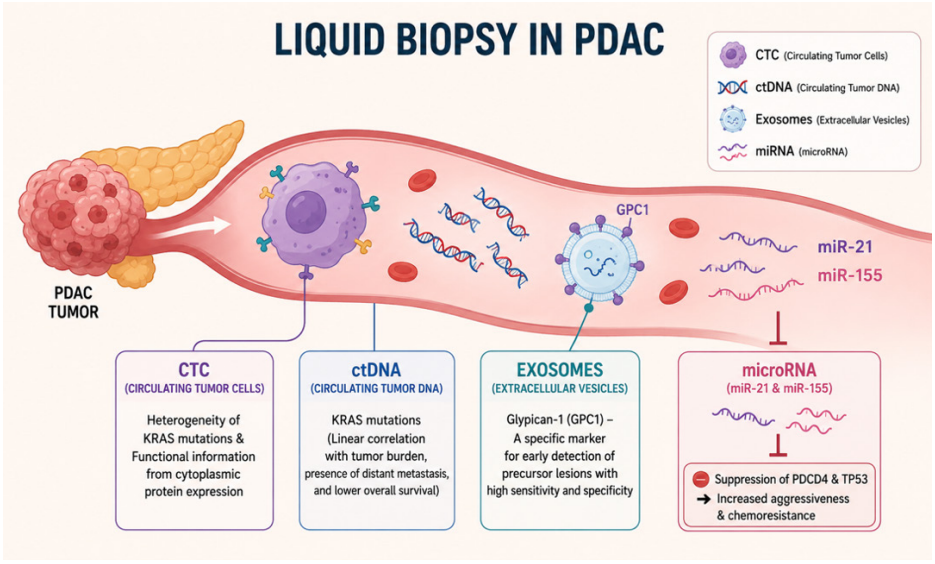

Figure 5. Liquid biopsy for early detection and clonal evolution in pancreatic ductal adenocarcinoma (PDAC).

4), serves as a central mediator in the transforming growth factor-beta (TGF-β) signaling pathway. Canonically, activation of this pathway begins when a TGF-β ligand binds to a cell surface receptor, triggering phosphorylation of R-SMADs (SMAD2 and SMAD3), which then form a heterotrimeric complex with SMAD4 to translocate into the nucleus. Inside the nucleus, this complex regulates the transcription of target genes responsible for cell cycle arrest, through induction of CDK inhibitors such as p15, p21, and p27, as well as activation of apoptotic pathways. Beyond this canonical role, recent studies have uncovered non-canonical, TGF-β-independent functions of SMAD4, such as its cytoplasmic interaction with NFATc1 to suppress pro-oncogenic transcriptional activity. Under normal physiological conditions, the integrity of SMAD4 signaling is essential for maintaining tissue homeostasis and preventing uncontrolled epithelial proliferation.[2,10,23]

In PDAC, loss of this signaling has substantial consequences. SMAD4 inactivation is one of the most prominent genetic features of pancreatic ductal adenocarcinoma, with mutation or deletion occurring in approximately 50 to 55% of cases. Temporally, disruption of the SMAD4 gene is considered a late-stage molecular event in the adenoma-to-carcinoma sequence. Unlike KRAS mutations, which appear in early premalignant lesions such as PanIN-1, SMAD4 inactivation is typically detected only in high-grade lesions (PanIN-3) or once the tumor has become invasive. Although loss of SMAD4 alone is insufficient to initiate tumor formation, this deficiency dramatically accelerates the progression of malignancy already initiated by oncogenic KRAS, speeds up primary tumor growth, and reshapes the tumor microenvironment into a more fibro-inflammatory state.[2,6,15]

This late-stage acceleration also has direct consequences for how the disease spreads and responds to treatment. Loss of SMAD4 function correlates strongly with a highly aggressive PDAC phenotype, particularly with respect to widespread metastatic capacity. Autopsy studies show that SMAD4 mutations are commonly found in distant metastatic lesions but are often absent in tumors that remain locally destructive without systemic spread. Beyond its role in metastasis, SMAD4 deficiency is also a major driver of resistance to standard treatment modalities. At the cellular level, SMAD4 loss increases autophagy and reactive oxygen species (ROS) production, both of which contribute to radioresistance. More recent mechanistic work shows that, under normal conditions, SMAD4 can bind PARP1 in the nucleus to inhibit the efficiency of double-strand break repair, meaning that its loss leaves cancer cells with a superior capacity to repair radiation-induced DNA damage. Clinically, patients with low or mutant SMAD4 also show notably poor responses to systemic chemotherapy and a substantially higher risk of metastatic recurrence.[4,8,15]

Reflecting these associations, SMAD4 status has become a valuable independent prognostic biomarker for patient risk stratification. Intact SMAD4 expression,

as detected by immunohistochemistry, is associated with a significant improvement in overall survival (OS), with a median survival of around 19.2 months compared with 14.[7] months in SMAD4-deficient patients. Determining SMAD4 status allows clinicians to distinguish between distinct patterns of disease progression: patients with intact SMAD4 tend to have more locally controlled disease, while those with mutant SMAD4 require more intensive systemic treatment strategies given their predisposition toward distant metastatic dominance. This stratification based on SMAD4 status is becoming increasingly important in the era of precision oncology, helping to identify patient subsets that may benefit from specific combination therapies.[10,15,23,24]

Despite this prognostic value, current clinical technology is still unable to directly restore the function of lost tumor suppressor genes like SMAD4. Treatment strategies have therefore shifted toward indirect approaches that modulate downstream or compensatory pathways. One major strategy involves inhibiting the TGF-β pathway using monoclonal antibodies such as fresolimumab or small-molecule inhibitors such as galunisertib, aiming to block the pro-tumorigenic effects that emerge once SMAD4 is lost. In addition, because SMAD4-deficient PDAC cells frequently show hyperactivation of the MAPK cascade, the use of MEK/ERK axis inhibitors represents a rational option for suppressing proliferation. Recent breakthroughs have also identified the SMAD4-NFATc1-STAT3 axis as a novel therapeutic vulnerability, with SMAD4-mutant PDAC cells showing strong dependence on STAT3 signaling, providing a foundation for the future use of STAT3 inhibitors as personalized therapeutic agents.[10,15]

Emerging biomarkers in precision oncology for PDAC

Recent advances in molecular profiling have shifted the diagnostic and therapeutic paradigm for pancreatic ductal adenocarcinoma (PDAC) away from conventional approaches toward a more dynamic, personalized strategy. Identifying new biological markers is not only critical for early detection at potentially resectable stages, but also essential for monitoring clonal tumor evolution and resistance mechanisms in real time. Molecular targets once considered too rare to matter are now opening new treatment avenues for specific patient subsets, offering therapies that are both more effective and less toxic.[2,25]

One of the most promising directions in this space is liquid biopsy, a non-invasive approach that allows analysis of tumor genetic material through body fluids. This technology provides a more comprehensive picture of intratumoral heterogeneity than a single tissue biopsy can capture, since the material released into circulation includes circulating tumor cells (CTCs), circulating cell-free nucleic acids (cfDNA and cfRNA), and extracellular vesicles such as exosomes.[2,15] Detection of KRAS mutations in circulating tumor DNA (ctDNA) has shown significant prognostic value, with higher ctDNA levels correlating strongly with greater tumor burden, the presence of distant metastasis, and worse overall survival (OS). CTCs, meanwhile, provide rich functional information, including cytoplasmic protein expression that cannot be obtained from free DNA alone. KRAS mutation heterogeneity in CTCs often does not match the primary tumor, reflecting the clonal evolutionary plasticity that occurs during metastatic spread.[2,5,15]

Exosomes add another layer to this picture, acting as stable intercellular messengers in circulation that carry tumor-specific molecular signatures. Glypican-1 (GPC1), detected on circulating exosomes, has been identified as a biomarker with remarkably high sensitivity and specificity for early PDAC detection, even at the precursor lesion stage. Complementing this diagnostic picture, microRNA profiling, particularly miR-21 and miR-155, shows considerable promise as both diagnostic and prognostic markers. miR-21 in particular is consistently upregulated in PDAC and closely linked to aggressive progression and chemoresistance through suppression of tumor suppressor genes such as PDCD4 and TP53.[5,14,15]

Patients with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) status, found in roughly 1-2% of PDAC cases, show high sensitivity to pembrolizumab. Data from the KEYNOTE-158 trial confirmed a promising objective response rate (ORR) in this group, making it a genuine therapeutic target despite its low frequency. Beyond MSI-H, tumor mutational burden (TMB) has also emerged as an important indicator, with high TMB correlating linearly with response to PD-1/PD-L1 blockade. Strategies to enhance tumor immunogenicity through modulation of the tumor microenvironment (TME) are currently being explored intensively to extend the benefits of immunotherapy to a broader PDAC population.[5,7,14,19,25] Beyond immunotherapy biomarkers, another important frontier lies in rare but actionable molecular targets. In KRAS wild-type PDAC tumors, various rare gene fusions and mutations emerge as alternative oncogenic drivers that take over the role KRAS would normally play in initiating tumorigenesis. Identifying these targets through routine genetic testing is increasingly important, given the availability of specific approved therapeutic agents.[15,25]

BRAF V600E mutations, found in around 3% of patients, represent a component of the downstream MAPK pathway that can be effectively targeted using a combination of BRAF and MEK inhibitors, such as dabrafenib and trametinib. FGFR2 gene fusions define a unique molecular subset that shows remarkable clinical response to kinase inhibitors such as erdafitinib. NTRK1/2/3 fusions, although extremely rare (<1%), represent an important precision target, with first-generation TRK inhibitors such as larotrectinib and entrectinib having received FDA approval for fusion-positive tumors on a tissue-agnostic basis. Finally, NRG1 gene fusions have emerged as a novel driver in KRAS wild-type tumors, activating ERBB3 signaling, and are currently being targeted using bispecific antibodies such as zenocutuzumab (MCLA-128) in late-stage clinical trials.[2,7,15,20]

Cancer cells, particularly the aggressive basal-like subtype, often increase YAP/TAZ transcriptional activity following pharmacological inhibition of KRAS. This bypass mechanism allows cells to maintain proliferation even when the

upstream MAPK cascade is suppressed. To address this, new therapeutic agents such as IAG933 and GNE-7883 have been designed to disrupt the interaction between YAP and the TEAD transcription factor. These inhibitors work by targeting the lipid pocket, a hydrophobic pocket on TEAD required for forming a functional complex with YAP/TAZ.[1,17] Given this mechanism, there is strong scientific rationale for combining KRAS inhibitors (such as MRTX1133) with YAP/TEAD pathway inhibitors or RTK inhibitors (such as EGFR blockade). These vertical and horizontal combination strategies aim to close off transcriptomic and adaptive escape routes, achieving deeper therapeutic responses and preventing the early relapse commonly seen in PDAC patients due to cellular phenotypic plasticity. Integrating YAP/TAZ markers into patient risk profiles is expected to refine therapy stratification strategies going forward.[6,8,17] This review is limited by the heterogeneity and potential publication bias of the included studies, as well as differences in molecular profiling approaches across PDAC cohorts. Additionally, the continuously evolving evidence on emerging biomarkers and targeted therapies may influence the applicability of current conclusions over time

CONCLUSION

PDAC remains a molecularly complex disease in which KRAS, BRCA1/2, and SMAD4 each contribute distinct and clinically meaningful information, ranging from direct therapeutic targets to prognostic indicators that shape treatment intensity. While targeted therapies and synthetic lethality approaches have introduced genuine progress for specific patient subsets, resistance mechanisms and the limited proportion of patients with actionable alterations continue to constrain overall impact. Emerging biomarkers, including liquid biopsy markers, rare gene fusions, and the YAP/TAZ pathway, offer promising avenues to expand the population that may benefit from personalized approaches and to address resistance through rational combination strategies. Continued integration of comprehensive molecular profiling into routine clinical practice, alongside further mechanistic research into pathway interactions, will be essential to translate these advances into meaningful survival improvements for patients with PDAC.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest about this article

AUTHOR CONTRIBUTION

MAKA, AAGCW, and IGPS conceptualized and developed the review outline. MAKA, AAGCW, IGBBAR, and IGAPS performed the literature search, evaluated and interpreted the selected studies, and drafted the manuscript. IGPS provided overall supervision, contributed to critical manuscript revision, and approved the final structure and content. All authors reviewed and approved the final manuscript.

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ETHICS APPROVAL

Not Applicable

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