Pancreatic cancer biomarkers and diagnostic tools (Review)

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) is characterized by late presentation, early systemic dissemination and profound therapeutic resistance. Biomarkers are therefore required not only for early detection, but also for prognosis, treatment selection and longitudinal monitoring. The present review summarizes established and emerging PDAC biomarkers across genomics, epigenomics, transcriptomics, proteomics, metabolomics and liquid biopsy. Particular attention is given to predictive biomarkers for personalized systemic therapy, including homologous-recombination repair defects associated with platinum sensitivity and eligibility for maintenance olaparib, as well as investigational markers of response to gemcitabine, fluoropyrimidines, irinotecan and oxaliplatin. The evolving role of companion diagnostics for germline BRCA1/2 variants and tumor-agnostic alterations is also discussed. In addition, the present review discusses biomarkers associated with occult or distant metastasis, including circulating tumor DNA, circulating tumor cells, extracellular vesicles, the SMAD4 status and multi-modal radiomic models. CA19-9 remains the most commonly used serum marker; however, it is unsuitable for population screening and cannot independently establish diagnosis or metastatic risk. The majority of multi-omics candidates remain at the discovery or retrospective-validation stage. Their clinical translation requires analytically standardized assays, prospective validation in defined clinical settings and evidence that biomarker-guided decisions improve patient outcomes.

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1. Introduction

Advances in genomics and high-throughput molecular profiling have enabled disease classification at increasing biological resolution (1,2). Pancreatic ductal adenocarcinoma (PDAC) remains a particularly urgent setting for precision medicine as the majority of patients present with unresectable or metastatic disease, while recurrence following apparently curative resection is common (3,4). Cross-sectional imaging, endoscopic ultrasound and tissue sampling remain central to diagnosis and staging. Multi-agent chemotherapy, most commonly FOLFIRINOX-based therapy or gemcitabine plus nab-paclitaxel, forms the backbone of systemic treatment (5).

A biomarker is not defined only by its molecular identity, but by its intended context of use (6). Diagnostic biomarkers support disease detection; prognostic biomarkers estimate outcome independent of a specific treatment; predictive biomarkers identify differential benefit or harm from an intervention; monitoring biomarkers track burden, response or molecular evolution. Failure to separate these functions has contributed to premature claims of clinical utility. The present review therefore discusses the analytical validity, clinical validity and clinical readiness of PDAC biomarkers, with emphasis on personalized therapy and the prediction of distant metastasis.

2. Current diagnostic framework and unmet needs

Pancreas-protocol multidetector computed tomography is the principal staging examination, with magnetic resonance imaging and endoscopic ultrasound used as complementary modalities and positron-emission tomography reserved for selected indications. Histological or cytological confirmation is generally required before systemic treatment (7). These methods may miss microscopic dissemination and do not fully capture spatial heterogeneity. Molecular testing can be

performed on tumor tissue and germline DNA; plasma testing can complement tissue analysis in selected settings, although a negative plasma result does not exclude an alteration, particularly in localized or low-volume PDAC (7,8).

PDAC arises through precursor lesions, including pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. KRAS activation and the subsequent disruption of CDKN2A, TP53 and SMAD4 are recurrent events (9,10). These alterations are biologically informative; however, as KRAS-mutant clones may occur in precursor lesions and cell-free tumor DNA shedding is limited in early disease, no single mutation is sufficiently sensitive and specific for population screening. As illustrated in Fig. 1, biomarker discovery therefore requires the coordinated analysis of clinically relevant specimens across genomic, transcriptomic, epigenomic, proteomic and metabolomic layers, followed by bioinformatic integration and validation against a prespecified clinical outcome.

3. Biomarkers for detection, prognosis and monitoring

Serum proteins. CA19-9 is the most well-established serum marker for PDAC management. It may support baseline assessment, prognosis and response monitoring when interpreted with imaging and clinical findings. Its value is limited by elevation in biliary obstruction and inflammation, low or absent expression in many Lewis-antigen-negative individuals and inadequate sensitivity for early-stage disease (11). Additional proteins have been investigated in research cohorts. For example, Brand *et al* (12) evaluated serum panels incorporating CA19-9 with ICAM-1 and osteoprotegerin, or with CEA and TIMP-1, in patients with PDAC, benign pancreatic conditions and healthy controls. Such panels require further validation and have not replaced routine assessment. Serial CA19-9 measurements may support monitoring, but an isolated biochemical change should not establish progression without clinical and radiological correlation (7,11).

Epigenomic, transcriptomic, proteomic and metabolomic markers. Aberrant DNA methylation has been investigated in tumor tissue and biological fluids as a candidate source of diagnostic biomarkers. Pre-analytical variation, bisulfite-conversion efficiency, low circulating DNA abundance and inconsistent cut-offs complicate comparison between studies (13). Transcriptomic candidates include miR-21, miR-155, miR-196a and miR-210. Wang *et al* (14) investigated these four microRNAs in plasma from patients with PDAC, providing proof-of-principle evidence rather than a clinically validated screening assay. Other RNA signatures remain investigational, and their interpretation requires standardized sampling, normalization and independent validation (15).

Oncogenic KRAS rewires glucose, glutamine and redox metabolism (16). Serum or tissue metabolomic profiles, including ethanolamine-related signatures, have been associated with survival (17). Proteomic and glycoproteomic studies have identified MUC5AC, CEACAM5, ANXA10 and other candidates (15). Although these approaches broaden biological coverage, they remain vulnerable to cohort composition, pancreatitis controls, platform effects and overfitting. Independent prospective validation is essential.

Liquid biopsy. Liquid biopsy includes circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles and circulating RNA. Detectable mutant KRAS in ctDNA is associated with tumor burden and adverse outcomes, whereas negative results do not exclude disease, particularly in localized PDAC (8,18,19). CTC analyses provide complementary evidence of dissemination (20). Cohen *et al* (21,22) investigated assays combining mutation detection with circulating proteins in research cohorts; their screening performance requires evaluation in the intended population and against clinically relevant benign controls. A summary of these biomarker classes is presented in Fig. 2. Tissue and blood-based assays provide complementary information, but repeated plasma sampling does not overcome limited sensitivity in low-volume disease (8,23).

4. Predictive biomarkers for personalized systemic therapy and companion diagnostics

Homologous-recombination deficiency and platinum therapy. The most clinically mature predictive association in PDAC involves defects in homologous-recombination repair. Pathogenic germline or somatic alterations in BRCA1, BRCA2 and PALB2 can impair the repair of double-strand DNA breaks and confer vulnerability to platinum compounds. In previous retrospective matched analyses, BRCA1/2- or PALB2-mutated PDAC exhibited a higher objective response rate and longer real-world progression-free survival with platinum therapy than mutation-negative controls (24). A randomized phase II study of cisplatin plus gemcitabine in germline BRCA/PALB2-mutated PDAC also demonstrated substantial activity, while the addition of veliparib did not significantly improve response (25). These findings support early germline testing and broad tumor profiling, as the results may affect first-line regimen selection. Nevertheless, 'BRCAness' signatures and genomic-scar scores are not interchangeable with pathogenic BRCA/PALB2 variants, and prospective cut-offs for PDAC remain unsettled.

PARP inhibitor selection and companion diagnostics. The phase III POLO trial established maintenance olaparib for patients with metastatic PDAC carrying deleterious or suspected deleterious germline BRCA1/2 variants whose disease had not progressed during at least 16 weeks of first-line platinum chemotherapy. The median progression-free survival improved, although a statistically significant overall-survival advantage was not demonstrated (26,27). BRACAnalysis CDx was approved by the US Food and Drug Administration (FDA) as a companion diagnostic for this indication (28). This represents a validated biomarker-drug-assay association; it should be distinguished from exploratory associations. Tissue or plasma comprehensive genomic profiling can identify additional homologous-recombination alterations, although eligibility and evidence vary by drug, regulatory jurisdiction and germline vs. somatic status (7).

Investigational biomarkers for conventional chemotherapy. High tumor expression of the nucleoside transporter hENT1 was associated with survival benefit from adjuvant gemcitabine in an analysis of ESPAC-3 specimens (29). This association has not established a routine companion assay

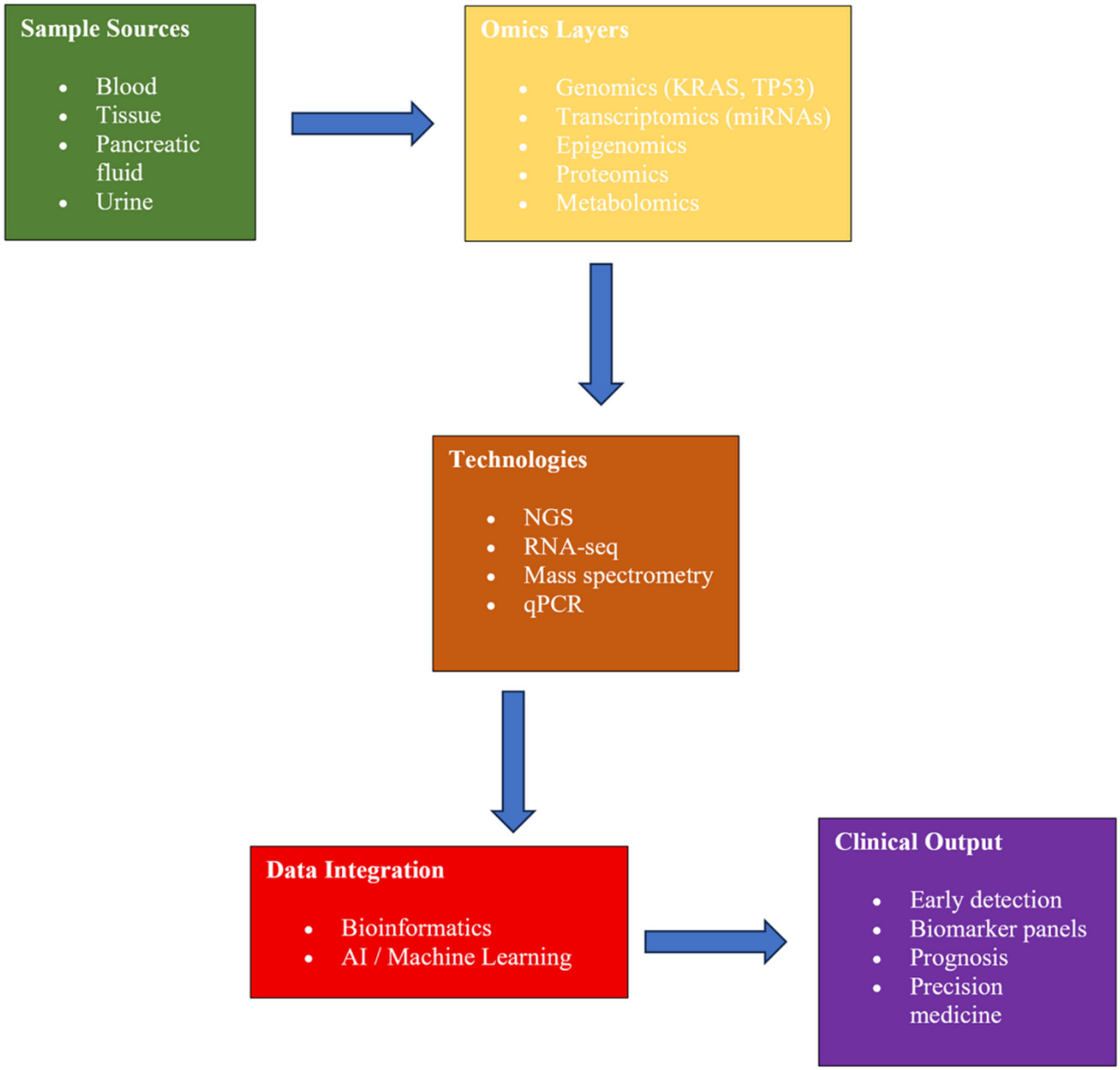


Figure 1. Multi-omics pipeline for biomarker discovery in pancreatic ductal adenocarcinoma. Biological specimens are analyzed across complementary omics layers and integrated with bioinformatic methods. The value of this pipeline lies in moving from isolated candidate markers to validated multi-analyte signatures for detection, prognosis and therapeutic stratification.

for treatment selection (7). Expression of hENT1, deoxycytidine kinase and RRM1 was also associated with outcome in a cohort of patients receiving adjuvant gemcitabine; such single-treatment cohort associations should not be equated with differential treatment benefit (30). CES2 expression and activity were investigated in experimental models and a neoadjuvant FOLFIRINOX-treated PDAC cohort as potential determinants of irinotecan sensitivity (31). These findings remain insufficient for independent regimen selection. DPYD and UGT1A1 testing have a distinct role in fluoropyrimidine- and irinotecan-related drug safety, respectively, as described in pharmacogenetic dosing guidelines (32,33). They are toxicity markers rather than PDAC-specific predictors of antitumor efficacy. Established clinical and molecular criteria should therefore guide treatment while these investigational markers undergo further validation (7).

Tumor-agnostic biomarkers and rare actionable subgroups. Comprehensive profiling may identify uncommon actionable alterations. Microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) can identify candidates for immune-checkpoint blockade, while NTRK fusions identify candidates for TRK inhibitors (34-36). Evidence for BRAF/MEK inhibition in BRAF V600E-mutated rare cancers includes the ROAR basket trial; this evidence should not be presented as a PDAC-specific randomized result (37). RET, NRG1 and HER2 also require alteration- and indication-specific interpretation. In the United States, selpercatinib has an indication for eligible previously treated RET fusion-positive solid tumors, supported by LIBRETTO-001 (NCT03157128) (38). Zenocutuzumab received accelerated FDA approval in December, 2024 for eligible previously treated advanced NRG1 fusion-positive pancreatic adenocarcinoma,

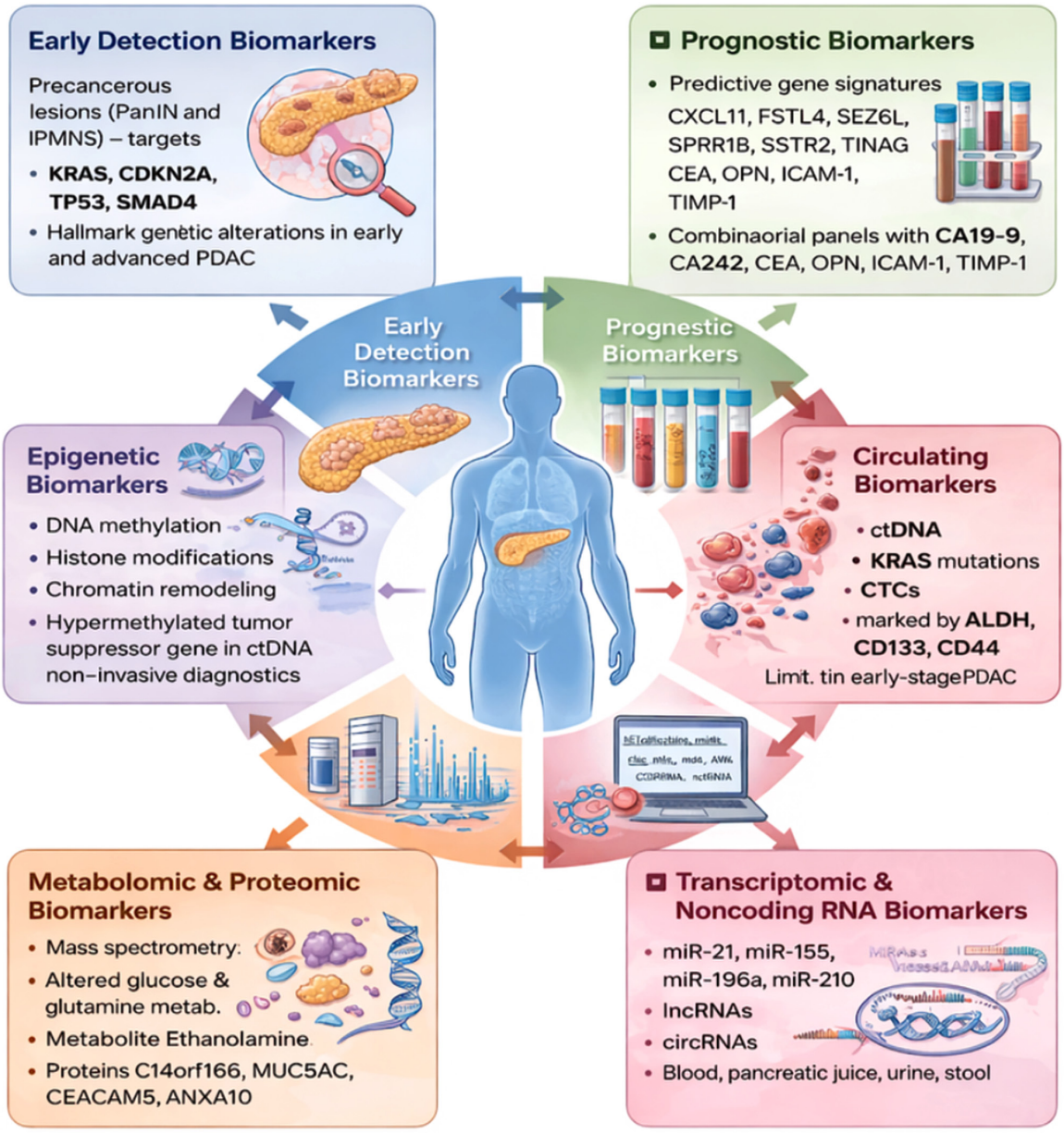


Figure 2. Integrated overview of PDAC biomarker categories. The figure links early-detection, prognostic, epigenetic, metabolomic, proteomic, transcriptomic and circulating biomarkers. Its organization highlights the need to interpret each class according to specimen, analytical platform and intended clinical use. PDAC, pancreatic ductal adenocarcinoma.

based on eNRGy (NCT02912949) (39). Fam-trastuzumab deruxtecan received accelerated FDA approval for eligible previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors, supported by studies including DESTINY-PanTumor02 (NCT04482309); HER2 amplification alone is not interchangeable with this IHC-based criterion (40). These examples concern molecular treatment selection, and eligibility must be checked against the applicable indication and jurisdiction.

5. Biomarkers for distant metastasis and early systemic dissemination

A clinically useful biomarker would identify occult systemic disease before it becomes radiologically visible, help distinguish patients likely to benefit from immediate surgery from those requiring systemic treatment, and detect metastatic relapse during surveillance. Current staging and treatment decisions require integration of imaging, pathological findings and clinical assessment; a circulating biomarker should not independently replace these assessments (7,8).

Circulating DNA and tumor cells. Detectable pre-operative ctDNA, particularly mutant KRAS, consistently marks biologically aggressive disease and is associated with early recurrence and distant failure. In localized PDAC, however, sensitivity is modest as small tumors shed minimal amounts of DNA. Post-operative persistence or re-emergence may indicate molecular residual disease, while serial increases during treatment can precede radiological progression (18,19). These signals provide prognostic information and may indicate occult dissemination; however, assay platforms, sampling intervals

Table I. Representative PDAC biomarkers classified by intended use and clinical readiness.

Biomarker	Specimen	Primary use	Readiness	Principal limitation
CA19-9	Serum	Monitoring/prognosis	Routine adjunct	Not screening; confounded by cholestasis; Lewis-negative non-secretors
gBRCA1/2	Blood germline DNA	Platinum/PARP selection	Clinically actionable	Variant interpretation and indication-specific eligibility
BRCA1/2/PALB2 and other HRR alterations	Tumor DNA; germline DNA as indicated	Platinum sensitivity; trials	Variant-specific/evolving	Evidence varies by gene and variant; HRD assays are not standardized
MSI-H/dMMR	Tumor tissue	Immune checkpoint therapy	Tumor-agnostic actionable	Rare in PDAC
NTRK fusion	Tumor RNA/DNA	TRK inhibitor selection	Tumor-agnostic actionable	Very rare; RNA testing often preferred
hENT1/RRM1	Tumor tissue	Gemcitabine response	Investigational	Assay and prospective-validation limitations
DPYD/UGT1A1	Germline DNA/phenotype	Drug toxicity	Clinically used in selected	Safety rather than PDAC-specific efficacy
ctDNA/KRAS	Plasma	Burden, MRD, metastasis risk	Investigational	Low sensitivity in localized disease
CTCs	Blood	Dissemination/prognosis	Investigational	Platform variability and low abundance
Exosomal cargo	Plasma/serum	Detection/organotropism	Early research	Isolation and normalization not standardized
SMAD4/DPC4	Tumor tissue	Pattern of failure	Investigational prognostic	Insufficient for individual decisions
Multi-modal/radiomic models	Imaging + clinical + molecular	Occult metastasis/risk	Investigational	External validation and calibration needed

gBRCA1/2, germline BRCA1/2; PARP, poly(ADP-ribose) polymerase; PDAC, pancreatic ductal adenocarcinoma; MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; HRR, homologous-recombination repair; MRD, molecular residual disease; ctDNA, circulating tumor DNA; CTCs, circulating tumor cells.

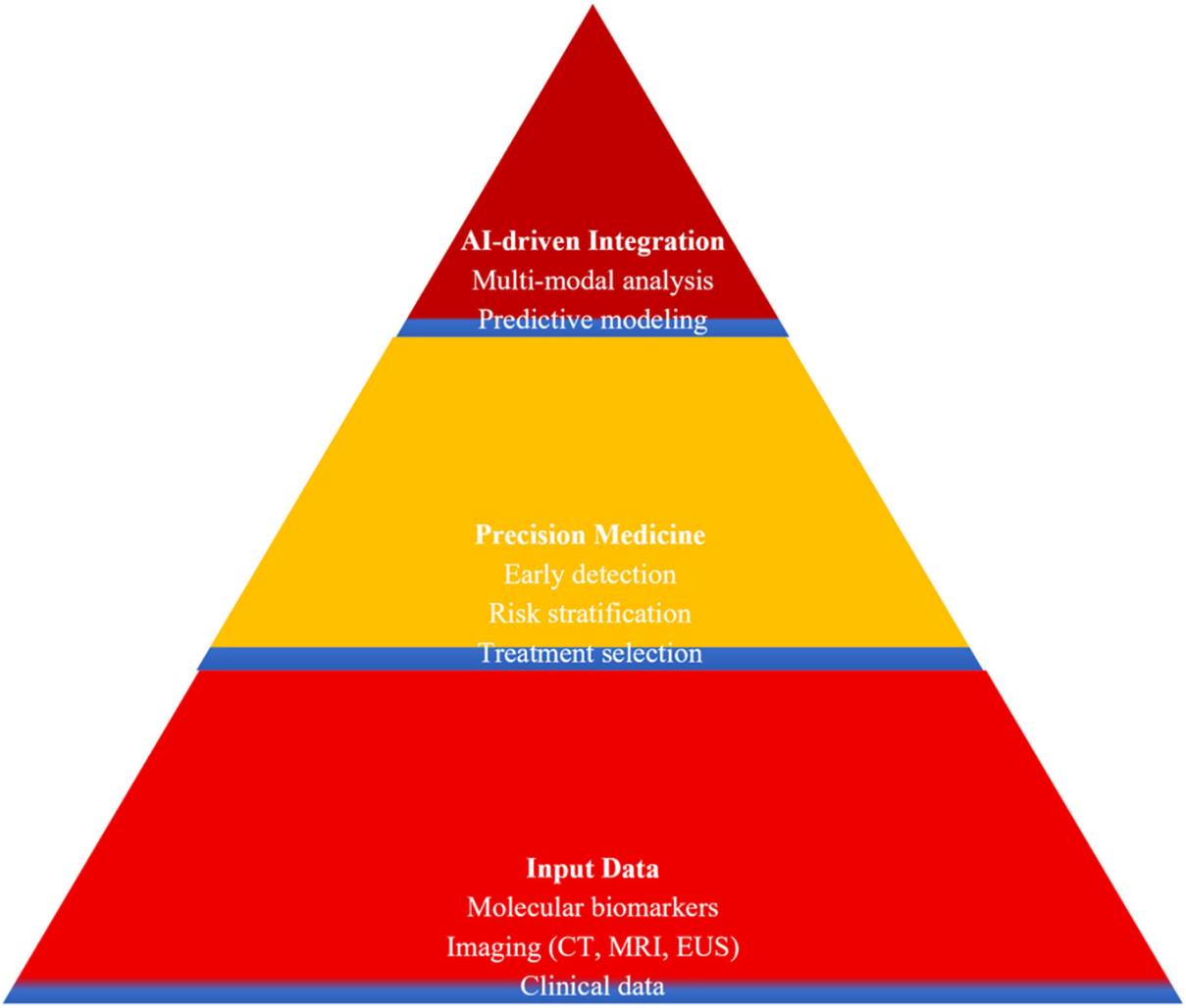


Figure 3. Integrative diagnostic model for pancreatic ductal adenocarcinoma. Molecular biomarkers, imaging and clinical data form the input layer for multi-modal analysis. Computational integration may support early detection, risk stratification and treatment selection, provided that the complete model is independently and prospectively validated.

and thresholds are not standardized. They should not yet be used alone to exclude resection7,8).

CTCs provide evidence of hematogenous dissemination, but their clinical interpretation is affected by low abundance and differences in enrichment and analytical methods. Yu *et al* (20) explored pharmacogenomic modeling of circulating tumor and invasive cells for chemotherapy-response assessment in PDAC. This exploratory application does not establish a validated test for selecting treatment or predicting metastatic relapse. Combining circulating analytes may broaden biological coverage; however, this requires prospective comparison against established staging and clinically meaningful outcomes (8,23).

6. Tissue, extracellular vesicles and multi-modal signatures

The loss of SMAD4/DPC4 in the primary tumor has been associated with widespread metastatic failure rather than a predominantly local pattern (41), although it is not sufficiently deterministic for individual treatment decisions. Transcriptional programs governing epithelial plasticity and clonal cooperation contribute to metastatic organotropism (42,43). Extracellular vesicle cargo is also of interest: Glypican-1-positive exosomes have been reported as a PDAC signal (44), and exosomal integrin profiles have been linked to organ-specific metastatic niches across cancers (45). These observations are mechanistically compelling, yet require independent PDAC-specific validation.

Routine clinical and pathological variables can be considered alongside imaging and molecular measurements when developing risk models (7). Any proposed multi-modal model should specify its intended use, report model development and validation transparently, and assess calibration and applicability in an external population (46,47). A higher discrimination estimate alone does not establish that using the model improves clinical decisions.

7. Clinical-readiness matrix

As summarized in Table I, clinical readiness differs markedly among PDAC biomarkers. CA19-9 is a routine adjunct for monitoring, but is not a screening test. Germline BRCA1/2 testing and selected tumor-agnostic alterations can directly guide approved treatments, whereas homologous-recombination

signatures beyond validated pathogenic variants remain an evolving area. hENT1, ctDNA-based molecular residual disease, CTCs, exosomal cargo, SMAD4 and multi-modal models are best regarded as investigational. This classification is critical as analytical detectability or prognostic association alone does not establish that a biomarker should guide a clinical decision (7,8,11,20,23,26-29,32-36,41,44,45).

8. Translational challenges and future directions

The main translational challenge is to establish a defined clinical use rather than merely identify additional candidates. Reviews of PDAC biomarker development describe limitations in assay standardization and clinical validation (8,10,15). Model development also requires explicit assessment of bias and applicability, including participant selection, predictor handling and outcome assessment (46,47). These issues should be addressed before a biomarker, or composite signature is deployed clinically.

Future studies should prespecify intended use, enroll patients at the relevant clinical decision point and report analytical failures and indeterminate results (46,47). Evaluation of predictive biomarkers should distinguish treatment-biomarker interactions from outcome associations alone (6). Metastasis models should be assessed against standardized staging and clinically meaningful outcomes (7). Longitudinal tissue, plasma and imaging analyses may help characterize tumor evolution (23). Kyrochristos *et al* (48) discussed the opportunities and challenges of next-generation sequencing for pancreatic cancer risk assessment and therapeutic-response prediction. The proposed translational pathway is illustrated in Fig. 3. Computational models integrating molecular, imaging and clinical data require transparent reporting, calibration and external validation before clinical deployment (46,47).

9. Conclusion

PDAC biomarker research is moving from broad discovery toward clinically defined applications. CA19-9 remains an imperfect adjunct for monitoring. Germline BRCA1/2 testing and the corresponding olaparib companion diagnostic constitute the clearest current example of biomarker-guided therapy, while BRCA1/2/PALB2 defects also support preferential consideration of platinum chemotherapy. The majority of proposed chemotherapy-response markers, including hENT1 and CES2, remain investigational. ctDNA, CTCs, extracellular vesicles, SMAD4 status and multi-modal models are being investigated for metastatic-risk stratification; however, none should replace staging imaging or independently determine resectability. Translation will require standardized assays, external and prospective validation, and trials showing that biomarker-guided decisions improve outcomes.

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Authors' contributions

VB was involved in the writing of the original draft of the manuscript. DAS was involved in the reviewing and editing of the manuscript. SPD conceptualized the study, and was also involved in project administration and in the writing, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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