Article 252 Supplementary Material 1 (Correia, Raquel A. P. F *et al.*)

Supplementary Table

Table SM1 | Biomarkers and proteomic insights from selected studies included in this mini-review. For each study, the sample type, key biomarkers and/or proteomic findings, omics layer, and clinical relevance are summarized: ADEX: aberrantly differentiated endocrine exocrine; AUC: area under the curve; CA19-9: carbohydrate antigen 19-9; cfDNA: circulating cell-free DNA; CPTAC: Clinical Proteomic Tumor Analysis Consortium; dCCA: distal cholangiocarcinoma; DDA: data-dependent acquisition; DIA: data-independent acquisition; ECM: extracellular matrix; ELISA: enzyme-linked immunosorbent assay; E-PDAC: early-stage pancreatic ductal adenocarcinoma; EV: extracellular vesicle; GPC1: glypican-1; ICAM-1: intercellular adhesion molecule 1; ICAT: isotope-coded affinity tag; IPMN: intraductal papillary mucinous neoplasm; IOPN: intraductal oncocytic papillary neoplasm; ITPN: intraductal tubulopapillary neoplasm; iTRAQ: isobaric tags for relative and absolute quantitation; LC–MS/MS: liquid chromatography–tandem mass spectrometry; LFQ: label-free quantification; LMD: laser microdissection; MALDI-MSI: matrix-assisted laser desorption/ionisation mass spectrometry imaging; MALDI-TOF/TOF: matrix-assisted laser desorption/ionisation tandem time-of-flight mass spectrometry; MCN: mucinous cystic neoplasm; MR: Mendelian randomisation; MRM: multiple reaction monitoring; MS: mass spectrometry; OPG: osteoprotegerin; PanIN: pancreatic intraepithelial neoplasia; PDAC: pancreatic ductal adenocarcinoma; pQTL: protein quantitative trait locus; PRM: parallel reaction monitoring; PTM: post-translational modification; PWAS: proteome-wide association study; RNA-seq: RNA sequencing; SILAC: stable isotope labelling by amino acids in cell culture; SRM: selected reaction monitoring; SWATH: sequential window acquisition of all theoretical fragment ion spectra; THBS2: thrombospondin-2; TMT: tandem mass tags; WES: whole-exome sequencing; WGS: whole-genome sequencing.

Ref.	Sample Type	Key Biomarkers / Proteomic Insights	Omics Layer	Clinical Relevance / Translational Stage
[1]	Tumour tissue (bulk)	Recurrent driver alterations and pathway-level disruption involving KRAS, TGF-β, WNT, NOTCH, ROBO/SLIT, cell-cycle, chromatin-remodelling, DNA-repair and RNA-processing pathways; four molecular subtypes defined: squamous, pancreatic progenitor, immunogenic and ADEX	Genomics and transcriptomics (WGS/WES and expression profiling)	Establishes the genomic framework and molecular subtype architecture of PDAC, providing biological context for proteomic and proteogenomic interpretation
[2]	PDAC histopathology, precursor lesions and molecular classification	PDAC heterogeneity; precursor lesions including PanIN, IPMN, IOPN, ITPN and MCN; integration of genomic, transcriptomic, proteomic and epigenetic data to refine molecular classification	Molecular pathology / Multi-omics review	Provides histopathological and molecular context for interpreting proteomic findings and supports integration of molecular profiles with pathology for patient stratification
[3]	Serum	Multiplex serum analysis of 83 circulating proteins identified a CA19-9, ICAM-1 and OPG panel with improved discrimination of PDAC from healthy controls compared with CA19-9 alone; performance was more limited for distinguishing PDAC from benign pancreatic conditions	Serum biomarker profiling / Immunoassay panel	Early evidence supporting serum multi-marker panels for PDAC detection; highlights the need for further validation in clinically relevant benign-control and high-risk screening populations
[4]	Tissue, biofluids, EVs and liquid biopsy compartments	Comprehensive overview of MS-based proteomics in pancreatic cancer, covering diagnostic/prognostic biomarkers, PTM networks, immune–stromal interactions, liquid biopsy approaches, and emerging single-cell and spatial proteomics strategies	Multi-compartment proteomics / Multi-omics review	Contextualizes the current state of pancreatic cancer proteomics, highlighting its potential for biomarker discovery, precision oncology and therapeutic target identification, while emphasizing the need for standardised workflows, large-cohort validation and advanced computational integration
[5]	Serum, plasma, tissue, pancreatic juice, cyst fluid, urine, cell lines, stroma and exosomes	Reviews proteomics-derived biomarker candidates across multiple PDAC sample types, including mucin-related markers, ECM/stromal proteins, inflammatory proteins and secreted factors; discusses secretome, plasma and exosome-based discovery strategies	Proteomics biomarker review	Catalogues candidate biomarkers and proteomic discovery workflows in PDAC, while emphasizing the need for standardised methods and independent multi-cohort validation

Table SM1 (continuation)

Ref.	Sample Type	Key Biomarkers / Proteomic Insights	Omics Layer	Clinical Relevance / Translational Stage
[6]	Tissue and plasma/serum studies	Functional and clinical proteomic exploration of PDAC, including tumour biology, stromal interactions, PTMs, therapeutic targets and biomarker discovery	Functional / Clinical proteomics review	Provides a conceptual framework for how proteomics contributes to PDAC biology, molecular classification, therapeutic target discovery and biomarker translation
[7]	Tumour tissue, adjacent normal tissue and normal pancreatic ductal tissue	Comprehensive proteogenomic characterization of 140 pancreatic cancers, including 135 PDACs and 5 pancreatic adenosquamous carcinomas, together with adjacent normal and normal pancreatic ductal tissues; links genomic alterations with protein expression, signalling pathways and PTM-level regulation	Proteogenomics / Proteomics / Phosphoproteomics / Glycoproteomics	Large-scale PDAC proteogenomic resource showing how integrated genomic and proteomic analyses can refine pathway interpretation, nominate candidate biomarkers and identify potential therapeutic vulnerabilities
[8]	Multi-cancer tissues from CPTAC cohorts	Harmonized genomic, transcriptomic, proteomic, phosphoproteomic and clinical datasets across more than 1,000 tumours from 10 cancer cohorts, enabling cross-cancer comparison of molecular alterations at the DNA, RNA, protein and PTM levels	Pan-cancer proteogenomics / Multi-omics resource	Provides a harmonized CPTAC resource for cross-cohort comparison and pathway-level interpretation, demonstrating the added value of protein and PTM measurements beyond genomic and transcriptomic data alone
[9]	PDAC tumour tissue analyzed by bulk sampling, coring and laser microdissection	Laser microdissection produced the most distinct proteomic profiles and the strongest enrichment of neoplastic-cell-associated features compared with bulk tissue and coring; KRAS mutations were also more readily detected in LMD-enriched samples	Tissue proteomics / Genomics methodology	Shows that LMD provides superior neoplastic cell enrichment for PDAC proteogenomic analyses, reducing stromal contamination and improving interpretation of tumour-associated molecular signals
[10]	PDAC tumour tissue heterogeneity and molecular profiling studies	Reviews PDAC heterogeneity as a dynamic continuum shaped by genomic alterations, epigenetic regulation, stromal interactions and tumour microenvironmental cues, rather than by genetic alterations alone	Genomics / Transcriptomics / Epigenetics / Tumour microenvironment review	Provides biological context for interpreting bulk proteomic data and supports the need for spatial, compartment-resolved and multi-omic approaches in PDAC
[11]	Tissue, serum, plasma, pancreatic juice, oral fluids, urine, cell/conditioned medium, EVs and ECM	Summarizes MS-based proteomics strategies across pancreatic cancer sample types, including gel-based proteomics, MALDI-TOF/TOF, LC-MS/MS, DDA-LFQ, DIA/SWATH, TMT, iTRAQ, ICAT, SILAC, MRM/SRM, PRM, glycoproteomics, phosphoproteomics and bioinformatic analysis workflows	MS methodology / Quantitative and qualitative proteomics review	Serves as a practical overview of MS platform selection for pancreatic cancer research, linking discovery, targeted validation and bioinformatic analysis to biomarker discovery, mechanistic interpretation and therapeutic target identification
[12]	Blood-derived samples and pancreatic tumour tissue	Reviews current proteomics applications in pancreatic cancer, including biomarker discovery, screening, diagnosis, treatment response and personalized therapy	Proteomics (review)	Highlights the potential of proteomics to improve PDAC detection and treatment stratification, while emphasizing the need for biomarker validation and standardised sample preparation and data analysis workflows
[13]	PDAC tissue and serum	DIA-MS-based proteomic and N-glycoproteomic analysis identified PDAC-associated serum-detectable glycoproteins, including 892 altered N-linked glycopeptides from 141 glycoproteins; selected candidates were further evaluated in independent PDAC and cancer-free serum cohorts	Glycoproteomics / Proteomics / DIA-MS	Bridges tissue discovery with blood-accessible N-glycosylation-associated protein candidates and supports minimally invasive serum biomarker development
[14]	Bodily fluids, tissues and cell lines	Reviews targeted proteomics strategies, including SRM/MRM, PRM and DIA-based targeted data extraction using high-resolution accurate-mass instruments, with emphasis on assay development, data analysis, specificity, multiplexing and throughput	Targeted proteomics / SRM-MRM / PRM methodology	Provides methodological foundation for translating discovery biomarkers into reproducible quantitative validation assays suitable for clinical biomarker development

Table SM1 (continuation)

Ref.	Sample Type	Key Biomarkers / Proteomic Insights	Omics Layer	Clinical Relevance / Translational Stage
[15]	Peptide/protein targets in complex proteomic samples	Introduces PRM using quadrupole-equipped high-resolution accurate-mass instruments, enabling parallel detection of all target product ions for specific, high-resolution targeted protein quantification	Targeted proteomics / PRM methodology	Supports the use of PRM for specific and reproducible quantification of selected candidate biomarkers during assay validation
[16]	Plasma; conditioned medium / secretome	THBS2 was identified through secretome-guided discovery and validated in plasma across phased cohorts; combined THBS2 + CA19-9 improved PDAC detection, including stage I disease, and improved discrimination between PDAC and control groups, including clinically relevant benign pancreatic conditions	Secretome-guided discovery / Plasma biomarker validation / ELISA	Landmark plasma biomarker study demonstrating that a THBS2 + CA19-9 blood-based panel can improve PDAC detection compared with CA19-9 alone, supporting further validation in high-risk and early-detection settings
[17]	Secretome of resected PDAC and distal cholangiocarcinoma tumour and matched normal tissue	Secretome profiling identified 696 discriminatory proteins and 21 candidate biomarkers, with THBS2 emerging as a promising marker; THBS2 + CA19-9 improved discrimination, including early- and late-stage disease, with an AUC of 0.952 overall	Secretome proteomics / Biomarker validation / ELISA	Supports THBS2 as a secretome-derived biomarker and demonstrates its additive diagnostic value with CA19-9 for distinguishing PDAC or dCCA from healthy and benign-disease controls
[18]	Prediagnostic serum and plasma samples collected 1–15 years before PDAC diagnosis	THBS2/CA19-9 did not achieve the predefined AUC threshold of 0.80 for discriminating future PDAC cases from controls in prediagnostic samples; findings suggest heterogeneous and sometimes rapid PDAC progression	Longitudinal plasma biomarker evaluation / THBS2–CA19-9	Demonstrates that diagnostic biomarker performance does not necessarily translate to prediagnostic detection, highlighting the need for longitudinal validation in screening-relevant cohorts
[19]	Pancreatic cancer and matched normal tissue	Proteomic landscape analysis identified a 20-protein diagnostic panel, four prognostic PDAC subtypes and an externally validated 18-protein risk score associated with overall survival and recurrence	Tissue proteomics / Prognostic stratification	Supports protein-based patient stratification and prognostic modelling, while requiring further clinical validation before use in treatment-guidance or personalized medicine settings
[20]	Plasma proteomics workflows	Discusses key pre-analytical and analytical variables in MS-based plasma proteomics, including sample collection, processing, storage, preparation, MS acquisition, quality control and data analysis considerations	Plasma proteomics methodology	Provides translational guidance for generating reproducible plasma proteomics data and highlights the need for standardised workflows from sample collection to clinical interpretation
[21]	Human plasma	Describes the complexity and extreme dynamic range of the human plasma proteome, including the dominance of high-abundance proteins and the challenge of detecting low-abundance diagnostic biomarkers	Plasma proteome biology / Diagnostic proteomics	Provides the analytical rationale for enrichment, depletion, fractionation and high-sensitivity workflows in blood-based biomarker discovery
[22]	Not sample-specific; MS-based biomarker discovery workflows	Provides best-practice recommendations for MS-based biomarker discovery, including study design, sample preparation, quality control, quantitative analysis, validation and reporting	MS biomarker discovery methodology	Supports rigorous experimental design, reproducibility and independent validation as essential requirements for translating proteomic biomarkers into clinically useful assays
[23]	Human plasma	Evaluates immunoaffinity depletion of abundant plasma proteins and its limitations, including sample loss and potential co-depletion of lower-abundance proteins bound to high-abundance carriers	Plasma proteomics methodology / Depletion strategies	Highlights technical trade-offs between plasma proteome depth, reproducibility and biomarker detectability, showing that even immunodepletion may remain insufficient for reliable discovery of low-abundance disease-specific biomarkers

Table SM1 (continuation)

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[24]	Serum from dCCA, PDAC, benign pancreatic disease and healthy donor cohorts	THBS2 + CA19-9 improved discrimination of dCCA/PDAC from healthy donors compared with CA19-9 alone (AUC: 0.92), with greater added value in early-stage disease; THBS2 did not improve discrimination from benign pancreatic disease	Serum biomarker validation / ELISA	Supports THBS2 + CA19-9 as a diagnostic panel for pancreaticobiliary malignancy, while highlighting limited added value in clinically relevant benign-control settings
[25]	Cancer cell secretome and tumour microenvironment-derived proteins	Reviews the cancer secretome as a source of secreted, shed and extracellular proteins with potential biomarker value, emphasizing that tumour- and stroma-derived proteins may be more likely to enter circulation than intracellular proteins	Secretome proteomics / Biomarker discovery review	Provides the conceptual basis for secretome-guided biomarker discovery and supports its use as a bridge between tissue proteomics and blood-based validation
[26]	Plasma EVs	A seven-protein EV signature distinguished PDAC from benign pancreatic diseases with 89% prediction accuracy; EV proteins including PDCD6IP, SERPINA12 and RUVBL2 were associated with PDAC, while other subsets correlated with metastasis and poor prognosis	EV proteomics (DIA)	A large-scale circulating-EV proteomics resource for PDAC; enables systematic biomarker discovery in tumour-enriched EV compartment
[27]	Serum exosomes and serum from PDAC, benign pancreatic tumour, chronic pancreatitis and healthy control cohorts	Exosomal and serum GPC1 distinguished early-stage PDAC from healthy controls but not from chronic pancreatitis or benign pancreatic tumours; both were independent predictors of early PDAC recurrence	EV-associated protein / Serum protein biomarker analysis / ELISA	Provides prognostic biomarker evidence for identifying early-stage PDAC patients at higher risk of early recurrence, while highlighting limited diagnostic specificity against clinically relevant benign pancreatic conditions
[28]	Serum EVs	ALPPL2-positive and THBS2-positive serum exosomes distinguished PDAC from healthy and non-cancer pancreatic controls, with AUCs of 0.983 and 0.993, respectively; dual-positive exosomes yielded an AUC of 0.983, and their longitudinal changes correlated with radiographic tumour-size changes during treatment	EV proteomics (targeted)	Supports serum exosomal ALPPL2 and THBS2 as candidate early-detection and treatment-monitoring biomarkers; prospective validation remains necessary; potential for longitudinal disease monitoring
[29]	Serum/plasma, tissue and extracellular glycoprotein studies	Reviews cancer-associated glycosylation changes, including truncated O-glycans, altered sialylation, fucosylation and branched glycan structures, and highlights MS-based glycoproteomics as a key approach for discovering extracellular glycoprotein biomarkers	Glycomics / Glycoproteomics (review)	Supports glycan remodelling as a biologically relevant source of biomarker and therapeutic targets, with links to tumour progression, immune modulation and personalized medicine strategies
[30]	Pancreatic cancer tissue and circulating glycan/glycoprotein studies	Reviews pancreatic cancer-associated glycosylation changes, including altered sialylation and fucosylation, and discusses CA19-9, emerging glycoproteins and N-glycoproteomics as approaches for improving biomarker specificity	Glycomics / Glycoproteomics review	Supports the biological and diagnostic relevance of glycosylation-based biomarkers in pancreatic cancer, particularly for improving specificity beyond total CA19-9 or protein abundance measurements
[31]	Serum CA19-9 / Lewis blood-group phenotype	CA19-9 expression depends on Lewis antigen status; Lewis antigen-negative individuals generally have absent or markedly reduced CA19-9 synthesis, which can produce false-negative results	CA19-9 biomarker biology / Glycan epitope	Defines a key biological limitation of CA19-9 and supports interpretation of serum CA19-9 levels according to Lewis phenotype
[32]	Serum glycan/glycoform biomarker studies	Reviews combined protein biomarker quantification and glycoform analysis as a strategy to improve cancer detection sensitivity and specificity beyond either approach alone	Glycomics / Glycoform biomarker review	Supports the potential for improved specificity through structural glycan and glycoform analysis and highlights the broader applicability of glycomic biomarker approaches across cancer types
[33]	Gastrointestinal cancer tissues and biofluids	Reviews glycoproteomic alterations in gastrointestinal cancers, emphasizing protein-linked glycans as less-invasive biomarker candidates and highlighting the diagnostic value of glycoform-level analysis	Glycoproteomics (review)	Supports the use of glycoform-specific biomarker strategies to improve diagnostic specificity beyond total protein abundance measurements

Table SM1 (continuation)

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[34]	Tissue and cell samples for spatial multi-omics applications	Reviews MSI as a spatially resolved approach for mapping metabolomic, lipidomic and proteomic distributions in tissue and cell samples; discusses MSI principles, capabilities, limitations and integration with other imaging modalities	Mass spectrometry imaging / Spatial multi-omics review	Provides methodological context for spatial proteomics and supports MSI-based molecular mapping as a strategy to investigate tissue and cellular heterogeneity
[35]	PDAC tissue sections	MALDI-MSI combined with neural-network models distinguished PDAC from other pancreatic tumour types based on spatial molecular signatures, achieving 86% accuracy and 82% sensitivity	MALDI-MSI / Spatial proteomics	Demonstrates the application of MSI-based molecular phenotyping to PDAC tissue classification and supports spatially resolved approaches for tumour characterization
[36]	PDAC tissue / tumour microenvironment	A 27-plex spatial profiling panel revealed intra- and intertumoral immune heterogeneity in PDAC and identified an immune spatial proximity signature involving IL10-positive myelomonocytes, PD-1-positive CD4-positive T cells and granzyme B-positive CD8-positive T cells associated with patient survival	Digital spatial profiling / Spatial immune profiling	Supports spatial compartment analysis of tumour–immune heterogeneity and highlights prognostic biomarker potential within the PDAC microenvironment
[37]	Clinical proteomics and molecular tumour board case studies	Reviews the integration of proteomic and proteogenomic data into molecular tumour boards, highlighting pathway-level protein information and clinically actionable findings from case-based precision oncology studies	Clinical proteomics / Precision oncology (review)	Provides a framework for incorporating proteomic data into clinical decision-making, particularly when genomic profiling alone does not fully explain tumour behaviour or therapeutic vulnerabilities
[38]	PDAC tumour transcriptomic datasets	pdacR provides an open-source platform for cross-cohort PDAC gene-expression analysis and supports a two-subtype transcriptomic model: classical and basal-like	Transcriptomics / Gene-expression resource	Supports cross-cohort molecular comparison and provides transcriptomic subtype context for interpreting proteomic and proteogenomic classifications
[39]	PDAC tumour tissue with paired adjacent non-tumour tissue	Proteogenomic analysis linked TP53 mutation, KRAS mutation and ADAM9 amplification to cell proliferation, WNT signalling, metastasis and poor prognosis, while defining three proteome-based PDAC subtypes with distinct clinical and molecular features	WES / RNA-seq / Proteomics / Phosphoproteomics	Provides a PDAC-focused multi-omics resource for linking genomic alterations to functional protein-level pathways, prognostic stratification and potential treatment-relevant vulnerabilities
[40]	Plasma proteome-wide association data with blood and tumour tissue validation cohorts	Plasma proteome-wide association analysis identified 78 proteins associated with pancreatic cancer risk, highlighting ROR1, FN1, APOA5 and ABO; FN1 and ABO were elevated in patient blood/tumour samples and linked to poorer survival	Plasma proteogenomics / PWAS / pQTL-informed analysis	Supports genetically anchored circulating biomarker and potential therapeutic target discovery, with FN1 and ABO emerging as candidate prognostic markers and FN1/ROR1 as potential targetable proteins
[41]	Plasma / blood-based liquid biopsy cohort	A composite blood-based assay combining CA19-9, THBS2 and cell-free DNA improved non-invasive discrimination of early-stage PDAC from healthy and benign pancreatic disease controls	Protein biomarkers + cfDNA / Liquid biopsy	Supports hybrid liquid biopsy panels that integrate protein and nucleic acid signals to improve differential diagnosis of early-stage PDAC beyond single-analyte biomarker strategies
[42]	E-PDAC tumour tissue with paired adjacent normal tissue; external validation datasets	Paired proteomic analysis identified 25 E-PDAC-specific proteins and supported 13 machine-learning models for early-stage PDAC prediction, with AUCs of approximately 0.9 in discovery and 0.8 in external validation; MR implicated STX7 as a risk factor, while LUM showed context-dependent roles across proteomic, MR and single-cell analyses involving fibroblast and T/B-cell populations	Tissue proteomics / Machine learning / Mendelian randomisation / Single-cell analysis	Supports early-stage PDAC biomarker discovery and screening-model development, while remaining at an exploratory validation stage requiring further clinical and prospective validation before screening application