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Review Article

Breaking the Silence: AI-Enhanced Multi-Omics biosensors for liquid Biopsy-Based early diagnosis of pancreatic cancer

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ABSTRACT

Pancreatic cancer remains one of the most lethal malignancies due to its asymptomatic progression, late-stage diagnosis, and limited treatment options. Current diagnostic modalities including imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), as well as Carbohydrate Antigen 19–9 (CA 19–9) biomarker testing still fall short of the sensitivity and specificity required

Abbreviations: ACC, Acinar-cell carcinoma; ADAM9, ADAM Metallopeptidase Domain 9; AEP, Asparagine endopeptidase; AI, Artificial Intelligence; ANEXINA1, Annexin I; ANXA2, Annexin A2; APLP2, Amyloid precursor-like protein 2; ATRX, Alpha-Thalassemia Syndrome; ASC, Adenosquamous carcinoma; ATM, Ataxia Telangiectasia Mutated; AUC, Area Under the Curve; AuNPs, Gold Nanoparticles; BCAAs, Branched-Chain Amino Acids; BRCA2, Breast Cancer gene 2; CA 19–9, Carbohydrate Antigen 19–9; CD151/Tspan8, Cluster of Differentiation 151/Tetraspanin 8; CD44V6, Cell Surface Adhesion Receptor; CD55, Complement Decay-Accelerating Factor; CDKN2A, Cyclin Dependent Kinase Inhibitor 2A; CEA, Carcinoembryonic Antigen; cfDNA, Cell-Free DNA; CircHIPK3, Circular homology domain-interacting protein kinase 3; circRNA, Circular RNA; CL, Chemiluminescence; CNNs, Convolutional Neural Networks; CNTs, Carbon Nanotubes; CSCs, Cancer Stem Cells; CT, Computed Tomography; CTCs, Circulating Tumor Cells; ctDNA, Circulating Tumor DNA; CV, Cyclic Voltammetry; dCCA, Distal Cholangiocarcinoma; DAXX, Death Domain Associated Protein; DL, Deep Learning; DM, Diabetes Mellitus; DNNs, Deep Neural Networks; DPV, Differential Pulse Voltammetry; ECL, Electrochemical Luminescence; EHRs, Electronic Health Records; ELISA, Enzyme-linked Immunosorbent Assay; EMA, European Medicines Agency; EMC, Electrochemical Microfluidic Chip; EMT, Epithelial-to-Mesenchymal Transition; EpCAM, Epithelial Cell Adhesion Molecule; Epi-sPNA, Epigenetic-specific Peptide Nucleic Acid; ER, Endoplasmic reticulum; EUS, Endoscopic Ultrasound; EZH2, Enhancer of Zeste Homolog 2; FDA, Food and Drug Administration; GDPR, General Data Protection Regulation; GFET, Graphene Field-Effect Transistor; GLP-1, Glucagon-like peptide-1; GO, Graphene Oxide; GPC1, Glypican-1; GQDs, Graphene Quantum Dots; H3K27me3, A Post-Translational Modification of Histone H3; H3K9me2/3, Histone 3 lysine 9 trimethylation; HDAC, Histone deacetylases; HIPAA, Health Insurance Portability and Accountability; HOMA-IR, Homeostasis Model Assessment-Estimated Insulin Resistance; HOTAIR, HOX Transcript Antisense RNA; IL-6, Inflammatory Cytokine Interleukin-6; IncRNA, Long Non-CodingRNA; IPMNs, Intraductal Papillary Mucinous Neoplasms; ITO, Indium-Tin Oxide; KRAS, Kirsten Rat Sarcoma; LAMC2, Laminin Subunit Gamma 2; LASSO, Least Absolute Shrinkage and Selection Operator; LIG, Laser-Induced Graphene; LIME, Local Interpretable Model; LNM, Lymph Node Metastasis; LOC, lab-on-a-Chip; LOD, Limit of Detection; LOQ, Limit of Quantitation; LSTM, Long Short-Term Memory; LYVE1, Lymphatic Vessel Endothelial Hyaluronan Receptor 1; MALAT1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; MEG3, Maternally Expressed Gene 3; MEN1, Multiple endocrine neoplasia type 1; miRNA, microRNA; ML, Machine Learning; MMP7, Matrix Metallopeptidase 7; MOFs, Metal–Organic Frameworks; MRI, Magnetic Resonance Imaging; mTOR, Mechanistic Target of Rapamycin Kinase; MUC1, Mucin 1; MUC4, Mucin 4; NGS, Next-Generation Sequencing; NSE, Neuron-Specific Enolase; NOD, New-Onset Diabetes; PACC, Pancreatic acinar cell carcinoma; PALB2, Partner and Localizer of BRCA2; PANDA, Pancreatic Cancer Detection Assay; PanNENs, Pancreatic Neuroendocrine Neoplasms; PanNETs, Pancreatic Neuroendocrine Tumors; PanNECs, Pancreatic Neuroendocrine Carcinomas; PC, Pancreatic cancer; PCR, Polymerase chain reaction; PDAC, Pancreatic Ductal Adenocarcinoma; PEAK1, Pseudopodium Enriched Atypical Kinase 1; PET-CT, Positron Emission Tomography-Computed Tomography Scan; PNET, Pancreatic Neuroendocrine Tumor; PoC, Point-of-Care; PTEN, Phosphatase and Tensin Homolog; REG1B, Regenerating Family Member 1 Beta; RF, Random Forests; rGO, Reduced Graphene Oxide; RNNs, Recurrent Neural Networks; SCC, Squamous cell carcinoma; SCNs, Serous Cystic Neoplasms; SERS, Surface-Enhanced Raman Spectroscopy; SHAP, Shapley Additive exPlanations; SMAD, Mothers against decapentaplegic homolog 4; SPR, Surface Plasmon Resonance; SPN, Solid Pseudopapillary Neoplasm; SVMs, Support Vector Machines; T2DM, Type 2 Diabetes Mellitus; TAM2, Tumor-Associated Macrophage; tdEVs, Tumor-Derived Extracellular Vesicles; TFF1, Trefoil Factor 1; THBS2, Thrombospondin-2; TIMP1, Tissue Inhibitor of Metalloproteinases 1; TNF-α, Tumor necrosis factor; TP53, Tumor Protein p53; TSC2, Tuberous Sclerosis 2; VIP, Vasoactive Intestinal Peptide; Wnt5b, Wnt Family Member 5B.

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for reliable early-stage detection, which may contribute to the persistently elevated mortality rates. Liquid biopsy has emerged as a minimally invasive alternative, enabling the detection of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomal biomarkers. However, single-biomarker approaches remain inadequate in capturing the molecular complexity of pancreatic cancer. This review presents a novel, integrative framework that combines advances in multi-omics biosensor technologies and artificial intelligence (AI)-driven analytics to overcome the limitations of traditional diagnostic tools. Unlike existing reviews, this work offers a comprehensive examination of biosensors tailored for liquid biopsy applications covering electrochemical, optical, and nanomaterial-enhanced systems and evaluates their capacity to detect a broad range of circulating biomarkers, including ctDNA, CTCs, exosomes, and metabolomic signatures. Unlike conventional biosensors, multi-omics biosensors utilize advanced nanomaterials, electrochemical and optical detection systems, and AI-driven predictive modeling to enhance diagnostic precision. The integration of AI enables the real-time interpretation of multi-layered biological data, optimizing sensitivity and specificity while supporting early-stage screening and personalized treatment strategies. The application of AI in interpreting complex biological datasets is critically evaluated, particularly in the context of early diagnosis, personalized treatment planning, and risk stratification in pancreatic cancer. In addition to highlighting scientific advances, this review also discusses key translational challenges such as regulatory hurdles, standardization needs, and cost-effectiveness. By bridging the gap between molecular diagnostics, biosensor engineering, and AI-powered analytics, this review provides a foundational perspective for the next generation of precision tools in pancreatic cancer diagnostics. This review serves as a critical resource for researchers and clinicians, offering insights into the next generation of precision oncology tools that integrate biosensing, AI, and liquid biopsy methodologies.

1. Introduction

Pancreatic cancer (PC), is a malignant disease that arises from the tissues of the pancreas, a vital organ located behind the stomach responsible for producing digestive enzymes and hormones that regulate blood sugar levels. It can develop from two primary cellular components of the pancreas including the exocrine cells and the endocrine cells. The vast majority of pancreatic cancers (over 90 %) originate from the exocrine cells, which produce digestive enzymes and are classified as pancreatic ductal adenocarcinoma (PDAC), the most common and aggressive subtype. In contrast, tumors that arise from the endocrine cells, which secrete hormones such as insulin and glucagon, are known as pancreatic neuroendocrine tumors (PNETs) [1,2]. These are much rarer and typically exhibit different biological behavior and clinical outcomes compared to PDAC. PC, predominantly PDAC, is among the most aggressive and lethal malignancies, with a global five-year survival rate of less than 10 % due to its late diagnosis and limited therapeutic options [1,2]. It currently ranks as the 7th leading cause of cancer-related deaths worldwide. One of the greatest challenges in managing pancreatic cancer is its asymptomatic or non-specific presentation during the early stages, which contributes to delayed detection in over 80 % of patients [3]. Symptoms such as jaundice, abdominal pain, back pain, unexplained weight loss, fatigue, and new-onset diabetes often emerge only when the disease has already progressed to an advanced or metastatic stage, at which point curative interventions are no longer feasible [4].

From a diagnostic standpoint, first-line clinical evaluations typically involve imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), along with serum-based biomarker testing, most notably carbohydrate antigen 19–9 (CA 19–9) [5–7]. However, these methods present several limitations. Imaging techniques can only detect tumors once they have reached a certain size, limiting their effectiveness for early-stage diagnosis [8]. CA 19–9, while widely used, lacks both sensitivity and specificity and can yield false-positive results in conditions such as cholangitis or pancreatitis [9,10]. Moreover, tissue biopsies, though confirmatory, are invasive and often impractical in inoperable cases [11,12]. This diagnostic inertia contributes to the poor clinical outcomes and high mortality rates associated with pancreatic cancer. Consequently, there is an urgent need for highly sensitive, non-invasive, and accessible diagnostic tools that can detect pancreatic cancer at its earliest stages [13,14].

Liquid biopsy has emerged as a promising alternative to traditional diagnostic techniques [15,16]. By analyzing tumor-derived components in biological fluids (such as blood, urine, and saliva), liquid biopsy offers a minimally invasive approach to cancer detection, disease monitoring, and treatment response evaluation [17,18]. Biological fluids such as blood (plasma or serum), urine, and saliva are increasingly utilized in liquid biopsy platforms for the detection of a broad spectrum of pancreatic cancer biomarkers. Key analytes detected in liquid biopsy include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and metabolic biomarkers, all of which provide valuable molecular insights into tumor biology [19,20]. Compared to traditional biopsies, liquid biopsy enables real-time disease monitoring and the potential for early detection, making it a transformative tool in cancer diagnostics [21]. However, current liquid biopsy techniques often rely on single-biomarker detection, limiting their ability to fully capture the complex molecular landscape of pancreatic cancer [22]. Pancreatic tumors exhibit significant heterogeneity at the genetic, epigenetic, proteomic, and metabolic levels, requiring multi-omics approaches that integrate diverse biomolecular data for accurate diagnosis. This review primarily focused on isolated biomarker classes (*e.g.,* ctDNA or exosomes) or traditional biosensing techniques, overlooking the synergistic potential of multi-omics biosensors enhanced with AI-driven analytics.

One of the most significant advancements in liquid biopsy-based diagnostics is the development of biosensors, which provide rapid, cost-effective, and highly sensitive detection of cancer biomarkers [23–25]. Biosensors are analytical devices that convert biological interactions into measurable signals, allowing for precise and real-time detection of tumor-derived analytes [26–29]. Fig. 1 illustrates the workflow of biosensor-based cancer detection. It illustrates the complete biosensing process, starting from biological sample collection (*e.g.*, serum, plasma, saliva) to multi-omics biomarker detection (DNA, RNA, proteins, exosomes). Biosensors incorporating various recognition elements and transducers such as electrochemical, optical, and AI-integrated platforms enable data analysis for clinical outcomes including diagnosis, prognosis, and risk stratification. Various biosensor technologies have been explored to improve the sensitivity and specificity of pancreatic cancer diagnostics, each offering unique advantages for detecting distinct biomarker classes. Ratiometric electrochemical biosensors, for example, have been employed for the sensitive detection of CA 19–9 using aptamer-functionalized functionalized nanocomposites, enabling real-time monitoring of this serum biomarker in clinical samples [30]. In another study, screen-printed carbon electrode (SPE) modified with functionalized multi-walled-carbon nanotubes demonstrated enhanced sensitivity for detecting pancreatic cancer–related microRNAs in plasma [31]. Microfluidic biosensors have also shown great promise in isolating and characterizing CTCs from blood

samples [32,33]. These applications collectively demonstrate how diverse biosensing modalities can be tailored for multi-omics integration and point-of-care deployment in pancreatic cancer diagnosis. Biosensors use recognition elements such as DNA probes, antibodies, and aptamers to detect these biomarkers, with transduction carried out by electrochemical, optical, microfluidic, nanomaterial-enhanced, and AI-integrated platforms. AI-powered data analysis enhances signal interpretation, enabling diagnosis, screening, prognosis, prediction, and risk assessment for early detection and personalized medicine. While conventional biosensors have traditionally focused on single-marker detection, the heterogeneous and dynamic nature of pancreatic cancer necessitates multi-omics approaches that integrate genomic, transcriptomic, proteomic, and metabolomic data [22,34,35]. Personalized medicine aims to tailor diagnostic and therapeutic approaches to individual patients based on their genetic, molecular, and clinical profiles [36,37]. In pancreatic cancer, where early detection remains a critical challenge, AI-driven personalized screening models offer significant potential to transform risk stratification, biomarker-based diagnostics, and clinical decision-making [38]. By integrating multi-omics biosensor outputs, machine learning algorithms, and patient-specific risk variables, AI systems can deliver highly accurate, real-time predictions of pancreatic cancer susceptibility and progression, thereby enabling earlier interventions for high-risk individuals.

Multi-omics biosensors represent the next generation of cancer diagnostics, as they offer a comprehensive and highly accurate assessment of disease state by simultaneously detecting multiple biomarkers [39]. These biosensors utilize nanomaterials, microfluidic platforms, and artificial intelligence (AI)-powered analysis to enhance sensitivity and specificity [40]. Their ability to detect low-abundance biomarkers in biofluids allows for early diagnosis, patient stratification, and personalized treatment planning, addressing critical challenges in pancreatic cancer detection [40,41]. Additionally, point-of-care biosensors make real-time cancer screening accessible in clinical and resource-limited settings, further expanding their applicability [42]. Unlike conventional biosensors, AI-integrated multi-omics biosensors enable the detection of multiple biomarker classes simultaneously, leveraging machine learning algorithms to enhance diagnostic accuracy [22]. These platforms have the potential to overcome the limitations of single-biomarker liquid biopsy methods, enable early-stage detection, and support precision oncology strategies tailored to individual patients [41].

While previous reviews have primarily focused on individual biomarkers or traditional biosensing techniques [23,28], this review uniquely integrates multi-omics biosensors, AI-driven predictive analytics, and real-time liquid biopsy applications in pancreatic cancer diagnosis. By utilizing AI-driven data processing, emerging biomarkers, and point-of-care biosensing, we provide a comprehensive perspective on the future of liquid biopsy-based early detection, bridging the gap between laboratory research and clinical applications. The key biomarkers, biosensor technologies, and clinical applications of these innovative platforms are discussed. Additionally, the challenges in clinical translation, including standardization, regulatory considerations, and cost-effectiveness are addressed. Finally, the future perspectives of multi-omics biosensors, particularly their potential to integrate AI-driven analytics, nanotechnology, and personalized medicine approaches for next-generation cancer diagnostics are highlighted. By offering early, non-invasive, and highly accurate detection, multi-omics biosensors have the potential to revolutionize pancreatic cancer management and significantly improve patient survival.

By bridging the gap between liquid biopsy research, AI-driven diagnostics, and multi-omics biosensor development, this review provides a critical resource for researchers, clinicians, and biomedical engineers. It lays the groundwork for the next generation of precision oncology tools that integrate biosensing, artificial intelligence, and liquid biopsy methodologies.

2. Multi-Omics biomarkers for pancreatic cancer in liquid biopsy

Recent studies have explored multi-omics approaches for identifying pancreatic cancer biomarkers in liquid biopsies, using platforms that integrate proteomics, metabolomics, transcriptomics, and genomics data from patient-derived biofluids [23,43–45]. Researchers have utilized comprehensive platforms to analyze proteins, metabolites, transcripts, and genes in blood samples from pancreatic cancer patients and healthy controls [46,47]. These studies aim to detect biological signals associated with pancreatic cancer and develop multivariate statistical models for early detection. While single biomarkers often lack sufficient sensitivity and specificity, combining multiple biomarkers into panel-based approaches can significantly improve diagnostic accuracy [48].

Current research focuses on integrating multi-omics data, including genomics, transcriptomics, proteomics, metabolomics, glycomics, and metagenomics, to identify novel biomarkers and gain deeper insights into pancreatic cancer biology [49]. Although CA19-9 remains the most well-established biomarker for pancreatic cancer, it has limitations, particularly in detecting early-stage disease. Therefore, combining

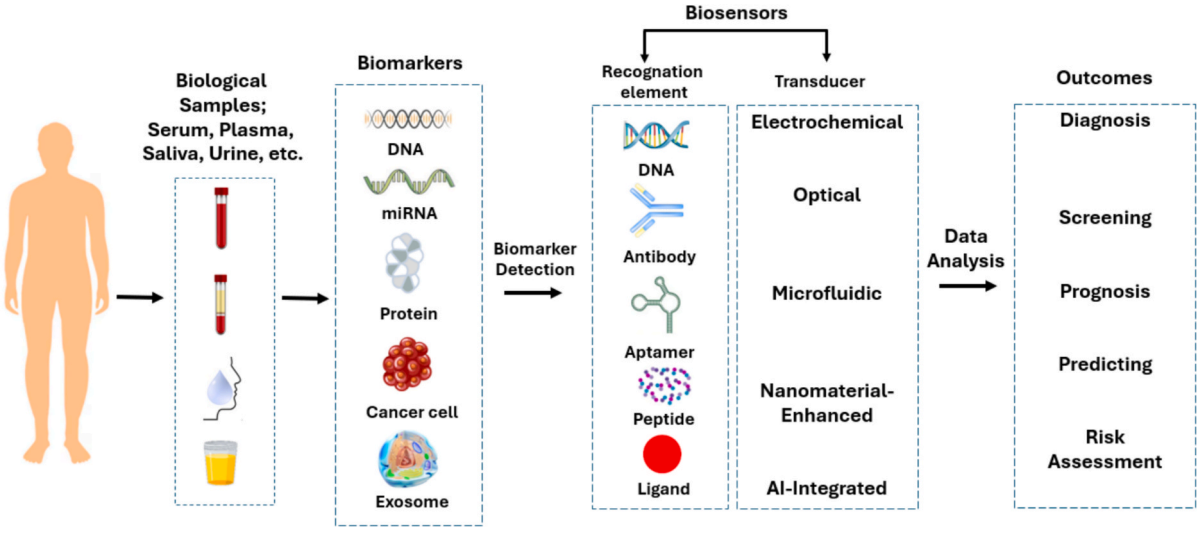


Fig. 1. Workflow of multi-omics biomarker detection using biosensor technologies: from biological sample collection to AI-driven cancer diagnosis and risk assessment.

CA19-9 with emerging biomarkers from different omics layers presents a promising strategy for improving early detection and risk stratification [49].

Fig. 2 illustrates the interconnected molecular mechanisms regulating KRAS expression and its downstream oncogenic effects [45]. It highlights the influence of environmental factors on DNA repair genes (epigenome), transcriptional regulation of KRAS, microRNA-mediated post-transcriptional modifications, KRAS protein expression (proteome), and its impact on metabolic pathways that drive cell growth, proliferation, transformation, invasion, and survival (metabolome).

To support early detection strategies and the development of precision biosensing platforms, it is essential to understand the clinicopathologic and molecular diversity of pancreatic neoplasms. Pancreatic cancer is not a single disease entity but encompasses a heterogeneous group of tumors with distinct histological subtypes, cellular origins, biomarker expression patterns, and genetic drivers. These differences significantly influence tumor behavior, clinical presentation, prognosis, and therapeutic response. Table 1 summarizes the major pancreatic tumor subtypes, comparing their histological variants, cell of origin, prevalence, associated biomarkers, dominant mutations, and prognostic implications. This comparative overview lays the foundation for developing subtype-aware, biomarker-specific diagnostic tools, particularly in the context of liquid biopsy and biosensor-based approaches.

2.1. Circulating tumor DNA: The genetic signature

Circulating tumor DNA and cell-free DNA (cfDNA) fragmentation patterns, along with methylation-based biomarkers, are rapidly emerging as valuable tools for non-invasive cancer detection, characterization, and monitoring [77–79]. These biomarkers provide critical insights into tumor biology, offering opportunities for early diagnosis, improved prognosis assessment, and real-time disease tracking [80]. Advances in liquid biopsy technologies have enhanced the sensitivity and specificity of detecting these molecular signatures, paving the way for more precise cancer diagnostics and personalized treatment strategies [81,82]. One of the most promising aspects of ctDNA analysis is its fragmentation patterns, which reflect tumor-specific chromatin organization and nucleosome positioning cv [83]. Compared to cfDNA from healthy individuals, ctDNA fragments tend to be shorter and display greater variability in length, providing a distinct molecular footprint of cancer-derived DNA [84]. This unique fragmentation profile enables early cancer detection, often before structural abnormalities become evident in imaging modalities [85]. Additionally, emerging research suggests that machine learning models trained on cfDNA fragmentation data can effectively distinguish cancer stages, highlighting the systematic nature of these genomic alterations [86]. The correlation between cfDNA fragmentation and cancer progression varies by tumor type, underscoring the potential for personalized liquid biopsy applications [87].

DNA methylation plays a fundamental role in gene regulation, and its dysregulation is a hallmark of tumorigenesis [88]. Recent advances in sequencing technologies have enabled the comprehensive characterization of tumor methylomes from ctDNA, leading to the identification of novel epigenetic markers that enhance clinical decision-making [89]. Notably, methylation profiling has shown promise for the early detection of PDAC, one of the most aggressive malignancies, by differentiating cancerous tissues from benign conditions [90,91]. Furthermore, integrating tissue-specific cfDNA methylation markers with plasma protein biomarkers has improved diagnostic accuracy, potentially allowing for earlier intervention in pancreatic cancer [92]. These

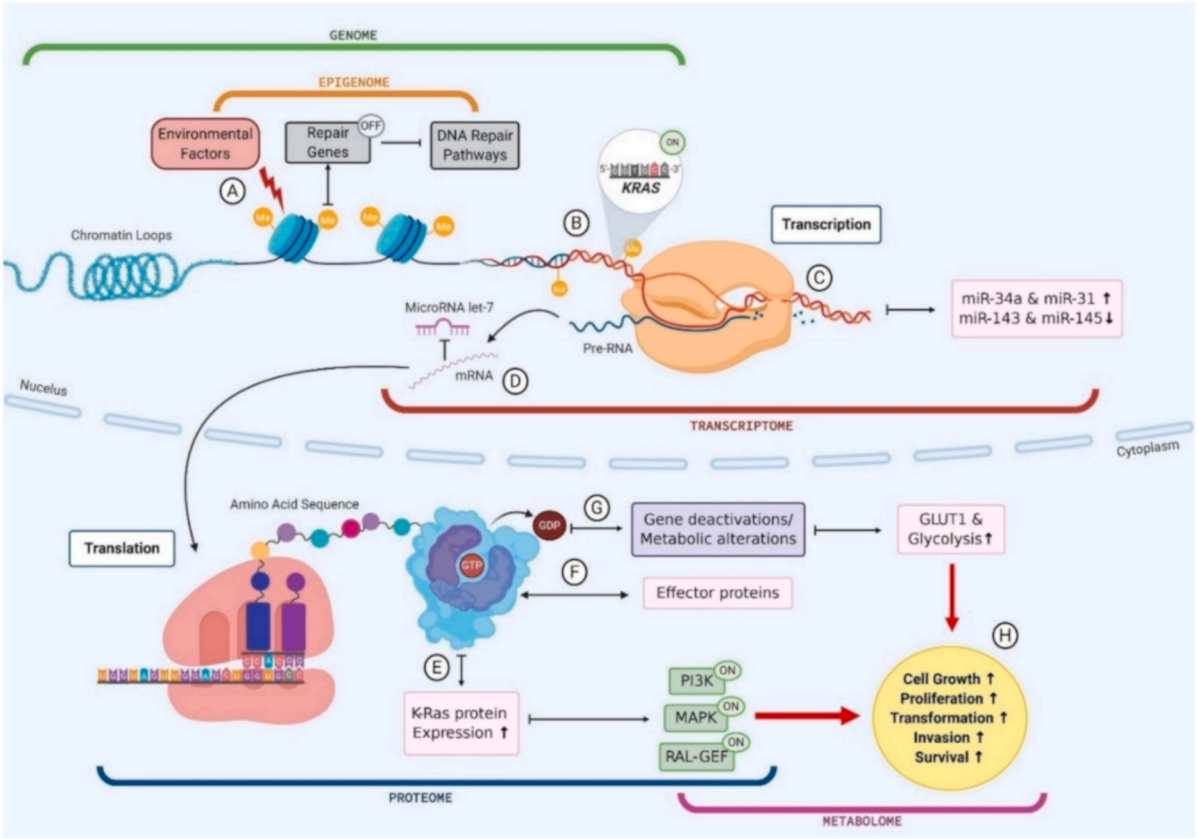


Fig. 2. Multi-omics regulation of KRAS in pancreatic cancer: epigenetic, transcriptomic, proteomic, and metabolic interactions driving tumor progression. 'Reprinted with the permission from [45] Licensed under a Creative Commons Attribution 4.0 (CC BY 4.0).' This figure illustrates how multi-omics layers, including epigenetic regulation, transcriptional and post-transcriptional control, protein expression, and metabolic reprogramming, collectively influence KRAS activation and downstream oncogenic signaling pathways in pancreatic cancer.

Table 1
Clinicopathologic and molecular features of major pancreatic tumor subtypes.

Pancreatic cancer subtype	Histological sub types	Cell of origin	Prevalence	Key Biomarkers	Dominant driver mutations	Prognosis
PDAC	• Adenosquamous carcinoma (ASC) / Squamous cell carcinoma (SCC) • Colloid carcinoma, hepatoid carcinoma • Signet-ring cell (poorly cohesive cell) carcinoma • Undifferentiated carcinoma • Undifferentiated carcinoma with osteoclast-like giant cells • Medullary carcinoma, micropapillary carcinoma • Rhabdoid cell undifferentiated carcinoma (rhabdoid carcinoma) [50]	Ductal epithelial cells lining the main and branch ducts[51]	~90 % of all pancreatic malignancies[51]	CA 19–9 (clinical sensitivity ~ 78 %) [51]	KRAS (~85 %), TP53 (~70–75 %), CDKN2A, SMAD4; MEN1/ ATRX very rare [51,52]	Extremely poor prognosis; 5-year survival rate around 10 % [50]
Pancreatic neuroendocrine neoplasms (PanNENs)	Low- to high-grade pancreatic neuroendocrine tumors (PanNETs) [53] • Fonctional PanNETs [54] ▪ İnsülinoma, ▪ Gastrinoma, ▪ Vazoaktif intestinal peptidoma (VIPoma) ▪ Glukagonoma, ▪ Somatostatinoma	Endocrine islet (α, β, δ, PP) cells [53]	PanNETs account for 5–10 % of pancreatic tumors; the majority are non-functional [55]	• Chromogranin A, • Synaptophysin, • NSE (Neuron-Specific Enolase), • Pancreatic polypeptide, • Pancreastatin, • CA 19–9, • Serotonin derivatives (5- • Hydroxyindoleacetic acid), • Insulin, • Glucagon, • Gastrin-1, • Vasoactive intestinal peptide [56,57]	Multiple endocrine neoplasia type 1 (MEN1), occasionally DAXX/ATRX [58]	PanNETs displays heterogeneous behavior with survival depending on tumor size, tumor grade, and treatment outcome. Patients with small (<2 cm) nonmetastatic grade 1 pNET have 5-year survival outcomes approaching 100 %. Meanwhile, patients with larger metastasized grade 2 pNET had a 5-year survival rate of less than 40 % [59] The 5-year survival rates of G1, G2 and G3 PanNETs were 79.54 %, 66.88 % and 22.53 %, respectively [60]
	• Non-fonctional (NF) PanNET [53,57]	Endocrine islet (α, β, δ, PP) cells [53]	PanNETs account for 5–10 % of pancreatic tumors; the majority are non-functional [55]	Chromogranin A (+), Synaptophysin (+), hormone stains (−) [61], Ki-67 for grading [61,62]	MEN1, DAXX/ ATRX, mTOR/ TSC2/PTEN pathway mutations [63,64]	Lymph node metastasis (LNM) is a significant prognostic factor for NF-PanNETs [65]
	High-grade pancreatic neuroendocrine carcinomas (PanNECs) [53]	Admixed components of other carcinoma types of non-neuroendocrine origin, this can be either ductal adenocarcinoma (PDAC) or acinar cell carcinoma (ACC) [53]	N/A	CA-19, CEA [66]	MEN1 (~35–40 %), ATRX (~18–20 %), DAXX (~20–25 %); KRAS/TP53 uncommon [64]	Highly aggressive and rapidly fatal [67] PanNEC relapse rates are high, and 5–year survival rates are between 25 % and 40 % [62]
Acinar-cell carcinoma / Pancreatic acinar cell carcinoma (ACC/PACC)	N/A	Most PACCs display a pure acinar cell histology although rarely some PACCs show mixed neuroendocrine or ductal differentiation [68]	Accounting for 1 %-2% of all pancreatic neoplasms [69]	Elevated serum lipase/ trypsin (24–58 %) [70]	There is no single dominant mutatio. CEA 15–24 %; CA19-9 33–45 % [70]	The prognosis of patients with PACC is somewhat better than that of patients of PDAC although even patients with surgically resectable PACC have a reported recurrence rate of approximately 50 %-70 % [71]
Solid pseudopapillary neoplasm (SPN)	Poorly cohesive epithelioid cells, forming solid and pseudopapillary structures [72]	Likely multipotent pancreatic progenitor cells (low-grade malignancy) [73]	Approximately 0.9 %-2.7 % of all exocrine pancreatic neoplasms and 5 %	Pathognomonic nuclear β-catenin (IHC) ± progesterone-receptor positivity	CTNNB1 activating mutations > 90 %; KRAS/TP53/	The overall prognosis is excellent with a cure rate of > 95 %

(*continued on next page*)

Table 1 (*continued*)

Pancreatic cancer subtype	Histological sub types	Cell of origin	Prevalence	Key Biomarkers	Dominant driver mutations	Prognosis
			of cystic pancreatic neoplasms [74]	Tumor markers' serum levels are within normal range, so they are not useful in the diagnostic workup [75]	MEN1/ATRX typically absent [76]	following complete surgical resection [74]

findings emphasize the growing role of multi-omics approaches in refining cancer diagnostics and enabling more targeted therapeutic strategies.

Despite their clinical promise, the implementation of ctDNA fragmentation and methylation-based biomarkers faces several challenges. Inherent variability in cfDNA fragmentation patterns, influenced by tumor heterogeneity and the tumor microenvironment, poses a hurdle for standardization [87]. Similarly, while targeted PCR and next-generation sequencing (NGS) techniques have significantly enhanced the sensitivity of methylation-based assays, further validation in large-scale clinical studies is required to establish their routine clinical utility [93]. Addressing these limitations will be crucial for integrating these biomarkers into standard oncology practice.

ctDNA fragmentation and methylation-based biomarkers offer significant promise for non-invasive cancer detection, prognosis, and treatment monitoring. Integrated into liquid biopsies, they enable earlier malignancy detection, accurate disease tracking, and personalized treatments. Further research and technological refinements will enhance their clinical utility, ultimately improving patient outcomes.

2.1.1. ctDNA Methylation-Based biomarkers

Circulating tumor DNA methylation has emerged as a promising biomarker for the early detection, diagnosis, and monitoring of PDAC. Given the challenges associated with traditional tissue-based diagnostic methods, researchers have increasingly focused on DNA methylation alterations in cfDNA as a more accessible and less invasive alternative [94].

Recent studies have demonstrated that cfDNA methylation-based diagnostic models can effectively differentiate PDAC patients from healthy individuals with high sensitivity and specificity [43]. One particularly notable advancement is the Pancreatic Cancer Detection Assay (PANDA), a targeted methylation-based test that has outperformed traditional biomarkers such as CA19-9. The PANDA assay achieved an area under the curve (AUC) of 0.906 when distinguishing PDAC from normal samples and 0.882 when differentiating PDAC from chronic pancreatitis [95]. These findings underscore the potential of methylation-based biomarkers to enhance diagnostic accuracy, particularly in cases where conventional markers provide limited specificity.

Beyond individual assays, multi-omics approaches have further refined the accuracy of PDAC detection. By integrating cfDNA methylation models with CA19-9 levels, researchers have achieved sensitivity rates of 95.7 % overall and 95.5 % in stage I cases, with a specificity of 93.3 % [43]. Additionally, combining ctDNA mutation analysis with protein biomarkers has led to significantly improved detection rates, capturing nearly two-thirds of pancreatic cancers at the time of surgical resection, even in cases without distant metastasis [96]. Another innovative method, the Epi-sPNA assay, which utilizes epigenetic-specific peptide nucleic acid technology, has shown strong diagnostic potential in both tissue and plasma samples [91].

One of the key advantages of cfDNA methylation analysis is its non-invasive nature, allowing for PDAC detection through liquid biopsies without the need for surgical tissue extraction [43]. This feature is particularly valuable for early cancer detection, as PDAC symptoms typically appear only in advanced stages, limiting the effectiveness of traditional diagnostic methods [96]. Moreover, cfDNA methylation markers have shown the ability to distinguish malignant PDAC from benign pancreatic conditions, which are often difficult to differentiate based on imaging alone [91]. Furthermore, validation in large and diverse patient cohorts is required to establish the reproducibility and clinical reliability of cfDNA methylation-based analyses for widespread clinical implementation [91]. In parallel, ongoing research compares cfDNA methylation markers with established biomarkers, such as CA19-9, to assess their additional diagnostic and prognostic value [95]. From a technical perspective, efforts continue to refine cfDNA methylation profiling to more accurately detect pancreas-specific or aberrant methylation signatures, particularly in high-risk pre-neoplastic lesions that may precede the development of PDAC [97].

In summary, ctDNA methylation analysis offers a significant leap in pancreatic cancer diagnostics by providing a non-invasive, highly sensitive, and specific method for early detection, disease tracking, and risk assessment. Further integration with multi-omics approaches holds the promise to transform precision oncology for PDAC, ultimately enabling earlier interventions and more personalized treatments that improve patient outcomes.

2.1.2. Non-Coding RNAs and histone modifications in pancreatic cancer

Pancreatic cancer is not only driven by genetic mutations but also by epigenetic and transcriptomic alterations, which significantly impact tumor progression and therapeutic resistance [98]. Among these, long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and histone modifications have emerged as key regulatory mechanisms in pancreatic tumor biology [99]. While microRNAs (miRNAs) play a crucial role in post-transcriptional regulation and are discussed in Section 2.3, lncRNAs and circRNAs represent another important class of non-coding RNAs that influence gene expression, chromatin remodeling, and signaling pathways in pancreatic cancer [100,101]. Additionally, histone modifications contribute to tumor development, immune evasion, and drug resistance by altering chromatin structure and transcriptional activity [102,103].

Long non-coding RNAs are transcripts longer than 200 nucleotides that do not encode proteins but regulate gene expression at the chromatin, transcriptional, and post-transcriptional levels [104,105]. Several lncRNAs have been identified as oncogenic or tumor-suppressive regulators in pancreatic cancer, making them valuable candidates for liquid biopsy-based detection [106]. HOTAIR (HOX Transcript Antisense RNA) is one of the most well-characterized oncogenic lncRNAs in pancreatic cancer, promoting epithelial-to-mesenchymal transition, metastasis, and chemoresistance by modulating chromatin structure [107]. MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) is another lncRNA that is significantly upregulated in pancreatic cancer and has been associated with poor survival, increased tumor cell migration, and resistance to gemcitabine chemotherapy [108,109]. On the other hand, MEG3 (Maternally Expressed Gene 3) functions as a tumor suppressor and is often downregulated in pancreatic cancer, leading to enhanced proliferation and immune escape mechanisms [110]. Since lncRNAs can be detected in circulating exosomes, plasma, and tumor-derived RNA, they serve as promising biomarkers for early-stage detection [111,112]. AI-driven machine learning algorithms are being developed to classify oncogenic versus tumor-suppressive lncRNA expression patterns, improving the accuracy of multi-omics risk stratification models.

Circular RNAs are a unique class of covalently closed RNA molecules

that serve as miRNA sponges, regulating gene expression by sequestering tumor-suppressive or oncogenic miRNAs [113]. Unlike linear RNAs, circRNAs are more stable in circulation, making them ideal candidates for biomarker discovery in liquid biopsy-based pancreatic cancer screening [114,115]. CircHIPK3 (Circular homology domain-interacting protein kinase 3) has been found to be significantly upregulated in pancreatic cancer and functions as a sponge for tumor-suppressive miRNAs, leading to increased tumor proliferation and invasion [116,117]. Another circRNA, circ_0007534, has been identified as a potential diagnostic marker, with elevated expression levels in pancreatic cancer tissues and plasma samples [118].

Recent advancements in AI-powered RNA biosensors have enabled real-time detection of circRNAs in biofluids, improving non-invasive pancreatic cancer diagnosis [119]. Integrating circRNA expression profiles with ctDNA mutations and proteomic markers may lead to more robust early detection strategies.

Beyond non-coding RNAs, histone modifications play a crucial role in the epigenetic landscape of pancreatic cancer [120,121]. Histones undergo post-translational modifications, including methylation, acetylation, phosphorylation, and ubiquitination, which alter chromatin structure and gene expression [122,123]. These modifications can either activate or repress tumor-promoting pathways and influence immune evasion, metastasis, and therapy resistance [124]. H3K27me3, regulated by Enhancer of Zeste Homolog 2 (EZH2), promotes the silencing of tumor-suppressor genes in pancreatic cancer, contributing to immune escape and chemotherapy resistance [125–127]. Another histone modification, H3K9me2/3, is associated with heterochromatin formation and repression of tumor-suppressor genes, playing a role in stemness and metastatic progression [128,129]. In contrast, H3K27ac marks active enhancer regions and is frequently enriched at super-enhancers of oncogenes, contributing to uncontrolled tumor growth in pancreatic cancer [130].

Histone modifications can be detected in circulating nucleosomes and cell-free DNA, and AI-based biosensor platforms are being developed to analyze epigenetic patterns in liquid biopsy samples. Machine learning algorithms can correlate histone modification signatures with patient-specific genetic and transcriptomic data, offering highly personalized prognostic models for pancreatic cancer risk assessment.

The discovery of lncRNAs, circRNAs, and histone modifications has expanded the molecular toolbox for pancreatic cancer detection beyond conventional genomic and proteomic biomarkers [100,131,132]. AI-enhanced liquid biopsy platforms integrating non-coding RNA signatures and epigenetic modifications with ctDNA mutations, proteomic panels, and metabolic markers could significantly improve early detection, prognosis prediction, and treatment response monitoring. Future clinical applications may involve AI-powered biosensors capable of detecting lncRNA and circRNA signatures in blood or urine samples with high specificity [133]. Machine learning models integrating epigenetic markers, such as histone modifications, with genomic and transcriptomic data may further enhance pancreatic cancer risk prediction algorithms [134,135]. AI-assisted personalized treatment planning, where histone modification patterns guide the selection of epigenetic inhibitors such as EZH2 and HDAC inhibitors, could refine therapeutic strategies for pancreatic cancer patients. By leveraging AI-driven biomarker discovery and epigenetic profiling, the integration of non-coding RNA signatures and histone modifications into pancreatic cancer screening programs could revolutionize early detection and personalized treatment strategies.

2.2. Circulating tumor cells (CTCs): Insights into tumor progression

Circulating Tumor Cells (CTCs) play a crucial role in the progression and metastasis of pancreatic cancer. The presence and quantity of CTCs in the bloodstream are directly associated with tumor aggressiveness and metastatic potential. Studies have shown that higher CTC counts correlate with an increased likelihood of distant lymph node metastasis and a poorer prognosis in pancreatic cancer [136]. Additionally, molecular analysis of CTCs has revealed specific genetic and epigenetic alterations, such as mutations in KRAS, TP53, and SMAD4, which are commonly associated with disease progression and therapeutic resistance [137,138].

Despite their significance, isolating and detecting CTCs remains a major challenge due to their extremely low concentration in the bloodstream and their physical similarities to other blood cells [139]. Conventional enrichment techniques, including density gradient centrifugation and immunomagnetic separation, have limitations in sensitivity and specificity [140,141]. To overcome these challenges, various established technologies have been developed for the detection and isolation of CTCs [142]. Immunomagnetic separation utilizes magnetic particles coated with antibodies to target specific antigen–antibody interactions, providing high specificity and compatibility with microfluidic integration [143,144]. However, this method may fail to capture CTCs that have undergone epithelial-to-mesenchymal transition (EMT) and thus exhibit low expression of targeted surface markers [145–147]. Microfluidic-based approaches offer an alternative strategy by utilizing physical properties such as size and deformability for CTC isolation. These systems enable high-throughput processing and can integrate multiple functions, including sorting and molecular analysis [142]. However, their effectiveness depends on precise control of fluid dynamics and sophisticated device fabrication, which can pose technical challenges. These devices use precisely engineered microstructures coated with antibodies targeting EpCAM (epithelial cell adhesion molecule) or other surface markers to selectively capture CTCs from whole blood samples. For instance, microfluidic platforms incorporating silicon nanowire arrays have demonstrated high efficiency in isolating CTCs, providing a non-invasive means to monitor tumor progression [94]. Additionally, microfluidic chips integrated with nanoparticle-based enrichment methods have improved CTC detection sensitivity, allowing for better characterization of tumor heterogeneity [148]. Moreover, microfluidic biosensors have enabled single-cell analysis of CTCs, facilitating the study of their molecular profiles, including mutational landscapes and gene expression patterns [142]. This technology has proven useful for tracking treatment responses in pancreatic cancer patients and identifying potential therapeutic targets [148]. By integrating biosensors with next-generation sequencing (NGS) and real-time PCR (Polymerase chain reaction), researchers can obtain high-resolution genetic and transcriptomic data from CTCs, providing valuable insights into tumor evolution and resistance mechanisms [149].

Additionally, digital PCR and BEAMing PCR provide high sensitivity for detecting specific genetic mutations in CTCs, making them particularly useful for analyzing minimal quantities of DNA. Nevertheless, these methods primarily focus on predefined genetic alterations, potentially overlooking the full heterogeneity of CTC populations. While these technologies have significantly improved CTC detection and isolation, further advancements in sensitivity, specificity, and adaptability are still required to enhance their clinical utility and facilitate their integration into liquid biopsy platforms for real-time cancer monitoring. Moreover, EMT in CTCs can lead to reduced EpCAM, further complicating their detection [150]. These challenges highlight the need for more advanced and reliable isolation techniques.

In conclusion, CTCs serve as critical biomarkers for assessing tumor progression and metastatic potential in pancreatic cancer. While challenges remain in their isolation and detection, advancements in microfluidic biosensor technology are paving the way for more efficient and precise CTC analysis. The continued development of these technologies holds great promise for early detection, personalized treatment strategies, and real-time monitoring of pancreatic cancer, ultimately improving patient outcomes.

2.3. Exosomal Biomarkers: The Hidden cancer Messenger

Exosomes, nanoscale extracellular vesicles secreted by cells, have

emerged as critical mediators of intercellular communication and are increasingly recognized as valuable biomarkers in pancreatic cancer [151]. These vesicles encapsulate a variety of molecular constituents, including miRNAs, proteins, and lipids, reflecting the physiological and pathological states of their cells of origin. Their stability in bodily fluids and ability to carry tumor-specific molecules make them promising candidates for non-invasive cancer diagnostics [152,153].

There are also studies showing that EVs act as vehicles for information exchange and establish a dynamically evolving and highly adaptable network between heterogeneous PDAC cell populations, thus enabling both PDAC and neighboring healthy cells to transform into a malignant phenotype [154]. Fig. 3 illustrates the molecular pathways through which cancer stem cells (CSCs) influence non-stem cancer cells and induce the malignant transformation of healthy cells. It presents how cancer stem cells influence tumor progression by secreting specific proteins and extracellular vesicles containing oncogenic cargo (*e.g.*, Agrin, Claudin, CD44v6). These mediators promote the proliferation of non-stem cancer cells and can also induce ER stress and unfolded protein response in healthy cells, contributing to malignant transformation and microenvironmental remodeling. Key factors, including Plectin, Wnt5b, ANEXINA1, AEP, CD151/Tspan8, CD44v6, Claudin, and extracellular vesicles (EVs) carrying Agrin, contribute to CSC-driven tumor heterogeneity and progression. Additionally, ER (Endoplasmic reticulum) stress and the unfolded protein response play a role in transforming healthy cells into malignant ones, further promoting cancer development.

Among the exosomal biomarkers, miRNAs such as miR-21, miR-155, and miR-196a play a significant role in pancreatic cancer progression, metastasis, and resistance to therapy. For instance, elevated levels of exosomal miR-21 have been associated with poor prognosis and increased tumor growth in pancreatic cancer patients [1]. Similarly, miR-196a has been shown to regulate tumor cell proliferation and invasion, making it a key biomarker for aggressive disease [155]. Additionally, Glypican-1 (GPC1), a cell surface proteoglycan, has been proposed as a specific marker for pancreatic cancer-derived exosomes, though its diagnostic utility remains under investigation. While some studies suggest that exosomal GPC1 is highly specific for PDAC, others argue that it lacks sufficient sensitivity to be a standalone biomarker [156].

Beyond nucleic acids, exosomes are enriched with proteins and lipids that provide insight into tumor biology. Proteomic analyses have identified several exosome-associated proteins, such as Laminin Subunit Gamma 2 (LAMC2), which is overexpressed in pancreatic cancer tissues and linked to poor prognosis [157]. LAMC2 expression is associated with tumor progression, enhanced self-renewal capacity, and metastatic potential, reinforcing its value as a biomarker for aggressive pancreatic cancer [158].

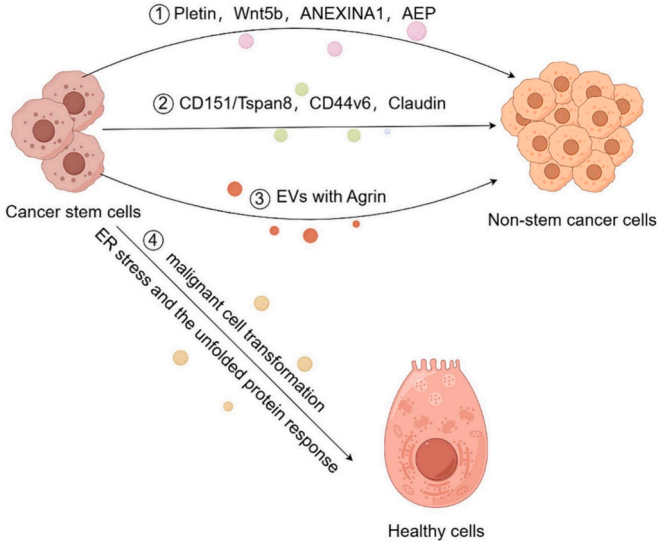


Fig. 3. Extracellular vesicle-mediated crosstalk between cancer stem cells, non-stem tumor cells, and healthy cells driving tumor progression and malignant transformation 'Reprinted with the permission from [154].'.

Additionally, exosomal lipid signatures contribute to cancer detection by influencing membrane fluidity and vesicle stability, ultimately affecting intercellular communication and tumor progression [158]. Comprehensive lipidomic profiling of exosomes may further reveal novel lipid-based biomarkers with diagnostic and therapeutic implications [158].

The detection and characterization of exosomes have been significantly enhanced by the development of electrochemical and plasmonic biosensors. Electrochemical biosensors, which measure electrical changes upon exosome binding, offer high sensitivity and specificity. For instance, graphene field-effect transistor (GFET) array biosensors have been developed for the detection of PDAC-specific exosomes expressing GPC1, enabling rapid and accurate diagnosis from patient plasma [159]. Similarly, plasmonic biosensors, including SPR (Surface plasmon resonance) platforms, provide label-free and real-time exosome detection by monitoring refractive index changes upon exosome interaction with the sensor surface [160]. Advances in nanoplasmonic sensors and plasmonic-enhanced fluorescence have further improved the sensitivity and throughput of exosome analysis, facilitating clinical applications in cancer diagnostics [156].

In conclusion, exosomal biomarkers, including miRNAs, proteins, and lipids, hold substantial promise for improving early detection, prognosis, and therapeutic monitoring in pancreatic cancer. The integration of advanced biosensing technologies, such as electrochemical and plasmonic biosensors, into clinical workflows has the potential to revolutionize exosome profiling, leading to more precise and personalized oncology care. Future research should focus on validating these biomarkers in large-scale clinical studies to enhance their reliability and applicability in routine cancer diagnostics.

2.4. *Protein biomarkers beyond CA 19–9: The proteomic approach*

Carbohydrate Antigen 19–9 (CA 19–9) has long been used as a biomarker for pancreatic cancer, yet its limited sensitivity and specificity highlight the need for more reliable diagnostic markers. To enhance diagnostic accuracy, recent proteomic studies have identified additional protein biomarkers that show promise in detecting pancreatic cancer at earlier stages and improving patient outcomes.

Among these emerging biomarkers, Thrombospondin-2 (THBS2) has gained attention due to its role in tissue remodeling and angiogenesis. Elevated levels of THBS2 in plasma have been observed in pancreatic cancer patients, suggesting its potential as a diagnostic marker [156,161].

Further underscoring its importance, a large-scale secretome-based proteomics study identified 696 discriminatory proteins from tumor and normal tissues, including 21 candidate biomarkers, with THBS2 emerging as particularly promising [161]. In the validation phase involving patients with pancreatic ductal adenocarcinoma (PDAC; $n = 82$), distal cholangiocarcinoma (dCCA; $n = 29$), benign disease ($n = 30$), and healthy donors ($n = 50$), THBS2 levels were significantly higher in cancer patients than in healthy individuals ($p < 0.001$, area under the curve [AUC] = 0.844). Notably, combining THBS2 with CA19-9 achieved an AUC of 0.952, effectively discriminating both early- and late-stage disease. This combination also provided an additive value for patients with elevated bilirubin levels, highlighting the potential of THBS2 to complement CA19-9 in challenging diagnostic scenarios [161].

Similarly, the Tissue Inhibitor of Metalloproteinases 1 (TIMP1), a regulator of extracellular matrix degradation, has been linked to tumor progression. Increased TIMP1 expression has been consistently reported

in pancreatic cancer tissues, making it a strong candidate for early detection [162].

In addition to blood-based markers, urinary biomarker panels have shown potential for non-invasive detection. A combination of Lymphatic Vessel Endothelial Hyaluronan Receptor 1 (LYVE1), Regenerating Family Member 1 Beta (REG1B), and Trefoil Factor 1 (TFF1) has demonstrated effectiveness in distinguishing pancreatic cancer from benign pancreatic diseases. This approach offers a promising alternative to traditional blood tests, facilitating earlier diagnosis and reducing the need for invasive procedures [163].

Technological advancements in biosensor development have further revolutionized the detection of these biomarkers, enabling the simultaneous measurement of multiple proteins with high sensitivity and specificity. Aptamer-based biosensors, which utilize synthetic oligonucleotides with high binding affinity, offer advantages such as enhanced stability and selectivity. These sensors have been successfully applied to detect Mucin 1 (MUC1) in breast cancer cells and hold potential for similar applications in pancreatic cancer diagnostics [164]. Another cutting-edge technology, SPR sensors, allows for real-time, label-free detection of biomolecular interactions. SPR assays have been developed to detect carcinoembryonic antigen (CEA) with high sensitivity, indicating their suitability for early cancer diagnosis [165].

As research continues to refine these biomarkers and biosensing technologies, the integration of proteomic approaches into pancreatic cancer diagnostics holds the potential to improve early detection, enhance prognostic accuracy, and guide personalized treatment strategies. The development of highly sensitive, non-invasive detection methods will be instrumental in overcoming current diagnostic limitations, ultimately improving patient outcomes.

2.5. Metabolomics and Lipidomics: The next Frontier

Metabolomics and lipidomics are transforming the landscape of pancreatic cancer research, offering groundbreaking insights into diagnosis, treatment, and biomarker discovery. These approaches provide a window into the metabolic reprogramming that fuels cancer progression, shedding light on how tumor cells adapt their biochemical pathways to survive and spread. Among these adaptations, lipid metabolism stands out as a crucial player, driving tumor growth, invasion, and metastasis.

One of the most striking features of pancreatic cancer is its altered lipid metabolism. Cancer cells enhance lipid uptake and activate de novo lipid synthesis to meet the demands of rapid proliferation and invasion [166]. This reprogramming is not unique to pancreatic cancer but is observed across many malignancies, where increased lipid biosynthesis supports membrane formation, energy storage, and oncogenic signaling [166]. Beyond fueling growth, lipid metabolism dysfunctions engage multiple pathways that promote tumor progression, resistance to therapy, and immune evasion [167].

Recent studies underscore the power of metabolomics and lipidomics in uncovering novel diagnostic markers for pancreatic cancer. Analysis of pancreatic cyst fluid and plasma from patients with intraductal papillary mucinous neoplasms (IPMNs) and serous cystic neoplasms (SCNs) has revealed significant alterations in lipid composition, offering a promising avenue for non-invasive disease classification [168]. Moreover, lipidomic profiling of serum samples has identified distinct lipid species such as very long-chain sphingomyelins, ceramides, and (lyso) phosphatidylcholines that differentiate pancreatic cancer patients from healthy individuals with remarkable accuracy [169]. These findings suggest that lipidomics may surpass traditional biomarkers like CA 19–9, providing earlier and more reliable detection.

Beyond its diagnostic potential, lipidomics is revolutionizing how we understand pancreatic cancer heterogeneity. Classifying tumors into metabolic subtypes based on their immune-metabolic signatures is a promising step toward precision medicine [170]. Such classifications can help identify patients who are more likely to respond to targeted therapies, leading to more effective, individualized treatment strategies. Additionally, molecular subtypes defined by tumor-associated macrophage (TAM2) related metabolic pathways offer new prognostic insights, with specific lipid signatures correlating with patient survival and treatment outcomes [170].

The growing clinical relevance of lipidomics extends beyond diagnostics and prognostics, it also offers therapeutic opportunities. Targeting cancer-specific lipid metabolism has emerged as a promising strategy, as disrupting lipid biosynthesis and uptake can selectively impair tumor growth while sparing normal cells [171]. As our understanding of lipid signaling in cancer deepens, novel therapeutic targets are likely to emerge, paving the way for new drugs that exploit metabolic vulnerabilities unique to pancreatic tumors. In brief, metabolomics and lipidomics are revolutionizing pancreatic cancer research, offering earlier detection, better prognostic tools, and novel therapeutic strategies. These approaches do more than reveal metabolic changes; they provide a blueprint for the future of precision oncology, where treatments are tailored to the unique biochemical landscape of each patient's tumor. As research advances, lipidomics is poised to become a cornerstone of pancreatic cancer management, ultimately improving survival and quality of life for patients facing this devastating disease.

Table 2 summarizes key biomarkers used for pancreatic cancer detection, prognosis, and disease monitoring through liquid biopsy, covering protein, ctDNA, miRNA, exosomal, and metabolic biomarkers. Each biomarker category is evaluated based on specificity, sensitivity, detection techniques, and clinical implications. Protein biomarkers such as CA 19–9, CEA, and THBS2 remain widely used in clinical practice, yet their limitations in sensitivity and specificity necessitate their incorporation into multi-marker panels for improved accuracy. ctDNA markers, including KRAS, TP53, SMAD4, and CDKN2A mutations, are detected *via* PCR and next-generation sequencing (NGS) and provide high specificity, though their sensitivity depends on tumor burden and disease stage. miRNAs, including miR-21, miR-210, and miR-155, offer promise as early detection markers, with qRT-PCR serving as the primary detection method; however, further validation is required before clinical translation.

In addition to these well-established biomarker types, exosomal and metabolic biomarkers have emerged as promising candidates for pancreatic cancer diagnostics. Exosomal biomarker GPC1, detected *via* flow cytometry and ELISA, has demonstrated strong potential in distinguishing pancreatic cancer from benign conditions. Metabolic biomarkers, such as branched-chain amino acids (BCAAs) detected *via* mass spectrometry, are still investigational but may serve as metabolic indicators of early-stage pancreatic cancer.

2.6. The interplay between endocrine disorders and pancreatic Cancer: A metabolic perspective

Pancreatic cancer is increasingly recognized as a disease with a strong metabolic and endocrine component, influenced by conditions such as diabetes mellitus (DM), insulin resistance, metabolic syndrome, and pancreatic neuroendocrine tumors (PanNETs) [178,179]. The bidirectional relationship between pancreatic cancer and endocrine dysfunction highlights the need for a deeper understanding of metabolic biomarkers that could serve as early indicators of malignancy. Given that pancreatic cancer often presents late due to its asymptomatic progression, AI-powered biosensors integrating endocrine biomarkers with multi-omics liquid biopsy data could play a crucial role in early detection and risk stratification.

2.6.1. Diabetes mellitus and pancreatic Cancer: A complex bidirectional relationship

A well-established link exists between diabetes and pancreatic ductal adenocarcinoma, the most common and aggressive form of pancreatic cancer. Long-standing type 2 diabetes mellitus (T2DM) has been identified as both a risk factor and a consequence of pancreatic cancer,

Table 2
Overview of multi-omics biomarkers for pancreatic cancer detection: sensitivity, specificity, detection techniques, and clinical utility [49,172–177].

Biomarker Type	Specific Biomarker	Sensivity (%)	Specificity (%)	Detection technique	Clinical Utility and Limitations
Protein	CA 19–9	70–90	68–91	ELISA, Mass Spectrometry	FDA-approved, but lacks specificity; often elevated in pancreatitis and other benign conditions.
	THBS2	87	98	ELISA	Higher specificity than CA 19–9; promising for early detection.
ctDNA	KRAS mutations	40–85	85–95	PCR, NGS	Highly specific, but sensitivity depends on tumor burden and stage.
	TP53, SMAD4, CDKN2A mutations	50–80	85–90	PCR, NGS	Typically analyzed in combination; useful for prognosis and monitoring recurrence.
miRNA	miR-21, miR-210, miR-155	64–89	80–90	qRT-PCR	Promising early detection markers; require further validation in large clinical trials.
	miR-1246, miR-4644, miR-4306	100	80	RNA squencing	Found in exosomes; high potential for non-invasive diagnostics.
Exosomal Biomarkers	GPC1	80–100	80–90	Flow Cytometry, ELISA	Strong potential for distinguishing cancerous vs. non-cancerous conditions
Metabolic Biomarkers	Branched-chain amino acids (BCAAs)	80–90	85–95	Mass Spectrometry	Investigational; may serve as metabolic indicators of early-stage pancreatic cancer.

creating a diagnostic challenge for clinicians [180,181]. Chronic hyperglycemia, hyperinsulinemia, and inflammation contribute to tumorigenesis by promoting cell proliferation, inhibiting apoptosis, and altering tumor microenvironment metabolism [182,183]. Several epidemiological studies suggest that individuals with T2DM have an approximately twofold increased risk of developing pancreatic cancer compared to non-diabetic individuals [184,185].

A more clinically relevant concern is new-onset diabetes (NOD), which frequently develops in pancreatic cancer patients months to years before a formal diagnosis [186,187]. Studies indicate that nearly 50 % of pancreatic cancer patients develop diabetes before tumor detection, suggesting that cancer-induced metabolic dysfunction can manifest before imaging-detectable tumors emerge [188,189]. Unlike typical T2DM, NOD in pancreatic cancer is characterized by rapid β-cell dysfunction, reduced insulin secretion, and profound weight loss, distinguishing it from obesity-associated diabetes [190]. The underlying mechanisms involve tumor-secreted exosomes, cytokines (*e.g.,* IL-6, TNF-α), and metabolic reprogramming driven by KRAS mutations, which alter glucose homeostasis [191].

Emerging AI-driven biosensor platforms offer promising approaches to differentiate pancreatic cancer-related diabetes from traditional T2DM. These biosensors can detect insulin resistance markers (*e.g.,* fasting insulin, HOMA-IR), pancreatic β-cell function indicators (*e.g.,* C-peptide, proinsulin levels), and inflammatory cytokines (*e.g.,* IL-6, CRP, adiponectin/leptin ratio) to enhance early-stage risk stratification. Additionally, AI models trained on metabolic biomarker panels can incorporate longitudinal glucose variability, lipidomic signatures, and gut microbiota-derived metabolites to refine predictive screening for pancreatic cancer in diabetic populations.

2.6.2. *Metabolomic and lipidomic profiling in pancreatic cancer diagnosis*

Metabolic alterations in pancreatic cancer extend beyond glucose homeostasis and involve profound changes in lipid metabolism, amino acid metabolism, and gut microbiome-derived metabolites. Tumor cells undergo metabolic reprogramming to sustain rapid proliferation, evade immune surveillance, and resist apoptosis [192–194]. Lipidomic analysis has revealed elevated levels of phospholipids, sphingolipids, and lysophosphatidylcholines in pancreatic cancer patients, distinguishing them from healthy controls and chronic pancreatitis cases [168]. These alterations are thought to reflect increased fatty acid synthesis and β-oxidation dysregulation, driven by oncogenic KRAS signaling.

AI-integrated biosensors can leverage metabolomic fingerprinting techniques, such as SERS and electrochemical biosensing, to identify tumor-specific metabolic signatures. By combining AI-driven pattern recognition with liquid biopsy-based metabolomic data, clinicians may be able to develop non-invasive, high-throughput screening tools capable of detecting early-stage pancreatic cancer in high-risk populations, particularly in individuals with unexplained metabolic dysfunction.

2.6.3. *Pancreatic neuroendocrine tumors and AI-Guided biomarker discovery*

While PDAC is the predominant form of pancreatic cancer, PanNETs represent a distinct subgroup with unique biological and metabolic features [195,196]. Unlike PDAC, which is typically aggressive and diagnosed at late stages, PanNETs can present with hormone-secreting or non-functional phenotypes, leading to variable clinical manifestations [197]. Functioning PanNETs secrete hormones such as insulin, glucagon, gastrin, and vasoactive intestinal peptide (VIP), leading to characteristic endocrine syndromes that can sometimes facilitate early diagnosis [198]. However, non-functioning PanNETs, which account for a significant proportion of cases, often remain asymptomatic until they reach an advanced stage [199].

Metabolomic and proteomic profiling studies have identified distinct amino acid and lipid signatures associated with PanNET metabolism, which could serve as potential diagnostic markers [200]. Given the heterogeneous nature of PanNETs, AI-powered biosensors trained on multi-omics datasets from functional and non-functional PanNET subtypes could enhance diagnostic precision and guide personalized treatment strategies.

Furthermore, AI algorithms can integrate imaging data (*e.g.,* PET-CT, MRI, and contrast-enhanced ultrasound) with liquid biopsy biomarker profiles to improve the accuracy of PanNET classification and prognosis prediction. The incorporation of machine learning-based radiomics into AI-assisted biosensing platforms could further enhance early detection and risk assessment for PanNETs, leading to more effective surveillance and management strategies.

2.6.4. *Ai-driven endocrine biomarker integration for personalized risk assessment*

As AI-driven multi-omics biosensors continue to evolve, the incorporation of endocrine biomarkers into pancreatic cancer screening algorithms will be essential for enhancing early detection and advancing personalized medicine [7]. Future developments should prioritize the integration of glucose metabolism biomarkers, such as glycated hemoglobin, fasting insulin, and GLP-1 (Glucagon-like peptide-1) response, alongside traditional liquid biopsy components to distinguish between pancreatic cancer-induced diabetes and primary metabolic disorders. Additionally, AI-powered risk prediction models should be leveraged to analyze patient-specific endocrine and metabolic profiles, enabling more precise risk stratification for individuals presenting with unexplained weight loss, diabetes, or abnormal lipid metabolism, all of which

may serve as early indicators of pancreatic malignancy [187,201]. Expanding prospective clinical trials incorporating AI-assisted biosensors will also be critical for validating endocrine and metabolic biomarker panels, ensuring their clinical applicability in pancreatic cancer screening programs, and improving diagnostic accuracy for high-risk populations. AI-enhanced endocrine biomarker integration holds great potential for bridging the gap between oncology and endocrinology, fostering a more comprehensive and personalized approach to pancreatic cancer screening [202,203].

3. Biosensor technologies for Multi-Omics pancreatic cancer detection

Despite significant advancements in therapeutic modalities, the five-year survival rate of pancreatic cancer remains alarmingly low, emphasizing the urgent need for innovative diagnostic strategies to enable early detection and precise disease characterization [204,205]. Recent progress in biosensor technologies has emerged as a promising approach for the early diagnosis and monitoring of pancreatic cancer, leveraging multi-omics methodologies [28]. These innovative platforms combine diverse biological recognition elements with advanced biomarkers and signal transduction mechanisms to provide simultaneous determination of multiple molecular biosignatures [206]. In this regard, a general visual presentation of biosensor technologies generally used for multi-omics pancreatic cancer detection is given in Fig. 4.

The integration of biosensors with multi-omics analysis offers extensive profiling of genomic, transcriptomic, proteomic, and metabolomic markers linked to pancreatic cancer [207]. These technologies present a number of advantages over traditional diagnostics, which include improved sensitivity, fast detection times, minimal sample required, and the potential for point-of-care testing. In particular, recent advances in nanomaterial-modified biosensors, microfluidic platforms, and systems integrated with artificial intelligence have further enhanced the capabilities of these diagnostic devices. This chapter highlights recent technological advances while reviewing the current state of the art of biosensor technologies for multi-omics pancreatic cancer detection.

Table 3 presents a comprehensive comparison of the four main types of biosensors including electrochemical, optical, microfluidic, and nanomaterial-modified electrochemical. These biosensors exhibit varied detection methodologies, with electrochemical sensors employing techniques such as amperometric and potentiometric detection, whereas optical biosensors leverage advanced strategies including Surface Plasmon Resonance and Surface-Enhanced Raman Spectroscopy. A thorough examination of the advantages and limitations of each type is provided, meticulously detailing the trade-offs between factors such as sensitivity, cost, and ease of utilization. For instance, whereas electrochemical biosensors exhibit cost-effectiveness and ease of operation, they encounter challenges such as surface fouling and matrix interference. In a similar manner, optical biosensors display a high level of specificity and the capacity for multi-analyte detection. However, it should be noted that they necessitate complex instrumentation and specialized training. Microfluidic systems are also demonstrated to be highly effective in the domain of sample processing and automation. Conversely, nanomaterial-modified sensors have been exhibited to be very sensitive, but they are not yet widely adopted because they are not easy to reproduce. The levels of preparation observed across the laboratory, clinical, and pilot scales suggest diverse degrees of technological readiness, with most types demonstrating high laboratory preparedness yet lower pilot-scale readiness.

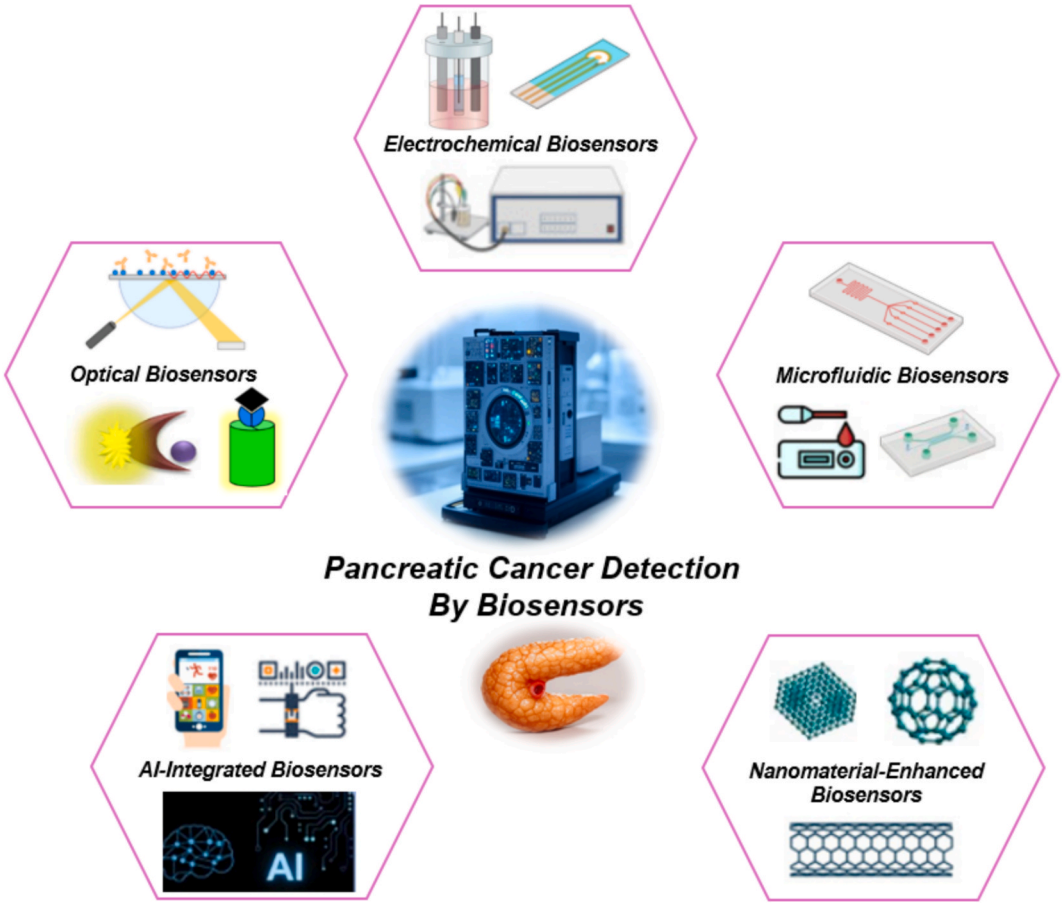


Fig. 4. Classification of biosensor technologies for multi-omics-based pancreatic cancer detection and clinical integration.

Table 3
A comprehensive comparison detailing the various types of biosensors [208–216].

Characteristics	Electrochemical Biosensors	Optical Biosensors	Microfluidic Biosensors	Nanomaterial Modified Electrochemical Biosensors
Detection Methods	– Amperometric – Potentiometric – Impedimetric – Enzymatic reactions- Aptamer-based detection	– Surface Plasmon Resonance (SPR) – Surface-Enhanced Raman Spectroscopy (SERS)- Fluorescence-based detection	– Lab-on-chip platforms – Continuous flow detection- Integrated optical/electrochemical sensing	– Enhanced electrochemical detection – Quantum dot-based sensing- Nanoparticle-modified detection
Advantages	– Fast response time – Cost-effective – High sensitivity – Real-time monitoring- Simple operation	– Label-free detection – High specificity – Multi-analyte detection – Non-destructive analysis- Real-time monitoring	– Minimal sample volume – Integrated sample processing – High throughput – Automated analysis- Precise fluid control	– Ultra-high sensitivity – Enhanced electron transfer – Improved surface area – Better catalytic activity- Superior stability
Limitations	– Surface fouling – Limited multiplexing – Matrix interference – Regular calibration needed- Environmental sensitivity	– Complex instrumentation – Higher cost – Background interference – Limited portability- Specialized training required	– Complex fabrication – Channel clogging – Flow rate optimization – Limited sensitivity- Integration challenges	– High production cost – Complex synthesis – Reproducibility issues – Standardization needed- Potential toxicity
Preparation Level	– Laboratory: High – Clinical: Medium- Pilot: Medium	– Laboratory: High – Clinical: High- Pilot: Low	– Laboratory: High – Clinical: Medium- Pilot: Low	– Laboratory: Very High – Clinical: Medium- Pilot: Low

3.1. Electrochemical biosensors

Electrochemical biosensors have represented a considerable advance in pancreatic cancer diagnostics, representing significant sensitivity and speedy detection abilities [217]. The integration of innovative surface modification techniques and enhanced electrode materials has enabled the performance of these devices to be further improved, which makes them particularly valuable, especially for early-stage cancer detection [218]. They can be classified based on their transduction mechanisms, particularly as “primary (label-free)” or “secondary (label-based or signal-amplified)” systems, depending on how the biochemical interaction is converted into an electrical signal [219]. This distinction is critical for understanding their diagnostic performance and clinical applicability in PC diagnosis. Primary transducer-based biosensors detect target interactions directly, without requiring additional labeling [220,221]. In contrast, secondary transducer-based biosensors incorporate amplification strategies involving enzymes, redox mediators, or nanomaterial-enhanced interfaces [222]. These systems are especially valuable when detecting low-abundance biomarkers or operating in complex biological matrices. Redox mediator-based designs using methylene blue– or ferrocene-labeled probes have demonstrated improved electron transfer efficiency and hybridization-dependent signal modulation [223,224]. Additionally, secondary transduction strategies often exploit nanomaterials to improve sensitivity and surface area [225]. Overall, the choice between primary and secondary electrochemical transducers depends on the target analyte, required sensitivity, assay complexity, and integration potential with clinical or point-of-care workflows.

The basic operating principle of electrochemical biosensors is represented by a highly developed interplay between biological recognition and electrical signal generation, accomplished by means of sensitively designed electrochemical transduction mechanisms [222,226]. On its basis, this sophisticated process depends on the careful orchestration of biological occurrences that generate scalable electrical responses, enabling highly sensitive detection of specific molecular targets [222]. The whole system operates *via* a thoughtfully designed framework involving three essential and interdependent elements. The first one, a biologically extremely specialized biological recognition element, carefully designed to demonstrate exceptional selectivity for the target analyte, simplifies precise molecular recognition phenomena [227]. Secondly, an improved transducer component converts these biological interactions into obviously defined electrical signals efficiently by way of diverse electrochemical processes [228]. The third, a state-of-the-art a highly advanced signal processing system that utilizes the latest amplification and quantification techniques to produce relevant analytical outputs [229]. The three critical components are seamlessly integrated and synchronized, creating a hugely efficient detection platform that ensures real-time monitoring. This extraordinary ability, together with the system’s remarkable sensitivity and phenomenal specificity in detecting even the smallest alterations in biological parameters, has positioned electrochemical biosensors as priceless tools in the early detection and monitoring of cancer, especially in cases where quick and correct diagnosis is essential for patient results. In this perspective, an example of an electrochemical biosensor for pancreatic cancer diagnosis is summarized in Fig. 5. This schematic illustrates the detection process of pancreatic cancer-associated biomarkers, including exosomes, ctDNA, miRNAs, proteins, lipid metabolites, and cancer stem cell markers, using an electrochemical biosensor. Target molecules are captured at the biorecognition site and converted into electrical signals by the transducer. The resulting data are processed and visualized as differential pulse voltammetry curves, enabling quantitative and multiplexed biomarker analysis for diagnostic applications.

Electrochemical biosensors can be classified according to their functional components into three principal platforms, namely enzyme-based, aptamer-based, and nanomaterial-enhanced systems [222,230]. Each platform contributes uniquely to improving the sensitivity and specificity of biomarker detection in clinical diagnostics [222,230].

Enzyme-based biosensors utilize biocatalytic reactions, where enzymes interact with target molecules to generate electrochemical signals, offering high specificity in detecting biomolecules such as glucose and cancer-related metabolites. Enzyme-based platforms, exploit the power of extremely specific enzymatic reactions to yield sensitive and measurable signals and represent a basic breakthrough in biosensor technology [217]. These highly developed platforms employ elaborately designed biological recognition components that interact with target molecules using complex lock and switch mechanisms, providing highly selective detection of pancreatic cancer biomarkers based on unprecedented precision [231]. Biological identification agents have been rigorously architected and optimized to deliver maximum specificity for their intended targets, at the same time as retaining stability in a variety of environmental situations [232]. Enzymatic reactions catalyze the transformation of particular substrates by means of well-characterized biochemical routes, thereby yielding detectable electrochemical or optical signals directly related to biomarker concentrations [233]. Such signals are being produced with complex molecular interactions including multiple steps of substrate modification and electron transfer that result in extremely accurate and reproducible measurements [234]. The platform’s outstanding performance can be even further developed with the use of advanced surface chemistry modifications and optimized reaction environments. It sustains remarkable specificity in complex

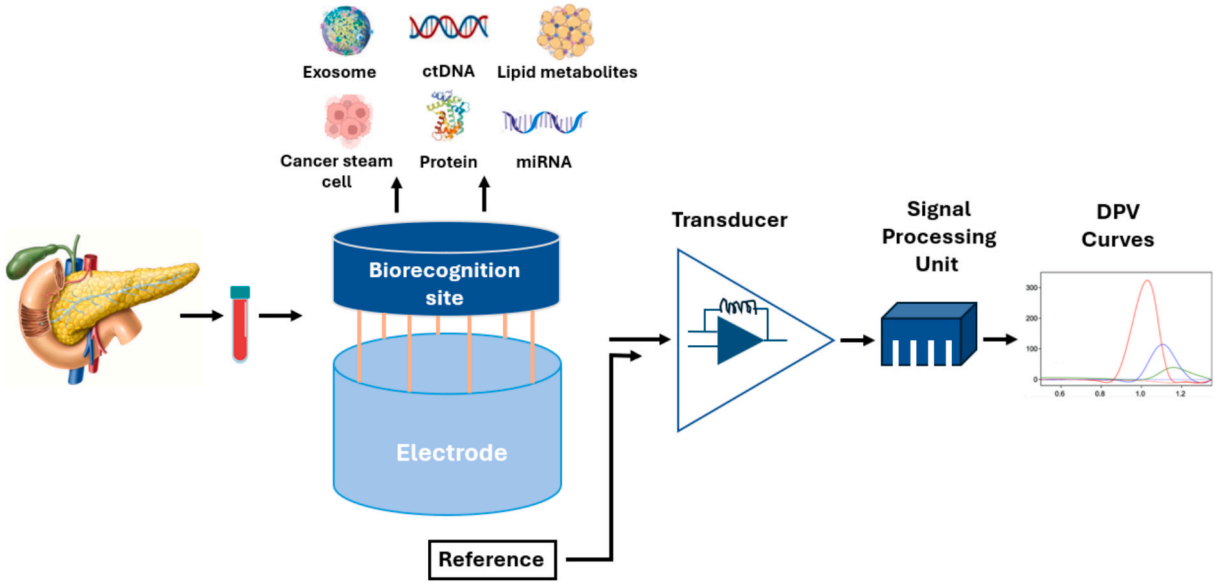


Fig. 5. Workflow of an electrochemical biosensor for multi-biomarker detection in pancreatic cancer diagnosis.

biological samples and minimal disruption from other biomolecules, even in the absence of competitive analytes and a variety of matrix effects that can compromise detection sensitivity [235].

Aptamer-based biosensors rely on synthetic single-stranded DNA or RNA sequences that selectively bind to target analytes, providing excellent stability and affinity for detecting nucleic acids and proteins [236]. Such elaborated platforms are based on DNA or RNA aptamers that are meticulously engineered to undergo defined conformational alterations upon binding to their target molecules, thus creating highly selective and durable molecular interactions [236,237]. The remarkable flexibility of aptamer-based systems derives from the fact that they can be systematically developed and optimized *via* improved selection processes, leading to the development of detection agents with fine-tuned binding properties [238]. Their platforms show notable robustness across a range of environmental circumstances and may be easily modified with functional groups to increase their analytical performance [238,239]. The unique combination of their outstanding binding specificity, great affinity for target molecules, and intrinsic chemical stability combine to make aptamer-based platforms especially promising for reliable and repeatable biomarker recognition in complex biological matrices. Moreover, the synthetic nature enables large-scale manufacturing with high batch-to-batch retention, which also enables large-scale fabrication, which makes them ideal nominations for applications in standardized diagnostics [239,240].

Electrochemical biosensors incorporating nanomaterials (nanomaterial-modified platforms) have attracted significant attention due to their enhanced sensitivity and improved signal transduction capabilities. In most electrochemical biosensor configurations, nanomaterials such as gold nanoparticles (AuNPs), carbon nanotubes (CNTs), graphene oxide (GO), reduced graphene oxide (rGO), and metal–organic frameworks (MOFs) are not used as independent platforms but are instead integrated as signal-enhancing components to improve electron transfer, increase surface area, and enhance biomolecule immobilization efficiency [241–244]. These platforms contribute to the development of highly efficient and reliable electrochemical biosensors for disease diagnosis and monitoring. These highly advanced platforms use a broad range of enhanced nanomaterials, which implicate precisely engineered quantum dots with tunable optical properties, meticulously synthesized metal nanoparticles featuring enhanced catalytic capabilities and innovative carbon-based structures with superior electrical conductivity [245,246]. The combination of these nanomaterials significantly improves the sensitivity of biosensor systems overall *via* multiple mechanisms, as well as enhanced electron transfer kinetics, increased surface area-to-volume ratios, and advanced signal amplification cascade [247,248]. The exceptional features of these nanomaterials, in combination with their unique physical and chemical properties at the nanoscale, lead to achieving unprecedented ultra-low detection limits inaccessible previously with conventional materials [247,249]. The advanced properties and studies enhanced with nanomaterials are discussed in more detail and presented in the following section (section 3.4).

Thanks to these advanced platforms, electrochemical biosensors have revolutionized the clinical applications of pancreatic cancer, early detection, and precise monitoring, and have shown remarkable potential. These cutting-edge diagnostic platforms provide rapid, highly precise results in both clinical and point-of-care settings. The integration of these biosensor technologies within common clinical practice represents a significant advance in pancreatic cancer management, leading to just-in-time interventions and better patient results. In this perspective, electrochemical biosensors greatly strengthen the three different molecular diagnostic approaches used in the diagnosis and treatment of pancreatic cancer [173]. Initially, ctDNA detection enables cancer-specific DNA fragments to be identified and quantified in blood plasma [250]. This method is non-invasive and offers significant insights into tumor genetics and disease progression [251]. Second, miRNA detection is an improved technique to analyze small non-coding RNA molecules which play a crucial role in gene regulation and cancer progression [252]. This method presents diagnostic markers and therapeutic targets *via* differential expression patterns in pancreatic cancer [252]. Finally, protein biomarker detection is a thorough approach that includes the identification and quantification of the specific proteins linked to pancreatic cancer [252]. This method yields vital information on disease status and response to therapy.

Several significant case studies have highlighted the successful clinical application of electrochemical biosensors in the diagnosis of pancreatic cancer. For instance, Genco *et al.* (2023) studied interesting work in which a bioelectronic single-molecule detection arrangement was generated for the concurrent analysis of both ctDNA and tumor protein markers [253]. In this research, a portable bioelectronic sensing sequence was utilized to screen 47 patients to detect pancreatic cancer precursors. By using state-of-the-art molecular tests, this method has been shown to be up to 80 % sensitive in diagnosing mucinous cysts, a forerunner of pancreatic cancer. It is composed of a single-use cartridge equipped with an organic transistor sensor sequence and a reusable

scanner. The results clearly support that multiplexed testing of biomarkers such as KRAS^{mut}, MUC1 and CD55 is possible within 1.5 h (Fig. 6). Machine learning analysis also categorizes pancreatic cancer precursors, obtaining at least 96 % diagnostic sensitivity and 100 % diagnostic specificity. Zhang *et al.* (2020) have been developed a material that is able to detect the expression of the KRAS oncogene, which is strongly mutated in pancreatic cancer [254]. They made use of graphene quantum dots (GQDs), a carbon nanomaterial well-known for its optical stability and biocompatibility. By adding nitrogen atoms to GQDs was created nitrogen-doped GQDs (N-GQDs) that dramatically increased electrochemical luminescence (ECL) efficiency. Then, controlling the distance between N-GQDs and gold nanoparticles (AuNPs) using DNA as a binding medium. The experimental results indicated that this GQDs-based composite may be utilized for the quantitative determination of K-Ras.

Another new study has developed from Liu *et al.* (2020), who developed an electrochemical microfluidic chip (EMC) to detect multiple cancer-relevant miRNAs [255]. The chip deploys a laser-induced graphene (LIG) electrode stack and enzyme-guided target recycling enhancement to boost sensitivity and specificity. The results have been successfully validated by measuring miRNAs miR-21, miR-1246 and miR-155 at concentrations as low as 0.17 pM, 0.24 pM and 0.11 pM, respectively, demonstrating the effective use of the EMC platform. The chip may be used to evaluate miRNA statement in exosomes and clinical serum examples and needs a minimal amount of blood samples. In this framework, the study revealed that the EMC platform has great potential in early many cancers detection based on miRNA analysis.

3.2. Optical Biosensors: SPR, SERS, and Fluorescence-Based detection

Optical biosensors have been amplifying another vital progress in pancreatic cancer diagnostics which offer exceedingly sensitive and label-free detection capabilities by means of diverse advanced optical techniques [28]. These cutting-edge diagnostic platforms leverage the complex characteristics of light-matter interactions at the molecular level to detect and accurately quantify intricate biological interactions with exceptional sensitivity and reliability [256]. Conventional diagnostic techniques, though indispensable, constantly display a lack of the necessary sensitivity and specificity to determine pancreatic cancer in its early phases. In response to this challenge, optical biosensors have appeared as a strong tool in the multi-omics analysis of pancreatic cancer, proposing unique capabilities in detecting biomolecular interplays with superior precision [257,258].

Optical biosensors make use of the principles of SPR, surface-enhanced Raman scattering (SERS), and fluorescence-based detection, and offer a versatile platform that is suitable for the analysis of complex biological samples [259]. These approaches have been working together to deliver comprehensive molecular profiling, facilitating a more detailed and nuanced understanding of pancreatic cancer progression and treatment response [257]. SPR is a state-of-the-art, label-free detection methodology that enables accurate measurement of minute changes in the permittivity occurring at the meticulously designed interface between a metal surface and a dielectric medium [260,261]. This sophisticated technique employs the distinctive optical characteristics of surface plasmons (collective oscillations of free electrons at metal surfaces) to permit high-precision, real-time observation of intricate biomolecular interactions [260,261]. The remarkable sensitivity exhibited by SPR is attributable to its capacity to detect minuscule variations in the local optical index triggered by molecular binding processes, obviating the necessity for fluorescent or radioactive labels [260]. This ability, when combined with its capacity to discern between diverse molecular interactions, renders SPR a highly valuable tool for studying the kinetics and thermodynamics of a range of biological processes associated with the development and progression of pancreatic cancer, as is the case with all cancers. On the other hand, SERS functions by utilizing the augmented Raman scattering signals that are produced during the adsorption of molecules on nanostructured metal surfaces [262]. This method is an advanced analytical technique that uses specially designed metallic nanostructures to make Raman signals stronger by several orders of measure [263]. In this way, facilitates the parallel identification and measurement of multiple cancer biomarkers with high precision. Furthermore, SERS is highly advantageous due to

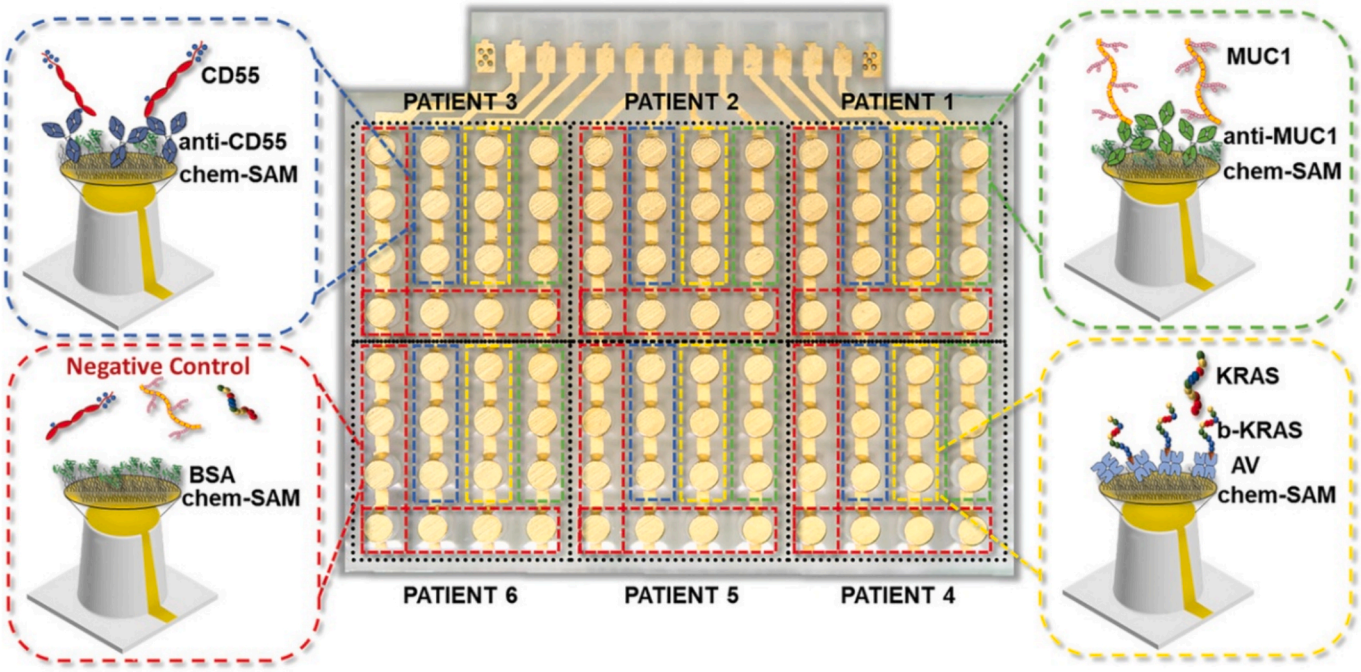


Fig. 6. A top perspective of the 3D-printed sensing gate plate illustrating the gold-plated circular fields and routes to the contact pads. It is divided into 6 spaces, each devoted to the sensing of a patient's fluid. Their color codes describe gates (in triplicate) biofunctionalized using capture antibodies against MUC1 and CD55 or probes to bind KRAS^{mut}. Every patient fluid is additionally exposed to 7 gates biofunctionalized by BSA for negative-check experiments, 'Reprinted with the permission from [253] Licensed under CC BY 4.0.'.

its capacity to yield molecular fingerprints that facilitate the differentiation between cancerous and non-cancerous states [264].

Fluorescence-based sensors are a cutting-edge analytical methodology that capitalizes on the accurate emission of light from meticulously designed fluorophores when they form specific molecular complexes of target analytes [265]. This advanced detection approach is predicated on the complex photophysical characteristics of fluorescent molecules, which exhibit distinctive alterations in their emission patterns upon binding to explicit biological targets [266]. The technique is versatile and robust which makes powerful capabilities for multiplexed detection and comprehensive screening of numerous biomarkers simultaneously possible. Fluorescence-based platforms can be adapted to develop assays for some specific nucleic acid or protein sequences [267,268]. These assay methods employ optimized fluorescent probes and detection systems to produce molecular profiles [269]. Thus, researchers may utilize these profiles to learn about genomic and transcriptomic alterations in pancreatic cancer research. Moreover, integrating improved fluorescence detection technologies together with data analysis facilitates researchers and clinicians to acquire comprehensive information from samples [267]. This, in turn, simplifies a profound understanding of disease mechanisms and potential therapeutic targets, particularly pancreatic cancer.

In the context of multi-omics concepts, such optical biosensing techniques are combined to introduce a comprehensive framework to detect pancreatic cancer. The specific studies offered in the literature support all the above-mentioned results. For instance, Jawad *et al.,* (2017) developed plasmonic gold nanotriangular architectures that may be employed as optically tunable substrates for the pancreatic cancer biomarker CA 19–9 and shown in Fig. 7 [270]. The sensitivity and controllability of the sequences were highlighted by the functionalization of the assemblies with near-infrared fluorophore-conjugated immunoassays. The obtained limit of detection for CA 19–9 of $7.7x10^{-7}$ $U.mL^{-1}$ is considerably more accurate than the commercially utilized immunoassays. In addition, the linear dynamic detection range of the sample arrays was measured to span from $1x10^{-6}$ $U.mL^{-1}$ to 1 $U.mL^{-1}$. Furthermore, the series showed high specificity and successful accuracy in serum samples. Another study, by Joshi *et al.*, (2014) investigated an LSPR sensor for detecting miRNAs in plasma [271]. This sensor is based on gold nanoprisms, eliminating the need for labeling or amplification of miRNAs. The direct hybridization approach enabled highly accurate detection of miRNA-X at subfemtomolar concentrations in human plasma from pancreatic cancer patients. The study proved with data that miRNA-10b concentrations in the plasma of pancreatic cancer patients were about 4 times higher than miRNA-21. Researchers believe that this highly sensitive approach can be applied to detect not only pancreatic cancer but also other types of cancer. They also suggest that this could lead to personalized treatment approaches, aiding early diagnosis and prognosis.

A dual SERS biosensor for the detection of a specific microRNA, microRNA-10b, in blood samples was developed by Pang *et al.*, (2019) [272]. The biosensor employs Fe3O4@Ag-DNA-Au@Ag@DTNB conjugates as SERS tags, which are deployed in the presence of the target microRNA. It was concluded that the developed biosensor can differentiate between samples from those with certain diseases and normal controls. Additionally, its detection limit was found to be 1 aM.

3.3. *Microfluidic Biosensors: Capturing Tumor-Derived components*

Microfluidic biosensors are revolutionary diagnostic tools for cancer detection, capturing and analyzing tumor-derived components at a microscopic scale [273,274]. Microfluidic biosensors process small volumes of biological samples in meticulously designed channels to isolate and analyze tumor-derived components, including circulating tumor cells CTCs, cell-free DNA, exosomes, and proteins [273,275]. These devices use the fundamentals of microscale fluid dynamics to enable efficient separation and detection, making it possible to process complex biological samples quickly and cost-effectively [213,273].

The integration of microfluidics with biosensing technologies offers versatile detection and comprehensive profiling of molecular markers, particularly those related to pancreatic cancer [273]. Thanks to this approach, it enables a holistic view of the biological landscape of the tumor, promoting the analysis of genomic, proteomic, and metabolomic data in parallel. In conclusion, microfluidic biosensors can capture tumor-derived components directly from patient samples, providing real-time monitoring of disease progression and therapeutic response.

Innovative lab-on-a-chip (LOC) platforms have made substantial progress in microfluidic biosensor technology with the capacity to integrate multiple advanced functions into compact, high-efficiency portable devices [213,276]. These instruments facilitate fast and accurate automated analysis of complex biological samples with unparalleled accuracy. Their miniaturized architecture decreases the sample volumes needed while retaining sensitivity and specificity in detecting cancer-specific markers [276]. The effectiveness of the platforms in capturing and analyzing both circulating tumor cells and exosomes is due to their carefully designed microfluidic channel design [277,278]. In this way, it aims to provide high-value molecular and cellular information that serves both diagnostic and prognostic applications in the treatment of pancreatic cancer.

On the other hand, portable biosensor devices have revolutionized continuous monitoring in pancreatic cancer management, enabling real-time monitoring of important biomarkers with minimally invasive methods [279,280]. These state-of-the-art systems have microfluidic components and highly sensitive detection mechanisms and enable frequent measurements of multiple cancer markers out of small samples

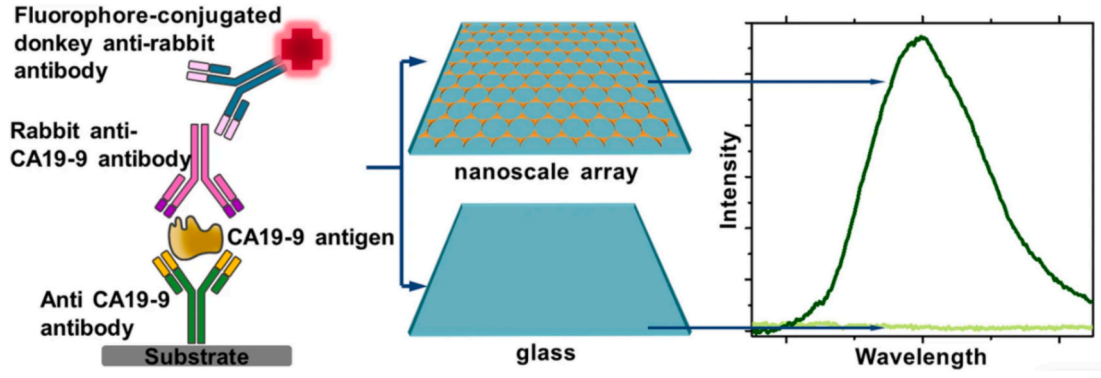


Fig. 7. The near-infrared fluorescence immunoassay is more sensitive than glass controls for measuring the pancreatic cancer biomarker CA 19–9. The diagram shows the CA 19–9 "sandwich" protein microarray performed on Au-nanotriangular substrates. It can enhance fluorescence intensity by up to two orders of magnitude compared to glass, 'Reprinted with the permission from [270] Licensed under a CC BY 4.0'.

[281]. Moreover, wireless connectivity and automated data analytics make the product more clinically beneficial by giving healthcare providers immediate access to vital diagnostic information to inform treatment decisions [282]. Consequently, the implementation of these platforms within the existing infrastructure signifies a crucial step in the development of personalized treatment for pancreatic cancer. Additionally, this integration aims to develop more precise strategies based on real-time information.

In the framework of multi-omics concepts, techniques such as microfluidic biosensors capturing tumor-derived components are brought together to present a comprehensive framework for detecting pancreatic cancer. In recent years, the studies carried out by many researchers have greatly contributed to this field and improved its quality. In the field of microfluidic biosensors, Gurudatt *et al.,* (2023) presented valuable new research as shown in Fig. 8 [283]. As is well known, tumor-derived extracellular vesicles (tdEVs) are regarded as a potentially promising biomarker for cancer detection. This worthwhile study focused on the investigation of EMT in cancer by utilizing tdEVs a tool to evaluate the risk of tumor transformation to malignancy. The researchers developed a microfluidic device based on an indium-tin oxide (ITO) sensor to detect and measure tdEVs. The device has two components: an ITO sensor and a MOFF channel. The MOFF channel extracts pure EVs by removing blood debris, whereas the GASI channel enriches and measures tdEVs. The device successfully enabled simultaneous evaluation of epithelial and mesenchymal markers, resulting in an EMT index of pancreatic cancer cells of interest. Another successful study was conducted by Zhang *et al.*, (2021) [284]. In this study, they proposed an immunoaffinity-based microfluidic device termed HBEXO-Chip that is able to isolate exosomes, nanovesicles with vital genetic and proteomic information, from plasma. The HBEXO-Chip showed outstanding performance in separating specific exosomes, evidenced by its capability to differentiate pancreatic cancer compared to healthy individuals and pancreatitis patients. Furthermore, miRNA for pancreatic cancer signature was determined by using RNA sequencing.

3.4. Nanomaterial-Modified electrochemical Biosensors: Improving sensitivity and selectivity

Recent developments in nanomaterial-modified biosensor technologies have had a deep impact on the field of pancreatic cancer diagnostics and led to a paradigm shift in the way multi-omics detection approaches are performed [285]. These state-of-the-art analytical platforms employ nanomaterials and biological recognition components designed to build efficient detection systems that can analyze multiple molecular signatures related to pancreatic cancer [285]. Nanomaterials have played a pivotal role in enhancing biosensor performance due to their high surface area and excellent electrical conductivity. The strategic involvement of a variety of nanomaterials, including quantum dots, metallic nanoparticles, and carbon-based nanostructures, has advanced the analytical abilities of traditional biosensors *via* multiple mechanisms [286]. The integration of gold nanoparticles, graphene oxide, and magnetic nanomaterials into biosensors has led to substantial improvements in sensitivity and specificity. These improvements include advanced electron transfer kinetics, increased surface area-to-volume ratios, and sophisticated signal amplification stages [247,287]. The combination of nanomaterial and multi-omics detection systems allows the profiling of genomic, transcriptomic, proteomic and metabolomic markers, leading to advances in the early detection and screening of pancreatic cancer [288,289]. The improved performance characteristics of these platforms (*e.g.,* low detection limits, high specificity, and

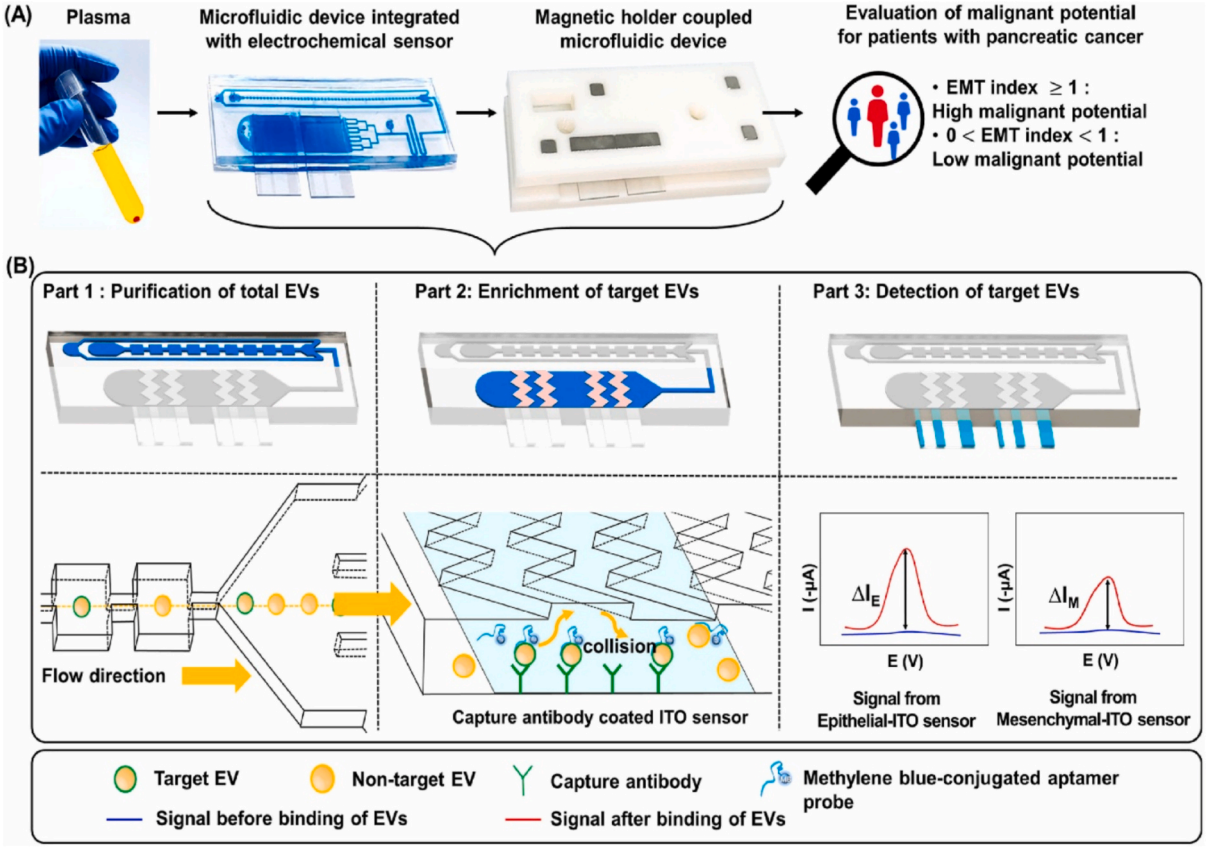


Fig. 8. (A) General Overview (B) The following sections present an integrated electrochemical microfluidic device for evaluating EMT-index-based malignancy potential in pancreatic cancer patient plasma via EVs. The first part of the study uses MOFF to focus total EVs. EVs and antibodies are made to collide using GASI channels to create an EMT index using electrochemical signals from ITO sensors, 'Reprinted with the permission from [283]'.

reproducibility) make them powerful tools for advancing pancreatic cancer diagnostics and improving patient outcomes.

Several studies have demonstrated the potential of electrochemical biosensors for microRNA detection in pancreatic cancer. For instance, a polydopamine-gold composite biosensor was developed for miR-196b detection, achieving a detection limit of 0.26 pM [290]. Another study showcased a biosensor capable of simultaneously detecting multiple microRNAs, including miRNA21, miRNA155, miRNA196a, and miRNA210, with an impressive sensitivity of 10 fM [291]. These advancements leverage amplification strategies and nanostructures to improve detection capabilities, ensuring high accuracy in identifying cancer-associated biomarkers.

Beyond microRNA detection, electrochemical biosensors have also been designed to target ctDNA with remarkable sensitivity. A target-driven rolling walker-based biosensor, utilizing rolling circle amplification and doxorubicin@tetrahedron-Au tags, achieved a detection limit of 0.29 fM for ctDNA [292]. Another study introduced a silicon nanowire array biosensor, which reached an ultralow detection limit of 10 aM [292]. These findings underscore the potential of biosensors in ctDNA detection, which is crucial for the early diagnosis and prognosis of pancreatic cancer.

A paper-based immunosensor utilizing graphene oxide for PEAK1 (Pseudopodium enriched atypical kinase 1) detection demonstrated an impressive detection limit of 10 $pg.mL^{-1}$, further proving the efficacy of nanomaterial-modified biosensors [293]. Additionally, magnetic nanomaterials have been employed to isolate diverse cancer biomarkers, further enhancing biosensing performance [293]. These nanomaterials also serve as signal amplifiers, increasing the output signals of biosensors and improving their ability to detect low concentrations of cancer biomarkers, thereby enhancing their overall diagnostic accuracy [247]. There are still several hurdles to the full adoption of biosensor technology in clinical settings. Rigorous validation, standardization, and reliability assessments are critical to ensure reproducibility, while the high cost of development restricts wider access [294].

Recent studies have enhanced diagnostic capabilities by integrating nanomaterial-modified biosensor platforms with artificial intelligence and machine learning algorithms. Computational aspects are able to identify fine molecular signatures and biomarker models that can indicate the evolution of early-stage pancreatic cancer and potentially result in opportunities to intervene earlier [294,295]. These studies indicate that the use of state-of-the-art nanomaterials, multi-omics detection strategies and enhanced data analytics to build more effective diagnostic instruments in the fight against pancreatic cancer is promising.

Soares and colleagues fabricated immunosensors utilizing polyamide 6 and poly(allylamine hydrochloride) electrospun nanofibers, which were coated with MWCNTs (multi-walled carbon nanotubes) or AuNPs [296]. In this study, the sensors were able to detect the pancreatic cancer biomarker CA19-9. The utilization of impedance spectroscopy enabled the sensors to gain a detection limit of 1.84 $U.mL^{-1}$ and 1.57 $U.mL^{-1}$ with the nanofibers containing MWCNTs and AuNPs, respectively. The sensitivity of the sensors was attributed to the adsorption of antibodies and antigens, confirmed by polarization modulated infrared reflection absorption spectroscopy. Test results showed the immunosensors exhibited high sensitivity, selectivity, and reliability in diagnosing early-stage pancreatic cancer. The immunosensors based on nanostructure and electrochemical results of the study are additionally shown in Fig. 9. In another study, Akın *et al.,* (2022) developed a label-free mobile device for the electrochemical detection of miR-141 as a biomarker of pancreatic cancer [297]. In this particular study, GoQdot (Graphene oxide quantum dots) were modified on SPE (Screen Printed Electrode) and thiolated single-stranded thiol-ss-DNA (DNA detection probes) interacted with miR-141 and gave remarkable outcomes in electron transfer. Differential Pulse Voltammetry (DPV) and Cyclic Voltammetry (CV) analyses indicated that attachment of ss-DNA to SPE and concentration-dependent increment of miR-141 reduced electron transfer. The obtained current was calculated for miR-141 concentrations of 2.3 and 6.1 nM and the limit of detection (LOD) 0.091 pM while the limit of quantitation (LOQ) was found to be 0.27 pM. This GoQdot-based sensor system represents a significant advancement in the early diagnosis of pancreatic cancer and other malignancies.

As is already known, carcinoembryonic antigen (CEA) is one of the most commonly used tumor markers in pancreatic cancer as well as in all types of cancer [298]. In this regard, Kumar *et al.,* (2022) presented a study to detect CEA by SPR biosensors with unique 2D structures [299]. Researchers conducted a study of three structures including Ti-Ag-

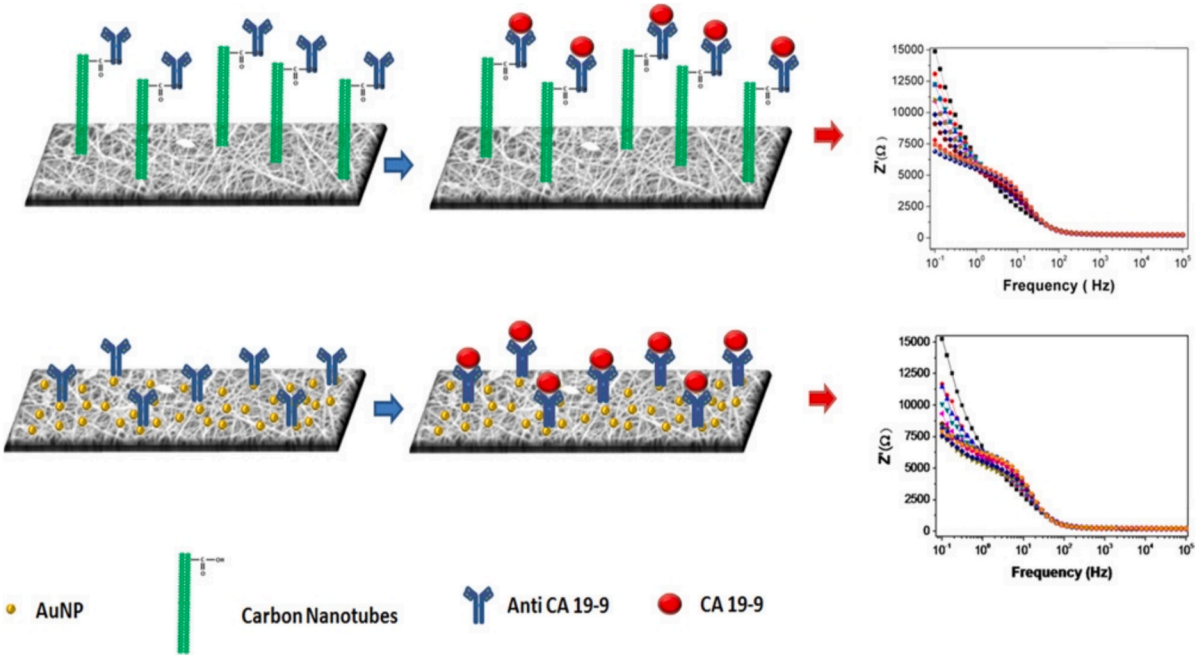


Fig. 9. Immunosensors based on nanostructure binding of CA19-9 biomarkers and electrochemical results, 'Reprinted with the permission from [296] Copyright © 2017 American Chemical Society. Licensed under the ACS AuthorChoice license'.

Graphene, Ti-Ag-MoS_2-Graphene, and Ti-Ag-Mxene-Graphene in selective CEA detection in PBS. The incorporation of MoS_2 and MXene layers between the silver and graphene layers resulted in enhanced performance parameters for the biosensor, yielding optimal outcomes. The MoS_2-Graphene structure demonstrated the highest sensitivity of 144.72 degrees/RIU and a detection precision of 2.24, thereby surpassing the performance of other reported works. This research highlights the importance of 2D materials in boosting the sensitivity of SPR biosensors and reveals their potential to have considerable influence on the improvement of detection methods. The visual scheme of different SPR biosensors proposed for CEA detection in the study is presented in Fig. 10.

In the light of the current knowledge given and described, the powerful convergence of nanotechnology and biosensor platforms has created revolutionary new possibilities in pancreatic cancer diagnosis. This advanced integration has been shown to provide unmatched sensing abilities by combining the special properties of designed nanomaterials with advanced biosensing mechanisms. The synergetic interaction among these two fields has led to notable advances in the sensitivity, specificity, and reliability of diagnostic utilities, as well as decreased sample volume needs and analysis times. Additionally, this technological fusion will represent a breakthrough in the development of next-generation diagnostic platforms for the detection and monitoring of pancreatic cancer.

3.5. *Ai-integrated Biosensors: Precision medicine for pancreatic cancer*

The integration of artificial intelligence with biosensor technology has revolutionized precision medicine for pancreatic cancer, enabling early detection, real-time monitoring, and personalized treatment strategies [41]. AI-powered biosensors utilize machine learning (ML)/deep learning (DL) algorithms to analyze multi-omics biomarker data, enhancing diagnostic accuracy and minimizing false positives. By combining advanced signal processing, microfluidic platforms, and predictive modeling, these intelligent systems offer a highly sensitive, non-invasive, and rapid approach to pancreatic cancer detection and management [280]. Fig. 11 illustrates the integration of artificial intelligence and machine learning with point-of-care testing (PoCT) devices to enhance biosensing applications [300]. AI-ML-assisted PoCT platforms incorporate various sensor technologies, including wearable sensors, lab-on-chip sensors, electrochemical sensors, colorimetric sensors, and (ECL)/chemiluminescence (CL) sensors, to enable rapid and accurate biomarker detection. The integration of these sensors with AI-driven data analysis enhances diagnostic capabilities by improving signal processing, pattern recognition, and predictive modeling. The workflow demonstrated in Fig. 11 highlights the transformation of biosensor-generated data into machine learning-based decision models, leading to accurate disease diagnosis, optimized treatment strategies, continuous patient monitoring, and also environmental safety assessments. This AI-enhanced approach is particularly promising for real-time biomarker analysis and early detection of pancreatic cancer, offering significant advancements in precision medicine and personalized healthcare [300].

The integration of AI with biosensor technology has opened new frontiers in pancreatic cancer diagnostics by allowing real-time biomarker interpretation, multi-omics data fusion, and predictive modeling [301]. These AI-improved frameworks harness advanced machine learning algorithms to analyze complex biosensor data streams in real-time, allowing for more precise interpretation of molecular signatures and increased diagnostic accuracy [301]. Furthermore, combining AI talents with multi-modal biosensor platforms effortlessly facilitates personalized treatment regimens by delivering detailed information on individual patient answers and disease progression models [302].

The highly refined data analysis of AI-integrated biosensors makes it possible to identify subtle patterns and correlations in biomarker profiles that otherwise would not be apparent with traditional analysis methods [280]. Such intelligent systems are constantly learning from and harmonizing with accumulated patient data and improving both their predictive precision and diagnostic reliability with time [280]. Additionally, by combining machine learning with biosensors, more precise treatments are possible. Fig. 12 illustrates the integration of AI with multi-source medical data for pancreatic cancer diagnosis [303]. AI models, including machine learning and deep learning algorithms, analyze diverse medical data forms, such as electronic health records (EHRs), medical imaging (MRI, CT, and endoscopic ultrasound – EUS), genomics (DNA, mRNA, and protein markers), and biosensors detecting blood and urine-based biomarkers *via* micro/nanofluidic platforms. By processing these heterogeneous data inputs, AI enhances diagnostic accuracy and predictive modeling, allowing classification into healthy pancreas, benign conditions, or PDAC. This AI-powered approach facilitates early detection, personalized treatment strategies, and

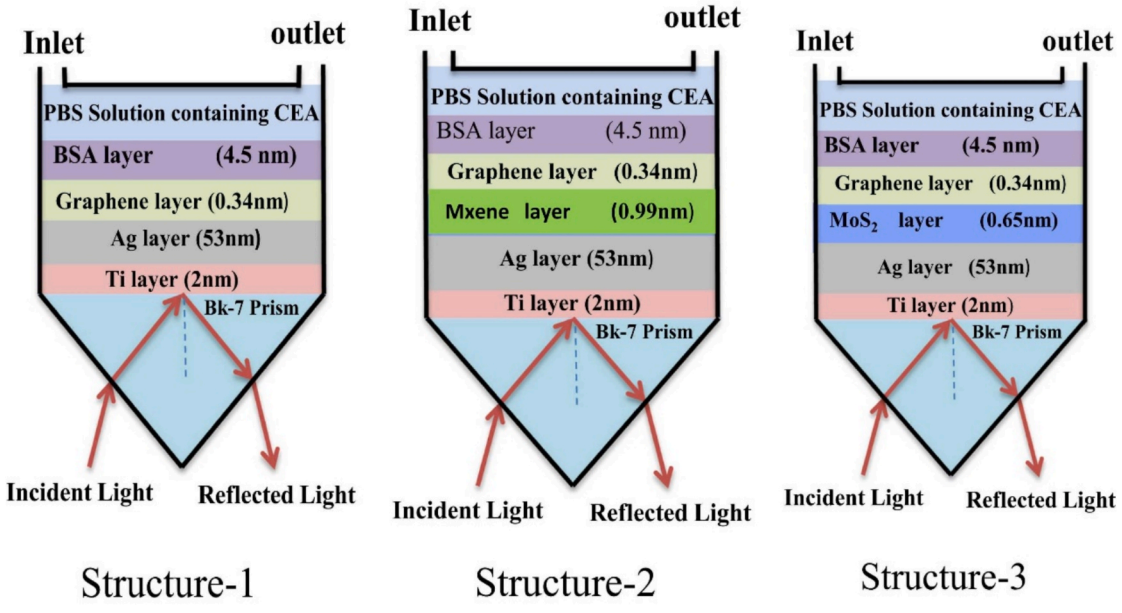


Fig. 10. The schematic diagrams illustrate the recommended SPR biosensors for the detection of CEA biomarkers, 'Reprinted with the permission from [299]'.

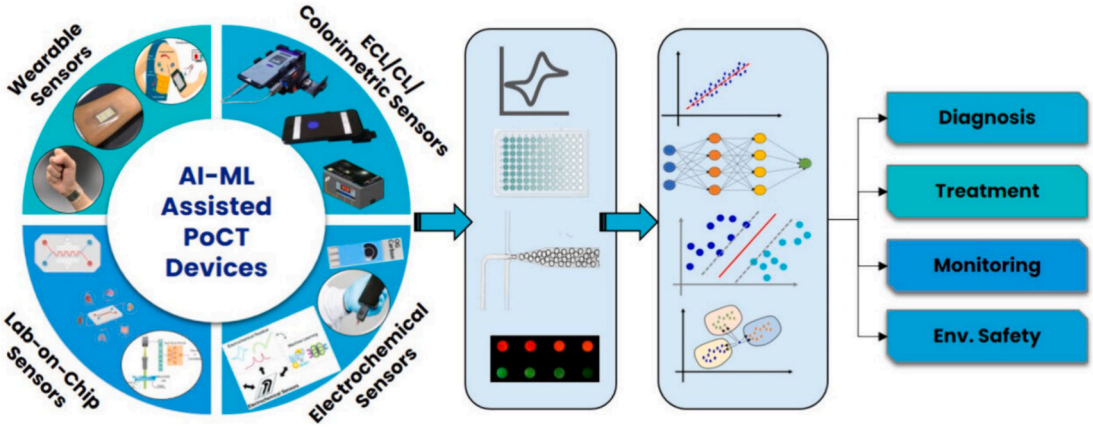


Fig. 11. Artificial intelligence-Machine learning assisted PoCT devices for biosensing applications, 'Reprinted with the permission from [300] Copyright © 2024 Published by American Chemical Society. Licensed under CC BY 4.0'.

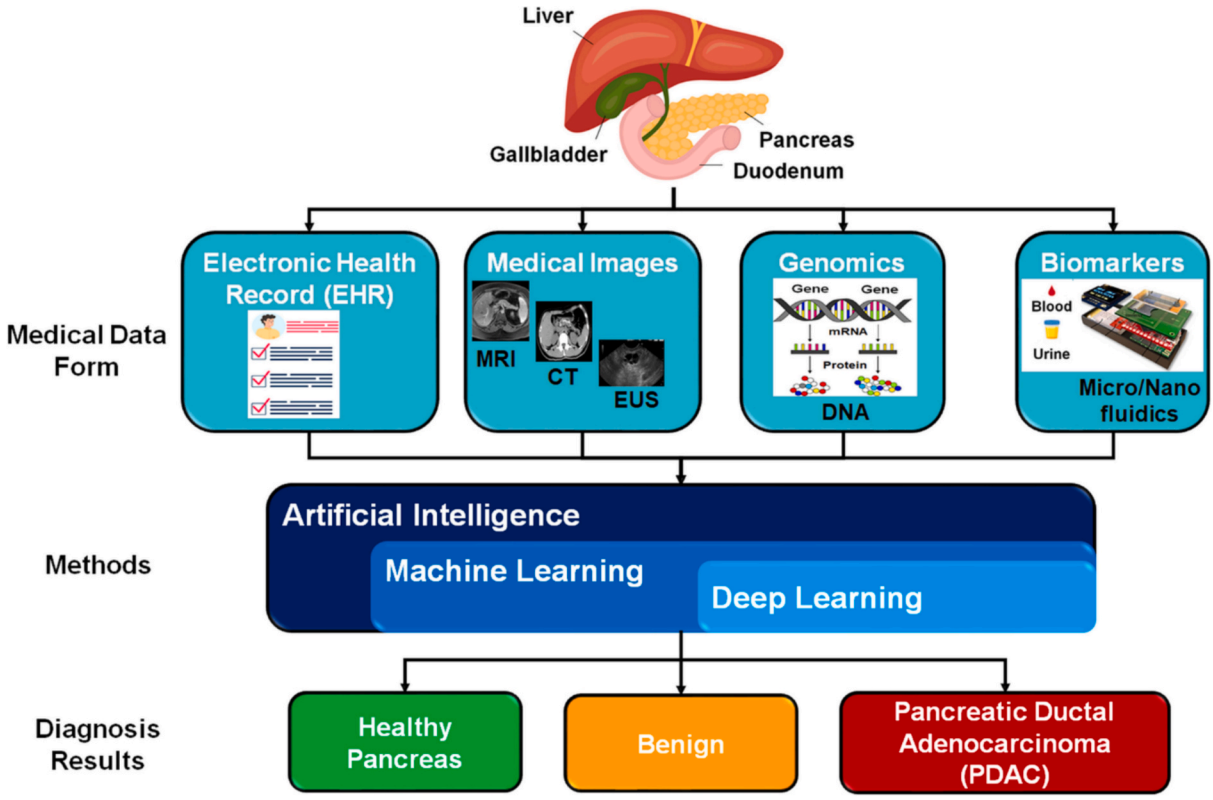


Fig. 12. AI-Driven multi-modal data integration for pancreatic cancer diagnosis, 'Reprinted with the permission from [303] Licensed under CC BY 4.0''.

improved clinical decision-making for pancreatic cancer management [303].

In a study by Karar *et al.* (2023), a deep learning-based model integrating 1D convolutional neural networks (1D-CNNs) and long short-term memory (LSTM) networks was developed for the automated diagnosis of PDAC using urine proteomic biomarkers (Fig. 13) [303]. By utilizing microfluidics technology and artificial intelligence, the model accurately analyzed creatinine, LYVE1, REG1B, and TFF1 biomarkers, achieving an accuracy of 97 % and an AUC of 98 % on a dataset of 590 urine samples. This approach provides a non-invasive, cost-effective, and highly precise diagnostic tool, distinguishing between healthy pancreas, benign hepatobiliary disease, and PDAC cases, and represents a significant advancement in early pancreatic cancer detection [303].

In a study by Long *et al.* (2019), an integrative multi-omics approach was employed to identify and validate robust biomarkers for the early diagnosis, prognosis, and management of pancreatic cancer [304]. By combining next-generation sequencing, transcriptome *meta*-analysis, immunohistochemistry, and statistical learning, the study validated LAMC2, ANXA2, ADAM9, and APLP2 as key biomarker candidates. The random forests (RF) model demonstrated excellent diagnostic performance, with these biomarkers significantly influencing its predictions. Experimental validation confirmed that LAMC2, ANXA2, ADAM9, and APLP2 were highly expressed in pancreatic patients, and survival analysis further revealed that high expression levels of ADAM9, ANXA2, and LAMC2 were associated with poorer survival outcomes [304].

The integration of artificial intelligence into biosensors has brought important breakthroughs with machine learning algorithms fulfilling a crucial role in the handling and interpretation of complex data produced

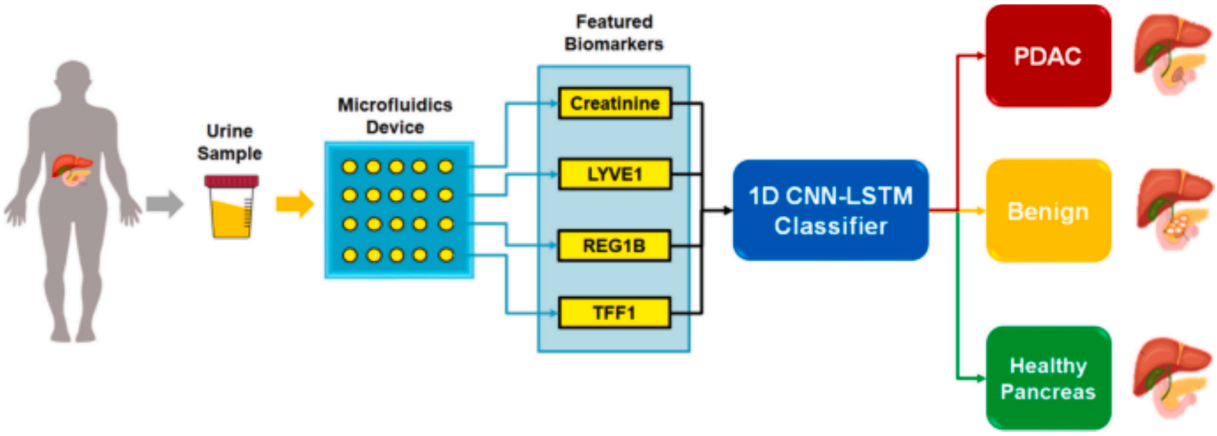


Fig. 13. AI-powered urine biomarker-based classification system for pancreatic cancer diagnosis, 'Reprinted with the permission from [303] Licensed under CC BY 4.0'.

by advanced biosensor platforms [280]. Such computational approaches are intended to facilitate more accurate and earlier detection of pancreatic cancer by enabling the extraction of meaningful patterns from a large number of molecular signatures [12]. The focus on these technologies in recent years has become groundbreaking not only for pancreatic cancer but also for all cancer testing and treatments.

Multi-omics biosensors generate vast amounts of data across genomic (ctDNA), transcriptomic (miRNA), proteomic (circulating proteins), and metabolomic (lipidomic and glycomic) levels [39]. Traditional biosensors struggle to process and correlate these multi-dimensional datasets in real-time. AI addresses this challenge by employing advanced computational models that learn from complex, high-throughput biosensing outputs (Table 4) [39,280]. Convolutional neural networks (CNNs) have been used for image-based biosensor analysis, such as microfluidic chip readouts and optical biosensors, enabling feature extraction with high accuracy in pattern recognition [305]. Recurrent neural networks (RNNs) and long short-term memory (LSTM) models are particularly effective for time-series biomarker monitoring, as they can capture sequential variations in circulating tumor biomarkers over time [306–308]. Support vector machines (SVMs) have demonstrated strong performance in classifying biosensor-generated electrochemical signals, while random forest and decision tree algorithms aid in feature selection for multi-omics biomarker panels [309,309]. More advanced techniques, such as autoencoders and variational autoencoders, are being explored to reduce noise and detect anomalies in biosensor outputs, enhancing signal clarity and enabling the detection of cancer at earlier stages [309–311].

Table 4
AI models and their applications in multi-omics biosensor-based pancreatic cancer diagnosis [280,312].

AI model	Application in Biosensor Based-Pancreatic Cancer Diagnosis	Key Benefits
Convolutional Neural Networks (CNNs)	Image-based biosensor analysis (*e.g.,* microfluidic chip readouts, optical biosensors)	Feature extraction, high accuracy in pattern recognition
Recurrent Neural Networks (RNNs) & Long Short-Term Memory (LSTM)	Time-series data interpretation for continuous monitoring (*e.g.,* real-time exosomal biomarker analysis)	Handles sequential biomarker variations over time
Support Vector Machines (SVMs)	Classification of biosensor-generated electrochemical signals	High specificity, effective for small datasets
Random Forest (RF) & Decision Trees	Feature selection for multi-omics biomarker panels	Identifies most relevant features, reduces computational burden
Autoencoders (AE) & Variational Autoencoders (VAE)	Noise reduction and anomaly detection in multi-omics data from biosensors	Improves signal clarity, aids in early cancer detection

The on-going evolution of machine learning algorithms and their integration into biosensor platforms has resulted in dramatic enhancements in early detection methods and a decline in false positives [313]. Such intelligent systems may process and analyze simultaneously a number of biomarker signatures, leading to more extensive and precise diagnostic assessments [313]. Furthermore, the unique ability to identify complex patterns in molecular data aims to open new ways to develop more effective therapeutic strategies, especially for pancreatic cancer treatment, by understanding disease mechanisms. In addition, in recent years, AI-supported biosensors have been further developed with machine learning algorithms, especially as wearable devices.

For this purpose of integrating AI into biosensors, Genco *et al.,* (2023) conducted a study that will shed light on this field [253]. In this study, 47 patients were monitored and with the help of portable bioelectronic detection, which can be used at the point of care, can analyze both nucleic acids and proteins at the single molecule level. By coupling state-of-the-art cytopathological molecular analyses and synchronous analyses of pancreatic cancer precursors, the diagnostic precision of malignant transformation-associated proteins has been enhanced. The bioelectronic sequence demonstrated a sensitivity of up to 80 % and had a very low false positive and false negative rate. Pancreatic cancer leads were classified by a machine learning analysis which revealed a diagnostic sensitivity of at a minimum of 96 % and a diagnostic specificity of 100 % [253]. In. In this process, a few details covering the detection step are given in Fig. 14.

Despite these advances, AI-integrated biosensors face several computational and clinical challenges [314]. Multi-omics biosensors generate diverse data formats, including electrochemical, optical, and molecular sequencing outputs, making cross-modality integration complex [315]. Standardized preprocessing pipelines are required to ensure reproducibility across different biosensor platforms. Another major limitation is the availability of sufficiently large and labeled datasets for training AI models, as multi-omics biosensor datasets are often small and proprietary [316,317]. Techniques such as transfer learning and synthetic data augmentation, including generative adversarial networks, can enhance model performance in data-limited scenarios [318,319]. AI models also risk overfitting when trained on small or biased datasets, which may result in false positives or misinterpretation of normal biomarker variations as pathological changes[270,271]. To address this, regularization techniques, feature selection algorithms such as SHAP and LIME, and external validation using independent datasets are critical for improving model robustness [320,321].

Deploying AI models in portable biosensors for real-time clinical use

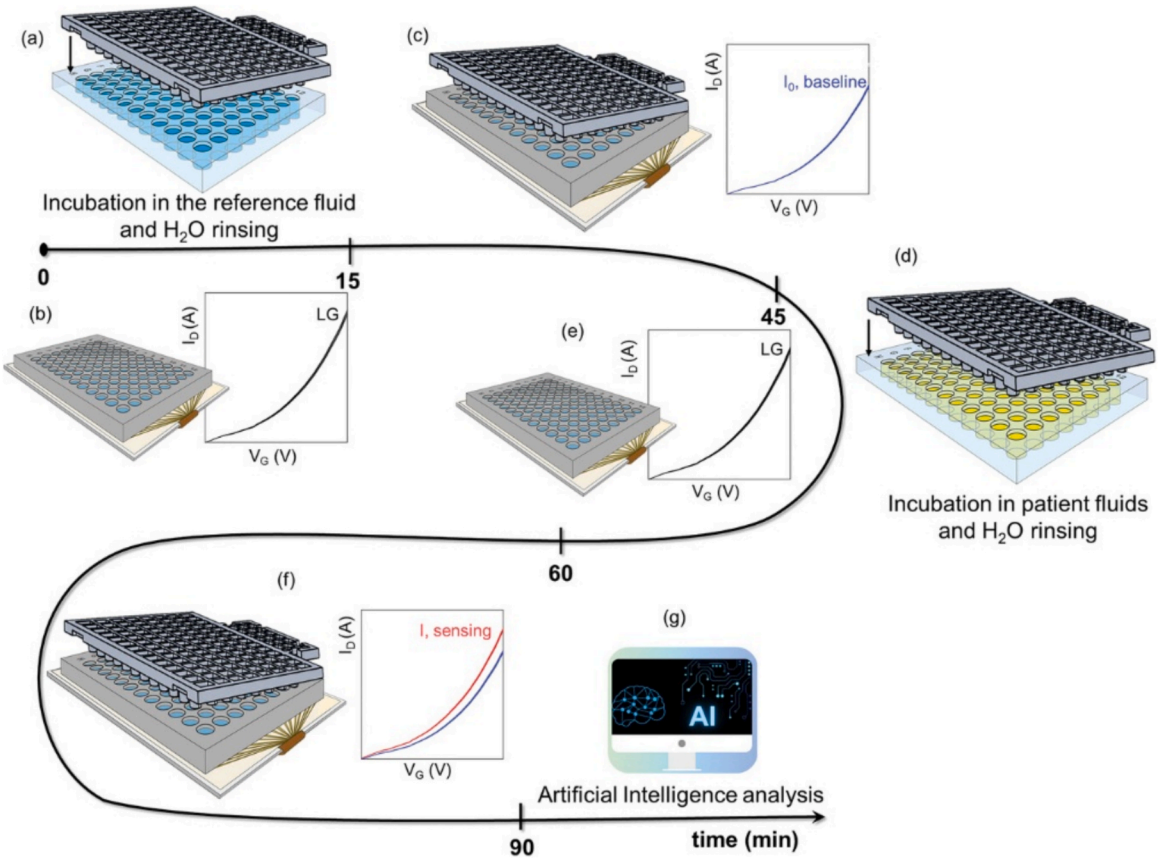


Fig. 14. Stages of the multiplexing detection procedure, 'Reprinted with the permission from [253] Licensed under CC BY 4.0'.

presents additional challenges related to hardware constraints [280,322]. Processing multi-omics biosensor data in real-time requires computational efficiency, yet many AI models are computationally intensive [280,323]. Edge AI solutions, incorporating low-power neural network accelerators such as Google Coral or NVIDIA Jetson Nano [324], have been proposed to enable on-device deep learning inference for biosensors without reliance on cloud computing. These advancements could facilitate the real-time deployment of AI-driven biosensors in clinical and point-of-care settings, making early pancreatic cancer screening more accessible and efficient [325].

The integration of AI with biosensor technologies is expected to evolve further with the development of multi-omics AI frameworks that combine electrochemical, optical, and sequencing-based biosensor outputs for higher diagnostic accuracy. Federated learning models, which enable AI training across multiple institutions without centralized data sharing, have been proposed to enhance privacy and security while improving the robustness of AI-powered diagnostic platforms [41,280]. In the future, AI-enhanced biosensors could also be tailored for personalized pancreatic cancer risk monitoring, particularly in high-risk populations such as individuals with BRCA2 mutations or chronic pancreatitis [41].

AI-powered biosensors have the potential to transform pancreatic cancer diagnostics by enabling early, non-invasive, and highly sensitive detection of tumor biomarkers [280]. However, their full clinical adoption depends on overcoming challenges related to data standardization, model training, and real-world validation. Future efforts should focus on integrating AI-driven biosensing platforms into routine cancer screening workflows, leveraging advances in deep learning, edge AI, and multi-omics data fusion to develop the next generation of precision oncology diagnostics [39,41]. In conclusion, the use of electrochemical, optical, microfluidic, microfluidic, nanomaterial-enhanced and artificial intelligence-integrated biosensors to measure the response of pancreatic cancers to biomarkers is described in detail. Table 5 shows the summarized performances of the most novel biosensors used for the detection of pancreatic cancer biomarkers.

4. Clinical applications and translational challenges

The integration of multi-omics biosensors into pancreatic cancer diagnostics represents a transformative advancement in precision medicine. By detecting circulating tumor DNA, exosomal RNA, metabolic markers, and proteomic signatures, these biosensors provide a non-invasive, highly sensitive, and real-time approach to identifying pancreatic cancer at earlier stages [207,358,359]. Multi-omics strategies, which incorporate genomics, transcriptomics, proteomics, metabolomics, glycomics, and metagenomics, enable a comprehensive analysis of tumor biology, offering valuable insights into biomarker discovery, drug target identification, and phenotype prediction [360,361]. AI-driven machine learning and statistical modeling further enhance the interpretation of these complex datasets, improving diagnostic accuracy and personalized treatment decisions (Fig. 15) [49]. However, the successful clinical implementation of these biosensors requires overcoming key challenges, including analytical validation, regulatory approvals, and cost-effective integration into healthcare systems. Fig. 15 illustrates the role of multi-omics approaches in pancreatic cancer diagnosis and personalized medicine [49,362]. Biological samples, including saliva, blood (serum/plasma), urine, stool, and pancreatic tissue, serve as sources for biomarker detection [362]. Various omics layers such as genomics, transcriptomics, proteomics, metabolomics, glycomics, and metagenomics are analyzed using machine learning, network biology, and statistical models to uncover disease-associated molecular signatures [363,364]. These multi-omics approaches facilitate biomarker discovery, phenotype prediction, and drug target identification, ultimately contributing to personalized

Table 5
Biosensor technologies developed for multi-omic pancreatic cancer detection [23,28].

Detection method	Biomarker	Sample	Detection Limit	Ref.
Electrochemical Biosensor	CA 199	Serum	–	[326]
Electrochemical Biosensor	CA19-9	Serum	0.0005 $U.mL^{-1}$	[327]
Electrochemical Biosensor	CA199, CA125, and CA242	Serum	0.02 $ng.mL^{-1}$, 0.4 $U.mL^{-1}$, 0.3 $U.mL^{-1}$ and 0.4 $U.mL^{-1}$	[328]
Electrochemical Biosensor	Glypican-1	Serum	5000 $pg.mL^{-1}$	[328]
Electrochemical Biosensor	miR-196a	Plasma	15 aM	[329]
Electrochemical Biosensor	Wnt7B gene	Cell	1.6 fM	[330]
Electrochemical Biosensor	CA19-9	Buffer	0.04 $U.mL^{-1}$	[331]
Electrochemical Biosensor	CA 19–9	Buffer	37 $U.mL^{-1}$	[332]
Electrochemical Biosensor	CEA	Pancreatic cyst	0.5 $ng.mL^{-1}$	[333]
Electrochemical Biosensor	CEA	Cell and tissue	0.5 $pg.mL^{-1}$	[334]
Electrochemical Biosensor	K-RAS^{mut}	Buffer	20.4 fM	[335]
Electrochemical Biosensor	miR-21	Saliva	1 pM	[336]
Optical Biosensor	Arginase, protease	Serum	$1x10^{-16}$ $mol.L^{-1}$	[337]
Optical Biosensor	Circulating tumor cells	Blood	1000 $cells.mL^{-1}$	[338]
Optical Biosensor	miR-21, miR-10b	Plasma	$5x10^{-14}$ $mol.L^{-1}$ (50 fM)	[271]
Optical Biosensor	miR-10b	Exosome	10^{-18} $mol.L^{-1}$	[339]
Optical Biosensor	CA 19–9	Serum	$7.7x10^{-7}$ $U.mL^{-1}$	[270]
Optical Biosensor	MUC4	Serum	1 $ng.mL^{-1}$	[340]
Optical Biosensor	Histone-and-DNA complex	Serum	1/1000 of serum	[341]
Optical Biosensor	CA19-9, MMP7, and MUC4	Sera	2 $ng.mL^{-1}$	[342]
Optical Biosensor	miRNA	Plasma	$1x10^{-18}$ $mol.L^{-1}$	[272]
Optical Biosensor	Exosome	Serum	–	[343]
Optical Biosensor	miR-21	Serum	$3.2x10^{-9}$ $mol.L^{-1}$	[344]
Optical Biosensor	CEA	Serum	160 $pg.mL^{-1}$	[345]
Optical Biosensor	Pancreatic polypeptide	Serum	$5.21x10^{-10}$ $mol.L^{-1}$	[346]
Optical Biosensor	CA 19–9	Plasma	5 $U.mL^{-1}$	[347]
Optical Biosensor	miR-215	Cell lysate	$6x10^{-11}$ $mol.L^{-1}$	[348]
Optical Biosensor	miR-21, −155 and −210	Serum	0.007 nM, 0.068 nM, and 0.017 nM	[349]
Microfluidic Biosensor	Exosome	Plasma	NM	[350]
Microfluidic Biosensor	GPC1 + exosome	Plasma	NM	[284]
Microfluidic Biosensor	Ligand	Plasma	NM	[351]
Nanomaterial-Enhanced Biosensor	CA 19–9	Cell lysates	0.12 $U.mL^{-1}$	[352]
Nanomaterial-Enhanced Biosensor	CA 19–9	Serum	0.35 $U.mL^{-1}$	[353]
Nanomaterial-Enhanced Biosensor	CA 19–9	Serum	1.84 $U.mL^{-1}$ and 1.57 $U.mL^{-1}$	[296]
Nanomaterial-Enhanced Biosensor	Tumor-derived extracellular vesicles	Plasma	0.23 $ng.mL^{-1}$	[354]
Nanomaterial-Enhanced Biosensor	MUC1	Cells	21 cells $m.L^{-1}$, 27 cells $m.L^{-1}$, and 41 cells $m.L^{-1}$	[355]
Nanomaterial-Enhanced Biosensor	K-RAS^{mut}	Buffer	NM	[356]
Nanomaterial-Enhanced Biosensor	Exosomes	Cells	400 particles $m.L^{-1}$	[357]
AI-Integrated Biosensor	creatinine, LYVE1, REG1B, and TFF1	Urine	–	[303]
AI-Integrated Biosensor	–	–	–	[253]

*CA199; carbohydrate antigen 199, *CEA; carcinoembryonic antigen, * MUC4; protein, * MMP7; protein, * MUC1; protein

treatment strategies for pancreatic cancer patients [49].

The clinical translation of biosensor-based diagnostics demands a structured and interdisciplinary approach, as the complexity of multi-omics analysis introduces challenges not commonly encountered in traditional cancer diagnostics [280,322]. While single-marker blood tests or imaging techniques follow well-established clinical workflows, multi-omics biosensors require a comprehensive framework for integrating vast molecular data into actionable clinical insights [39,314]. This necessitates collaborations among material scientists, bioengineers, oncologists, and regulatory agencies, as well as the development of standardized methodologies to ensure consistency across different platforms [365]. Current regulatory frameworks, such as the FDA's Software as a Medical Device (SaMD) initiative and emerging EU AI Act provisions, do not yet fully account for the dynamic nature of multi-omics biosensors, especially those incorporating real-time learning AI models or multiplexed biomarker panels [365].

Clinical validation of multi-omics biosensors presents a unique challenge, as performance must be tested across diverse patient cohorts with varying molecular profiles. Traditional trial endpoints may not sufficiently capture the diagnostic utility of multiplexed outputs, calling for novel trial designs that emphasize real-time predictive value, longitudinal monitoring, and integration with clinical decision-making systems. Furthermore, the transition from experimental models to clinical-grade devices requires addressing real-world challenges such as patient variability, biomarker heterogeneity, and device scalability [366,367]. Unlike conventional biomarker assays that rely on a single molecular target, biosensor-based systems incorporate multiple biological pathways, increasing the likelihood of detecting subtle disease signatures. However, this multi-targeted approach also introduces complexity in data interpretation and clinical decision-making, necessitating AI-driven models and big data analytics to optimize diagnostic accuracy [322,368].

While biosensor technology offers a paradigm shift in cancer detection, the absence of standardized regulatory pathways, the need for rigorous clinical validation, and the challenges of healthcare integration remain major obstacles. This section examines these hurdles in detail, highlighting the current status of biosensors in pancreatic cancer diagnostics, the limitations of existing approaches, and the necessary advancements required for their successful clinical implementation. Addressing these issues will be crucial in ensuring that biosensor-based diagnostics evolve from promising research tools into reliable, accessible, and clinically endorsed solutions for pancreatic cancer management.

4.1. Current state of liquid Biopsy-Based biosensors in pancreatic cancer

Current approaches such as imaging techniques, serum biomarker tests, and tissue biopsies play an essential role in the pancreatic cancer diagnosis and monitoring of the disease [3,13,16]. However, each of these methods has significant drawbacks, particularly in detecting

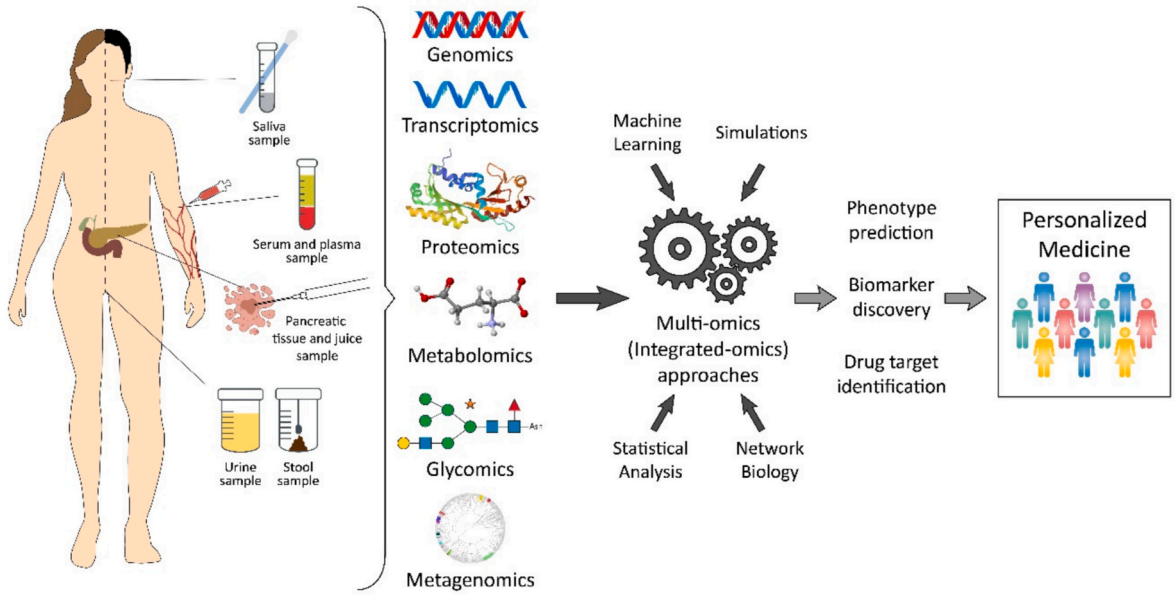


Fig. 15. Multi-omics approaches for biomarker discovery and personalized medicine in pancreatic cancer, 'Reprinted with the permission from [49] Licensed under CC BY 4.0.'.

tumors before they reach an advanced stage [3]. Imaging techniques, including CT, MRI, and EUS, are widely used for pancreatic cancer detection [369]. However, these methods primarily rely on the identification of structural abnormalities within the pancreas, meaning that they are often unable to detect tumors in their earliest stages [3]. By the time a pancreatic tumor is visible on imaging, it has often already reached a size that makes curative treatment difficult.

Serum biomarker tests, particularly CA 19–9, are commonly used in pancreatic cancer diagnosis and disease monitoring. Although CA 19–9 levels are often elevated in pancreatic cancer patients, this biomarker lacks the necessary specificity to be used as a standalone diagnostic tool. Elevated levels of CA 19–9 can also be observed in other conditions, including benign pancreatic diseases and certain gastrointestinal cancers [370,371]. Furthermore, not all pancreatic cancer patients exhibit increased CA 19–9 levels, particularly in the early stages of the disease [371,372]. This variability limits the utility of serum biomarkers in early detection efforts.

Tissue biopsy remains the gold standard for definitive diagnosis, providing crucial histopathological and molecular information about the tumor [373]. However, obtaining pancreatic tissue samples is a highly invasive procedure that may not be feasible for all patients, particularly those with inoperable tumors [373–375]. The deep anatomical location of the pancreas and its proximity to major blood vessels make biopsy procedures technically challenging and increase the risk of complications [376]. Additionally, tissue biopsies only provide a snapshot of the tumor at a single time point, limiting their usefulness in monitoring disease progression or treatment response [376,377].

Given the limitations of these conventional methods, liquid biopsy-based biosensors have emerged as a promising alternative for the detection and monitoring of pancreatic cancer [378]. These biosensors enable the analysis of tumor-derived biomarkers in biological fluids such as blood, urine, and saliva, offering a non-invasive and potentially more sensitive approach to disease detection [379]. By leveraging various detection mechanisms, including electrochemical, optical, and microfluidic technologies, biosensors can identify key cancer-related molecules, such as circulating tumor DNA (ctDNA), CTCs, exosomal RNA, and metabolic markers [273,380]. The ability to detect multiple biomarkers simultaneously allows for a more comprehensive assessment of tumor biology, improving the chances of identifying pancreatic cancer at an earlier and more treatable stage [273].

Biosensor-based liquid biopsy platforms offer several advantages over conventional diagnostic approaches. Their non-invasive nature makes them more patient-friendly, reducing the need for invasive procedures like tissue biopsies [381]. Additionally, biosensors provide rapid results, allowing for real-time monitoring of biomarker fluctuations, which can be particularly useful in tracking disease progression or assessing treatment response [217]. The potential for miniaturization and portability also means that biosensors could be adapted for point-of-care testing, bringing advanced diagnostic capabilities to settings where access to specialized medical facilities is limited [280,382].

Despite these advantages, most biosensor-based liquid biopsy platforms are still in the experimental stage and have yet to be widely implemented in clinical practice [383,384]. While preclinical studies have demonstrated promising results, large-scale clinical trials evaluating the real-world effectiveness of these technologies remain limited. One of the key challenges in the clinical translation of biosensors is ensuring that they perform reliably across different patient populations and healthcare settings [217]. Variability in biomarker levels, differences in sample collection methods, and the complexity of biological fluids can all impact the accuracy and reproducibility of biosensor-based assays [385]. Ensuring that biosensors can consistently provide accurate and clinically meaningful results is essential for their widespread adoption.

Standardization is another major hurdle in the development of biosensor-based diagnostics [217]. Unlike established laboratory tests, biosensors often rely on unique materials, detection techniques, and signal processing methods, making it difficult to compare results across different platforms [228]. The lack of standardized protocols for biomarker detection and data interpretation complicates regulatory approval processes and slows the transition of biosensors from research laboratories to clinical settings [386,387]. Addressing these issues requires collaboration between researchers, clinicians, and regulatory agencies to develop clear guidelines for biosensor validation and implementation.

Another factor influencing the adoption of biosensors in pancreatic cancer diagnostics is their scalability and cost-effectiveness. While these devices have the potential to reduce diagnostic costs in the long run, the initial investment required for research, development, and manufacturing remains high [388]. Advanced biosensor platforms often incorporate nanomaterials, microfluidic chips, or artificial intelligence-

based data analysis, all of which add to the overall cost of production [388,389]. The cost of integrating multi-omics biosensors into routine diagnostics is compounded by the need for specialized equipment, high-throughput molecular assays, and advanced data storage and computational infrastructure. Without scalable production models and centralized analytic platforms, these systems remain inaccessible to many healthcare settings, particularly in resource-limited environments [388]. For biosensors to become viable alternatives to existing diagnostic tools, efforts must be made to optimize manufacturing processes and develop cost-efficient production techniques without compromising sensitivity and specificity.

In addition to technical and economic considerations, the successful integration of biosensor-based diagnostics into clinical workflows will require healthcare infrastructure adjustments [388]. The widespread use of biosensors will necessitate training for healthcare providers on how to interpret biosensor-generated data and integrate it into decision-making processes [386,390]. Furthermore, regulatory frameworks must evolve to accommodate these new technologies, ensuring that they meet rigorous safety and performance standards before they can be deployed in routine medical practice. Beyond pre-market validation, post-market surveillance and real-world data collection will be essential to assess the long-term safety, reliability, and cost-effectiveness of biosensor platforms across diverse patient populations and clinical settings.

Although biosensor technology is still in the early stages of clinical adoption, ongoing research continues to advance the field. New developments in material science, bioengineering, and computational data analysis are driving improvements in biosensor performance, increasing their sensitivity, and reducing the likelihood of false-positive or false-negative results. Machine learning algorithms and artificial intelligence are also being integrated into biosensor platforms to enhance the accuracy of biomarker analysis, enabling more precise diagnostic predictions [322].

While challenges remain, the potential impact of biosensor-based liquid biopsy platforms on pancreatic cancer detection and management is significant. These technologies offer a path toward earlier diagnosis, improved patient outcomes, and more personalized treatment approaches. With continued advancements in biosensor technology and increased collaboration between the scientific and medical communities, the clinical implementation of these innovative diagnostic tools may soon become a reality, transforming the landscape of pancreatic cancer care.

4.2. Overcoming challenges in clinical translation

Biosensors hold great promises for improving pancreatic cancer diagnosis, but their transition from research laboratories to clinical practice remains a complex process. One of the biggest challenges is the lack of standardized validation protocols. Unlike well-established diagnostic tests such as PCR and ELISA, biosensors often rely on novel detection mechanisms that require extensive refinement before they can be widely adopted [26,389,390]. The absence of universal analytical standards makes it difficult to compare the performance of different biosensor platforms. This inconsistency poses a major barrier to regulatory approval and clinical implementation, as medical devices must demonstrate reproducibility and reliability across multiple testing environments [391]. Moreover, clinical trials designed to evaluate multi-omics biosensors must account for their multiplexed outputs, diverse biomarker profiles, and real-world variability, which may require novel validation endpoints and longitudinal monitoring strategies. To address these issues, researchers, clinicians, and regulatory agencies must work together to develop standardized guidelines for biosensor fabrication, biomarker detection, and data analysis, ensuring that results are both accurate and comparable across different laboratories and clinical settings.

Another challenge in bringing biosensors to clinical practice is ensuring their sensitivity and specificity in real-world biological samples [392,393]. Many biosensors have demonstrated excellent analytical performance under controlled laboratory conditions, where they successfully detect target molecules at very low concentrations. However, when tested in complex biological fluids such as blood, saliva, or urine, biosensor performance may be compromised due to interfering substances, sample matrix effects, and cross-reactivity with non-target molecules [394]. These factors can lead to false-positive or false-negative results, which reduce the reliability of biosensor-based diagnostics [394]. Overcoming these issues requires improvements in sensor design, surface chemistry, and signal amplification strategies. The use of advanced nanomaterials, biofunctionalized detection surfaces, and machine learning-based data filtering methods can enhance biosensor accuracy by reducing non-specific interactions and improving biomarker recognition in patient samples [395].

The high cost of biosensor development and production is another significant obstacle to widespread clinical adoption. While biosensors have the potential to be more cost-effective than traditional diagnostic methods, their initial development requires expensive materials, specialized equipment, and advanced fabrication techniques [393]. The integration of nanotechnology, microfluidics, and AI into biosensor platforms further increases production costs, making large-scale manufacturing a challenge [119,396,397]. To facilitate wider adoption, researchers and industry stakeholders must work on optimizing cost-effective biosensor production methods, such as scalable printing technologies, low-cost biomaterials, and simplified fabrication techniques [398]. The development of paper-based biosensors or disposable microfluidic chips may offer an affordable alternative while maintaining high sensitivity and specificity [399,400].

The successful integration of biosensors into healthcare systems also depends on their compatibility with existing medical infrastructures. AI-powered biosensors generate large volumes of complex molecular data, requiring advanced computational tools for interpretation and clinical decision-making. However, many healthcare institutions still rely on traditional diagnostic workflows that do not support real-time biosensor data processing [401,402]. Ensuring that biosensor-based diagnostics can be seamlessly integrated into electronic health records (EHRs) and hospital information systems is critical for enabling their routine clinical use [217,322]. Additionally, strong cybersecurity measures and data privacy regulations must be in place to protect patient information and ensure compliance with ethical guidelines [403]. Addressing these concerns will require collaboration between medical professionals, bioinformatics experts, and regulatory authorities to develop frameworks that facilitate the responsible use of AI-driven biosensor technologies. Regulatory frameworks such as the FDA's Software as a Medical Device (SaMD) guidance and the EU's In Vitro Diagnostic Regulation (IVDR) offer emerging models but are still evolving to accommodate dynamic, AI-enabled multi-analyte biosensing systems.

While these challenges are significant, they are not insurmountable. With ongoing technological advancements, increased interdisciplinary collaboration, and regulatory progress, biosensors have the potential to transform pancreatic cancer diagnostics by enabling early detection, real-time disease monitoring, and more personalized treatment strategies. Overcoming these barriers will require sustained efforts in standardization, cost reduction, data security, and healthcare system integration, ultimately paving the way for biosensors to become a routine part of clinical cancer diagnostics.

4.3. Regulatory, Ethical, and technical challenges in clinical translation

Bringing biosensor-based diagnostics into clinical use requires navigating complex regulatory frameworks and addressing ethical concerns related to their implementation [404]. Unlike traditional diagnostic tools, biosensors combine nanotechnology, biological recognition elements, and AI-driven analytics, which makes their regulatory approval process more complicated [280]. Global health authorities, such as the U.S. Food and Drug Administration (FDA) and the

European Medicines Agency (EMA), enforce strict validation protocols to ensure that any new diagnostic technology is safe, effective, and reliable [405,406]. These agencies require extensive preclinical and clinical data demonstrating that biosensors consistently produce accurate results before they can be approved for use in real-world medical settings.

One of the primary regulatory challenges in biosensor approval is ensuring reproducibility across different laboratories and patient populations [407,408]. Biosensor-based diagnostics often vary in terms of fabrication methods, biomarker detection techniques, and data analysis algorithms, leading to differences in diagnostic accuracy. A biosensor that performs well in one laboratory setting may produce inconsistent results in another due to variations in sample handling, environmental factors, and manufacturing processes [409]. Regulatory agencies require multi-center clinical trials to confirm that biosensors deliver high sensitivity and specificity across diverse populations [410]. These trials must also account for differences in disease progression, genetic variability, and potential confounding factors that could impact test outcomes [411,412]. Establishing universal performance benchmarks and standardized protocols is critical for ensuring that biosensor-based diagnostics meet the same reliability standards as existing clinical tests [392,411].

Beyond regulatory approval, ethical considerations play a significant role in the adoption of AI-powered biosensors [119,280]. Machine learning algorithms integrated into biosensor platforms are designed to analyze complex biological data and aid in disease classification [413]. However, these AI-driven models rely heavily on training datasets, and if these datasets are incomplete or biased, the algorithms may produce skewed results. This could lead to misdiagnosis or disparities in healthcare outcomes, disproportionately affecting certain patient groups [414]. To prevent such issues, it is necessary to train AI models on diverse datasets, ensuring that biosensors are equally effective across different demographics. Additionally, AI-based biosensors must be designed with transparent decision-making processes, allowing clinicians to understand how diagnostic recommendations are generated and reducing the risk of errors caused by algorithmic bias.

Another ethical concern is data security and patient privacy. Biosensor-based liquid biopsy platforms generate large volumes of sensitive health data, which must be protected against unauthorized access and cyber threats [415]. Strict cybersecurity measures should be implemented to prevent data breaches and ensure that patient information remains confidential [416]. Compliance with international regulations such as the Health Insurance Portability and Accountability Act (HIPAA) in the U.S. and the General Data Protection Regulation (GDPR) in Europe is essential for maintaining public trust in biosensor technology [417]. These regulations require that patient data be securely stored, anonymized where possible, and accessed only by authorized personnel.

To complement these regulatory and ethical considerations, several technical challenges must be addressed to enable real-world deployment of AI-integrated biosensors. One major challenge is scalability, as biosensors that perform optimally in controlled laboratory environments may underperform in clinical workflows due to variability in sample quality, instrumentation, or user handling. Interoperability also remains a critical concern, as biosensor platforms must be compatible with existing electronic health record (EHR) systems and laboratory information infrastructures to ensure seamless integration. Additionally, the explainability of AI models is vital for clinical acceptance; black-box predictions without interpretability can erode trust among healthcare providers. Finally, continuous post-deployment validation is necessary to monitor biosensor performance and update AI models in response to evolving clinical data and population trends. Overcoming these challenges requires interdisciplinary collaboration among engineers, data scientists, and healthcare practitioners to ensure biosensors are robust, transparent, and clinically adaptable.

For biosensors to be widely accepted and successfully integrated into clinical practice, regulatory bodies, researchers, and healthcare professionals must work together to develop clear guidelines for validation, standardization, and ethical implementation. Addressing regulatory, ethical, and technical challenges early in the development process will help accelerate biosensor adoption, ensuring that these promising technologies can be safely and effectively used for pancreatic cancer diagnostics.

5. Future perspectives and emerging trends

5.1. Next-Generation Multi-Omics biosensors for pancreatic cancer

Research is increasingly focusing on developing highly sensitive, real-time diagnostic platforms that can provide continuous monitoring of molecular changes associated with early-stage pancreatic cancer [389,417]. Wearable and implantable biosensors, which are currently in experimental stages, are expected to become crucial tools for monitoring high-risk individuals by detecting circulating biomarkers in real-time. These devices will enable the early identification of disease onset and progression, providing physicians with actionable data before symptoms appear [418,419].

Point-of-care biosensors, particularly those using lab-on-a-chip and microfluidic technologies, are being refined to offer rapid, miniaturized, and automated analysis systems [420,421]. These platforms are expected to bridge the gap between laboratory-based testing and real-time clinical decision-making by enabling early cancer screening in resource-limited settings. Researchers are also developing integrated biosensor arrays that can simultaneously detect genomic, transcriptomic, proteomic, and metabolomic markers, offering a more comprehensive molecular fingerprint of pancreatic cancer [418,422]. These multiplexed platforms will reduce the reliance on single-marker tests, which often lack sensitivity and specificity in heterogeneous tumors like pancreatic cancer.

Nanomaterial-enhanced biosensors, particularly those utilizing MXenes, carbon-based materials, metal nanoparticles, and quantum dots, continue to improve detection sensitivity and selectivity. These nanomaterials provide high surface-area interactions with biomarkers, allowing for ultra-sensitive detection at low concentrations [423,424]. Additionally, plasmonic biosensors based on surface plasmon resonance and surface-enhanced Raman scattering are expected to play a significant role in pancreatic cancer diagnostics due to their ability to enable label-free, real-time biomarker quantification with high specificity [425–427].

Looking ahead, the integration of artificial intelligence, nanotechnology, and biosensor engineering is expected to play a pivotal role in shaping the next generation of personalized diagnostic tools. AI algorithms trained on multi-omics datasets can guide the design of highly specific nanomaterials with optimized surface chemistries for selective biomarker recognition. Concurrently, advancements in nanofabrication such as laser-induced forward transfer (LIFT), 3D printing, and self-assembling nano-architectures will enable the development of modular, scalable biosensor platforms that adapt to patient-specific diagnostic needs. Combining these innovations with real-time data processing and cloud-based analytics may lead to fully integrated, AI-assisted biosensing systems capable of continuous health monitoring, early pancreatic cancer detection, and individualized treatment planning at the point of care.

5.2. The role of AI and big data in liquid Biopsy-Based diagnostics

Artificial intelligence and big data analytics are expected to drive significant advancements in the field of liquid biopsy-based biosensors. AI-powered biosensor platforms will enable the analysis of large-scale, multi-omics datasets, improving the accuracy and predictive power of pancreatic cancer diagnostics [119]. Machine learning algorithms will allow for the identification of complex biomarker signatures that may be

undetectable through traditional statistical methods, enhancing the early detection and risk stratification of pancreatic cancer patients [119,280].

Deep learning-assisted biosensors will refine diagnostic accuracy by filtering out background noise and distinguishing cancer-specific signals from non-malignant biological variations [413]. These models will significantly enhance the sensitivity of biosensors used for detecting rare tumor-derived components, such as circulating tumor DNA and exosomal biomarkers, which are often present in extremely low concentrations in bodily fluids. Furthermore, federated learning and cloud-based AI frameworks are expected to facilitate global collaboration in biomarker discovery, enabling the aggregation and analysis of multi-institutional datasets for more robust diagnostic models.

Beyond improving detection, AI integration will play a vital role in risk prediction and patient stratification. By combining biosensor-generated molecular data with patient clinical profiles, machine learning models will be able to predict tumor progression, assess treatment responses, and guide personalized therapy recommendations [428,429]. The future of pancreatic cancer management may involve AI-driven biosensors that continuously monitor biomarker fluctuations in high-risk individuals, providing real-time alerts for early intervention.

AI-powered biosensors will also improve accessibility to cancer diagnostics through the development of portable, smartphone-integrated devices [430,431]. These smart biosensor systems will allow patients to perform self-monitoring at home, reducing the need for frequent hospital visits. Such advancements could revolutionize screening strategies, particularly for individuals with genetic predisposition or metabolic conditions associated with pancreatic cancer risk.

5.3. Ai-driven personalized medicine and risk prediction for early pancreatic cancer screening

5.3.1. Ai-driven risk stratification for High-Risk populations

Pancreatic cancer has a well-established set of genetic and lifestyle-related risk factors, including germline mutations (*e.g.,* BRCA1/2, ATM, PALB2), chronic pancreatitis, diabetes mellitus, obesity, and tobacco [37]. Despite these known risk factors, current screening strategies are largely inadequate for identifying individuals at the highest risk of developing pancreatic cancer. AI-driven risk prediction models have the potential to analyze large-scale clinical, genetic, and biosensor-based biomarker data to provide individualized risk assessments.

Recent studies have demonstrated the effectiveness of deep learning models trained on multi-omics data for cancer risk prediction [432,433]. Machine learning algorithms such as random forests, support vector machines, and deep neural networks (DNNs) can be applied to identify individuals with a high probability of harboring early-stage pancreatic tumors based on liquid biopsy-derived biomarker profiles. AI-enhanced biosensors, which integrate ctDNA, exosomal miRNA signatures, and metabolic biomarkers, can improve the precision of risk assessment models [434].

5.3.2. Ai-powered Multi-Omics biomarker panels for personalized screening

Traditional biomarker-based screening approaches have been limited by low specificity and high false-positive rates, particularly in pancreatic cancer, where CA 19–9 lacks sufficient reliability for early detection [435,436]. AI-powered multi-omics biosensor platforms offer a novel solution by integrating multiple biomarker classes including genomic, transcriptomic, proteomic, and metabolomic data into a single predictive framework [361].

AI algorithms can process complex biosensor-generated datasets to distinguish between benign conditions (*e.g.,* pancreatitis) and malignant pancreatic tumors [437]. By applying feature selection algorithms such as SHAP and LASSO regression, AI models can identify the most relevant biomarkers for pancreatic cancer risk prediction, minimizing unnecessary testing and improving diagnostic efficiency [438].

One promising approach in AI-driven personalized screening is the development of multi-biomarker risk panels that integrate diverse molecular signatures to enhance pancreatic cancer detection [187,439]. These panels incorporate circulating tumor DNA (ctDNA) mutations, including KRAS, TP53, CDKN2A, and SMAD4, which are frequently associated with pancreatic tumorigenesis. In addition to genetic alterations, exosomal microRNA signatures such as miR-21, miR-155, and miR-196a provide valuable insights into tumor-derived RNA expression patterns that contribute to cancer progression [440]. Beyond nucleic acid-based markers, glycoprotein biomarkers, including MUC1, MUC5AC, and CEA, serve as potential indicators of malignant transformation, offering an alternative to the widely used but limited CA 19–9 test [441]. Furthermore, metabolomic profiling has revealed distinct lipid-based signatures indicative of altered tumor metabolism, which can serve as an additional layer of diagnostic precision. By integrating these diverse biomarker classes, AI-powered risk panels can generate highly accurate, multi-dimensional assessments of pancreatic cancer risk, significantly improving early detection and personalized surveillance strategies [439].

When integrated into machine learning-based classification systems, these biosensor-derived biomarkers have shown higher accuracy in distinguishing early-stage pancreatic cancer from healthy and benign pancreatic disease states. AI models can analyze temporal changes in biomarker expression, improving the reliability of longitudinal cancer screening programs for high-risk patients.

5.3.3. Ai-guided surveillance strategies for early detection

For individuals at high risk of developing pancreatic cancer, AI-assisted screening strategies can provide personalized surveillance plans based on real-time biosensor readings and predictive modeling [280]. AI can analyze longitudinal biomarker trends to determine the optimal timing for follow-up testing and imaging, reducing unnecessary procedures while ensuring timely detection of malignant transformations.

An AI-guided surveillance framework for pancreatic cancer screening involves a multi-step process that begins with an initial risk assessment using AI-powered biosensor screening, which integrates genetic data and multi-omics liquid biopsy profiles to establish an individualized baseline [280]. Following this assessment, continuous monitoring is conducted through non-invasive biosensors that track fluctuations in key biomarkers over time, allowing for real-time detection of molecular changes associated with early tumor development [187]. When significant deviations in biomarker levels occur, automated alerts generated by AI models notify clinicians, prompting further diagnostic evaluations to confirm malignancy or assess disease progression [442]. This dynamic, data-driven approach enables early intervention, minimizes unnecessary invasive procedures, and enhances the efficiency of pancreatic cancer surveillance in high-risk individuals. These AI-driven surveillance strategies could significantly reduce the time to diagnosis for pancreatic cancer, which is often detected at an advanced stage due to the absence of symptoms in early disease progression.

5.3.4. Clinical case studies demonstrating translational applications

The real-world translation of AI-integrated biosensor technologies is advancing rapidly, with several studies demonstrating successful implementation in clinical or near-clinical environments for pancreatic cancer diagnostics.

The study conducted by Lee *et al.,* (2025) presents artificial intelligence–based diagnostic models developed through microbiome profiling of microbial EVs derived from blood samples for the early detection of PC [443]. The investigation utilized EV data extracted from serum samples of 38 patients with pancreatic cancer and 51 healthy controls. Microbial biomarkers were identified using multivariate feature selection techniques such as Least Absolute Shrinkage and Selection Operator (LASSO) and stepwise regression, and these features were subsequently used to train various machine learning models,

including logistic regression, random forest, support vector machines, and DNNs. At the phylum level, a DNN model trained using microbial taxa such as Verrucomicrobia, Actinobacteria, and Proteobacteria achieved a test AUC of 95.9 %. At the genus level, a DNN model trained with 11 selected features—including Akkermansia, Propionibacterium, and Ruminiclostridium—demonstrated the highest performance with an AUC of 96.1 %. This study suggests that microbial signatures derived from serum EVs offer a non-invasive and systemic approach for cancer screening, potentially more applicable to clinical settings than conventional stool- or tissue-based microbiome analyses. The high AUC values reported highlight the diagnostic potential of microbiome-derived biomarkers in the early detection of PC. Nevertheless, the authors emphasize the need for further validation studies with larger patient cohorts to ensure clinical applicability and generalizability [443].

Lee *et al.,* (2020) developed a needle-compatible, miniaturized optoelectronic sensor for the real-time, in situ diagnosis of pancreatic cancer during endoscopic ultrasound-guided fine-needle aspiration procedures [444]. Recognizing the limitations of conventional cytopathological analysis, namely its subjectivity, dependency on cell quality, and delayed turnaround, the authors designed a sensor system capable of objective optical tissue characterization through dual-wavelength (460 nm and 650 nm) reflectance measurements. The sensor, engineered to fit within a 19-gauge FNA needle (850 μm inner diameter), integrates multiple sensing units and enables multisite tissue interrogation. Monte Carlo simulations confirmed that the optical penetration depth (~350–500 μm) was sufficient for epithelial and stromal tissue assessment, and that local thermal elevations remained within safe limits. In ex vivo experiments conducted on 48 tissue samples from four patients, the sensor successfully distinguished malignant, chronic inflammatory, and normal pancreatic tissues with statistically significant reflectance differences. This proof-of-concept study demonstrates the clinical feasibility of a compact, low-power optical biosensor for label-free differentiation of pancreatic lesions, laying the groundwork for future integration of such AI-compatible biosensors into routine diagnostic workflows. The modular architecture of the system also suggests potential adaptability for other solid organ cancers, including those of the liver and lung [444].

The AI-integrated thermal liquid biopsy model developed by Hermoso-Durán *et al.,* (2023) represents a robust example of the clinical applicability of this technology for the diagnosis of PDAC [445]. In this study, differential scanning calorimetry was used to obtain serum thermograms, from which high diagnostic accuracy was achieved using only three specific temperature pairs. The model demonstrated a sensitivity of 97.35 % and an AUC of 0.83 in an external clinical validation cohort consisting of 113 PDAC patients. Notably, the entire modeling process was conducted using real serum samples from patients, and the AI-assisted model outperformed the conventional biomarker CA19-9 in terms of negative predictive value. These findings underline the potential of AI-driven biosensors as reliable, interpretable, and rapid decision-support tools in clinical diagnostic workflows [445].

5.4. Moving toward Early-Stage screening in High-Risk populations

One of the most promising applications of multi-omics biosensors is their potential role in early-stage pancreatic cancer screening, particularly in high-risk populations [187]. Individuals with a family history of pancreatic cancer, genetic predispositions such as BRCA1/BRCA2 mutations, chronic pancreatitis, or new-onset diabetes represent key groups that could benefit from regular monitoring through non-invasive biosensor technology [446,447].

Advancements in urine- and saliva-based biosensors are expected to expand early screening efforts [448,449]. Unlike blood-based tests, these biosensors eliminate the need for venipuncture, making the process more patient-friendly and accessible for widespread screening programs. By enabling routine biomarker monitoring in asymptomatic individuals, these non-invasive biosensors could facilitate the early detection of pancreatic cancer at its most treatable stages, ultimately improving survival rates.

The integration of AI-driven multi-omics biosensors into screening programs will allow for the continuous refinement of risk prediction algorithms [39,314]. These systems will not only enhance the accuracy of early detection but also improve the differentiation between benign and malignant conditions, reducing false-positive rates that often lead to unnecessary medical procedures.

6. Conclusion

Pancreatic cancer continues to pose a significant global health challenge due to its late-stage diagnosis and poor survival rates. The inadequacy of traditional diagnostic methods, including imaging, CA 19–9 testing, and tissue biopsies, has fueled the demand for innovative, non-invasive, and highly sensitive detection strategies. The advent of liquid biopsy-based diagnostics has transformed the landscape of early cancer detection, offering a means to analyze tumor-derived components in bodily fluids without requiring invasive procedures. However, single-biomarker approaches often fall short in capturing the full complexity of the disease, necessitating the transition to multi-omics biosensors capable of detecting multiple biomarker classes simultaneously.

Multi-omics biosensors utilize advances in nanotechnology, electrochemical sensing, and optical detection to improve diagnostic accuracy and enable real-time cancer monitoring. By integrating genomic alterations, transcriptomic signatures, protein biomarkers, and metabolic changes, these platforms provide a more holistic and precise assessment of pancreatic cancer. The incorporation of artificial intelligence further refines their utility, allowing for automated pattern recognition, risk stratification, and predictive modeling. These technological innovations not only enhance early detection but also support more personalized and effective treatment planning, ultimately improving patient outcomes.

Despite their promise, the clinical translation of biosensor-based liquid biopsy technologies faces challenges, including regulatory approval, large-scale validation, and cost-effectiveness. Addressing these barriers requires interdisciplinary collaboration among researchers, clinicians, and industry stakeholders to refine biosensor designs, standardize protocols, and establish their reliability in clinical settings. The future of multi-omics biosensors lies in wearable, implantable, and point-of-care devices that allow continuous biomarker monitoring for high-risk individuals. The combination of AI-driven data interpretation, nanomaterials, and miniaturized lab-on-a-chip platforms will enable the next generation of non-invasive, ultra-sensitive, and real-time pancreatic cancer diagnostics. With ongoing advancements in biosensor fabrication and multi-omics integration, the development of a clinically viable multi-omics biosensor is within reach.

As research progresses, multi-omics biosensors have the potential to redefine the early detection paradigm for pancreatic cancer, making proactive screening more feasible and significantly improving survival rates. Biosensor technology, AI-driven analysis, and liquid biopsy methods are revolutionizing cancer diagnostics. These advancements enhance sensitivity and specificity, marking a shift toward early detection and precision oncology.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

CRediT authorship contribution statement

Mustafa Aydemir: Writing – original draft. **Ali İhsan Kömür:** Writing – original draft, Visualization. **Emine Selda Gündüz:** Writing – original draft. **Ceren Karaman:** Writing – original draft, Visualization, Supervision, Conceptualization. **Onur Karaman:** Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] M.H. Uddin, M.N. Al-Hallak, P.A. Philip, R.M. Mohammad, N. Viola, K.-U. Wagner, A.S. Azmi, Exosomal microRNA in Pancreatic Cancer Diagnosis, Prognosis, and Treatment: From Bench to Bedside, Cancers (Basel) 13 (2021) 2777, https://doi.org/10.3390/cancers13112777.

[2] B. Kenner, S.T. Chari, D. Kelsen, D.S. Klimstra, S.J. Pandol, M. Rosenthal, A. K. Rustgi, J.A. Taylor, A. Yala, N. Abul-Husn, D.K. Andersen, D. Bernstein, S. Brunak, M.I. Canto, Y.C. Eldar, E.K. Fishman, J. Fleshman, V.L.W. Go, J. M. Holt, B. Field, A. Goldberg, W. Hoos, C. Iacobuzio-Donahue, D. Li, G. Lidgard, A. Maitra, L.M. Matrisian, S. Poblete, L. Rothschild, C. Sander, L.H. Schwartz, U. Shalit, S. Srivastava, B. Wolpin, Artificial Intelligence and Early Detection of Pancreatic Cancer, Pancreas 50 (2021) 251–279, https://doi.org/10.1097/MPA.0000000000001762.

[3] J. Yang, R. Xu, C. Wang, J. Qiu, B. Ren, L. You, Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review, Cancer Commun. 41 (2021) 1257–1274, https://doi.org/10.1002/cac2.12204.

[4] G.-Y. Liou, C.J. Byrd, Diagnostic Bioliquid Markers for Pancreatic Cancer: What We Have vs. What We Need, Cancers (Basel) 15 (2023) 2446, https://doi.org/10.3390/cancers15092446.

[5] K. Søreide, W. Ismail, M. Roalsø, J. Ghotbi, C. Zaharia, Early Diagnosis of Pancreatic Cancer: Clinical Premonitions, Timely Precursor Detection and Increased Curative-Intent Surgery, Cancer Control 30 (2023), https://doi.org/10.1177/10732748231154711.

[6] S.F. Șolea, M.C. Brisc, A. Orășeanu, F.C. Venter, C.M. Brisc, R.M. Șolea, L. Davidescu, A. Venter, C. Brisc, Revolutionizing the Pancreatic Tumor Diagnosis: Emerging Trends in Imaging Technologies, A Systematic Review, Medicina (b. Aires) 60 (2024) 695, https://doi.org/10.3390/medicina60050695.

[7] A.C. Faur, D.C. Lazar, L.A. Ghenciu, Artificial intelligence as a noninvasive tool for pancreatic cancer prediction and diagnosis, World J. Gastroenterol. 29 (2023) 1811–1823, https://doi.org/10.3748/wjg.v29.i12.1811.

[8] M. Caban, E. Małecka-Wojciesko, Gaps and Opportunities in the Diagnosis and Treatment of Pancreatic Cancer, Cancers (Basel) 15 (2023) 5577, https://doi.org/10.3390/cancers15235577.

[9] R.S. O'Neill, A. Stoita, Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket? World J. Gastroenterol. 27 (2021) 4045–4087, https://doi.org/10.3748/wjg.v27.i26.4045.

[10] G. Luo, K. Jin, S. Deng, H. Cheng, Z. Fan, Y. Gong, Y. Qian, Q. Huang, Q. Ni, C. Liu, X. Yu, Roles of CA19-9 in pancreatic cancer: Biomarker, predictor and promoter, Biochim. Biophys. Acta - Rev. Cancer 1875 (2021) 188409, https://doi.org/10.1016/j.bbcan.2020.188409.

[11] A. Mukund, M.A. Afridi, A. Karolak, M.A. Park, J.B. Permuth, G. Rasool, Pancreatic Ductal Adenocarcinoma (PDAC): A Review of Recent Advancements Enabled by Artificial Intelligence, Cancers (Basel) 16 (2024) 2240, https://doi.org/10.3390/cancers16122240.

[12] K. Cao, Y. Xia, J. Yao, X. Han, L. Lambert, T. Zhang, W. Tang, G. Jin, H. Jiang, X. Fang, I. Nogues, X. Li, W. Guo, Y. Wang, W. Fang, M. Qiu, Y. Hou, T. Kovarnik, M. Vocka, Y. Lu, Y. Chen, X. Chen, Z. Liu, J. Zhou, C. Xie, R. Zhang, H. Lu, G. D. Hager, A.L. Yuille, L. Lu, C. Shao, Y. Shi, Q. Zhang, T. Liang, L. Zhang, J. Lu, Large-scale pancreatic cancer detection via non-contrast CT and deep learning, Nat. Med. 29 (2023) 3033–3043, https://doi.org/10.1038/s41591-023-02640-w.

[13] K.P. Farr, D. Moses, K.S. Haghighi, P.A. Phillips, C.M. Hillenbrand, B.H. Chua, Imaging Modalities for Early Detection of Pancreatic Cancer: Current State and Future Research Opportunities, Cancers (Basel) 14 (2022) 2539, https://doi.org/10.3390/cancers14102539.

[14] A.D. Singhi, L.D. Wood, Early detection of pancreatic cancer using DNA-based molecular approaches, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 457–468, https://doi.org/10.1038/s41575-021-00470-0.

[15] S.N. Lone, S. Nisar, T. Masoodi, M. Singh, A. Rizwan, S. Hashem, W. El-Rifai, D. Bedognetti, S.K. Batra, M. Haris, A.A. Bhat, M.A. Macha, Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments, Mol. Cancer 21 (2022) 79, https://doi.org/10.1186/s12943-022-01543-7.

[16] K. Wang, X. Wang, Q. Pan, B. Zhao, Liquid biopsy techniques and pancreatic cancer: diagnosis, monitoring, and evaluation, Mol. Cancer 22 (2023) 167, https://doi.org/10.1186/s12943-023-01870-3.

[17] L. Ma, H. Guo, Y. Zhao, Z. Liu, C. Wang, J. Bu, T. Sun, J. Wei, Liquid biopsy in cancer: current status, challenges and future prospects, Signal Transduct. Target. Ther. 9 (2024) 336, https://doi.org/10.1038/s41392-024-02021-w.

[18] M. Nikanjam, S. Kato, R. Kurzrock, Liquid biopsy: current technology and clinical applications, J. Hematol. Oncol. 15 (2022) 131, https://doi.org/10.1186/s13045-022-01351-y.

[19] H.-Y. Ho, K.-S. (Kasey) Chung, C.-M. Kan, S.-C. (Cesar), Wong, Liquid Biopsy in the Clinical Management of Cancers, Int. J. Mol. Sci. 25 (2024) 8594, https://doi.org/10.3390/ijms25168594.

[20] X. Wang, L. Wang, H. Lin, Y. Zhu, D. Huang, M. Lai, X. Xi, J. Huang, W. Zhang, T. Zhong, Research progress of CTC, ctDNA, and EVs in cancer liquid biopsy, Front. Oncol. 14 (2024), https://doi.org/10.3389/fonc.2024.1303335.

[21] A. Armakolas, M. Kotsari, J. Koskinas, Liquid Biopsies, Novel Approaches and Future Directions, Cancers (Basel) 15 (2023) 1579, https://doi.org/10.3390/cancers15051579.

[22] S. Zhou, B. Tao, Y. Guo, J. Gu, H. Li, C. Zou, S. Tang, S. Jiang, D. Fu, J. Li, Integrating plasma protein-centric multi-omics to identify potential therapeutic targets for pancreatic cancer, J. Transl. Med. 22 (2024) 557, https://doi.org/10.1186/s12967-024-05363-9.

[23] N.F. de Brito, L.F. Ribeiro Pinto, M.E. Melendez, Biosensors for liquid biopsy of pancreatic cancer, Microchem. J. 196 (2024) 109679, https://doi.org/10.1016/j.microc.2023.109679.

[24] S. Singh, P.S. Podder, M. Russo, C. Henry, S. Cinti, Tailored point-of-care biosensors for liquid biopsy in the field of oncology, Lab Chip 23 (2023) 44–61, https://doi.org/10.1039/D2LC00666A.

[25] S. Singh, A. Miglione, A. Raucci, A. Numan, S. Cinti, Towards sense and sensitivity-based electrochemical biosensors for liquid biopsy-based breast cancer detection, TrAC Trends Anal. Chem. 163 (2023) 117050, https://doi.org/10.1016/j.trac.2023.117050.

[26] M.J. Iqbal, Z. Javed, J. Herrera-Bravo, H. Sadia, F. Anum, S. Raza, A. Tahir, M. N. Shahwani, J. Sharifi-Rad, D. Calina, W.C. Cho, Biosensing chips for cancer diagnosis and treatment: a new wave towards clinical innovation, Cancer Cell Int. 22 (2022) 354, https://doi.org/10.1186/s12935-022-02777-7.

[27] H. Nasrollahpour, A. Mirzaie, M. Sharifi, A. Rezabakhsh, B. Khalilzadeh, R. Rahbarghazi, H. Yousefi, D.J. Klionsky, Biosensors; a novel concept in real-time detection of autophagy, Biosens. Bioelectron. 254 (2024) 116204, https://doi.org/10.1016/j.bios.2024.116204.

[28] L. Qian, Q. Li, K. Baryeh, W. Qiu, K. Li, J. Zhang, Q. Yu, D. Xu, W. Liu, R.E. Brand, X. Zhang, W. Chen, G. Liu, Biosensors for early diagnosis of pancreatic cancer: a review, Transl. Res. 213 (2019) 67–89, https://doi.org/10.1016/j.trsl.2019.08.002.

[29] Z. Rezaei, N. Wang, A.D.J.A. Rodriguez, S. Higashi, S.R. Shin, Biosensors in biomedical research: Bridging cell and tissue engineering and real-time monitoring, Curr. Opin. Biomed. Eng. 34 (2025) 100582, https://doi.org/10.1016/j.cobme.2025.100582.

[30] F. Lin, X. Li, J. Zhang, H. Zhang, Z. Zhang, L. Hou, B. Shen, L. Jin, Ratiometric electrochemical aptasensor based on functionalized graphene nanocomposites for detection of CA19-9, Anal. Sci. (2025), https://doi.org/10.1007/s44211-025-00743-7.

[31] M. Bekmezci, R. Bayat, M. Akin, Z.K. Coguplugil, F. Sen, Modified screen-printed electrochemical biosensor design compatible with mobile phones for detection of miR-141 used to pancreatic cancer biomarker, Carbon Lett. 33 (2023) 1863–1873, https://doi.org/10.1007/s42823-023-00545-9.

[32] M. Sancho-Albero, V. Sebastián, J. Sesé, R. Pazo-Cid, G. Mendoza, M. Arruebo, P. Martín-Duque, J. Santamaría, Isolation of exosomes from whole blood by a new microfluidic device: proof of concept application in the diagnosis and monitoring of pancreatic cancer, J. Nanobiotechnology 18 (2020) 150, https://doi.org/10.1186/s12951-020-00701-7.

[33] Z. Zhu, Y. Zhang, W. Zhang, D. Tang, S. Zhang, L. Wang, X. Zou, Z. Ni, S. Zhang, Y. Lv, N. Xiang, High-throughput enrichment of portal venous circulating tumor cells for highly sensitive diagnosis of CA19-9-negative pancreatic cancer patients using inertial microfluidics, Biosens. Bioelectron. 259 (2024) 116411, https://doi.org/10.1016/j.bios.2024.116411.

[34] S. Chakraborty, G. Sharma, S. Karmakar, S. Banerjee, Multi-OMICS approaches in cancer biology: New era in cancer therapy, Biochim. Biophys. Acta - Mol. Basis Dis. 1870 (2024) 167120, https://doi.org/10.1016/j.bbadis.2024.167120.

[35] H. Chang, H. Chen, T. Ma, K. Ma, Y. Li, L. Suo, X. Liang, K. Jia, J. Ma, J. Li, D. Sun, Multi-omics pan-cancer study of SPTBN2 and its value as a potential therapeutic target in pancreatic cancer, Sci. Rep. 14 (2024) 9764, https://doi.org/10.1038/s41598-024-60780-6.

[36] M. Verma, Personalized Medicine and Cancer, J. Pers. Med. 2 (2012) 1–14, https://doi.org/10.3390/jpm2010001.

[37] E.R. Malone, M. Oliva, P.J.B. Sabatini, T.L. Stockley, L.L. Siu, Molecular profiling for precision cancer therapies, Genome Med. 12 (2020) 8, https://doi.org/10.1186/s13073-019-0703-1.

[38] V.M. Oza, N. Mittal, A. Antony, S. Mukherjee, A.H. Goenka, Advancements and Challenges in Artificial Intelligence-Driven Diagnosis and Management of Pancreatic Cancer, AI Precis. Oncol. 1 (2024) 207–215, https://doi.org/10.1089/aipo.2024.0032.

[39] A.E. Mohr, C.P. Ortega-Santos, C.M. Whisner, J. Klein-Seetharaman, P. Jasbi, Navigating Challenges and Opportunities in Multi-Omics Integration for Personalized Healthcare, Biomedicines 12 (2024) 1496, https://doi.org/10.3390/biomedicines12071496.

[40] M. Karunanidhi, H. Kanniyappan, E. Zhan, R. Mathew, Y. Sun, J. Wu, Y. Yan, G. Munirathinum, M.T. Mathew, Abstract 7289: PancreaAlert: Intelligent nanoengineered biosensor for pancreatic cancer, Cancer Res. 84 (2024) 7289, https://doi.org/10.1158/1538-7445.AM2024-7289.
[41] H. Daher, S.A. Punchayil, A.A.E. Ismail, R.R. Fernandes, J. Jacob, M.H. Algazzar, M. Mansour, Advancements in Pancreatic Cancer Detection: Integrating Biomarkers, Imaging Technologies, and Machine Learning for Early Diagnosis, Cureus (2024), https://doi.org/10.7759/cureus.56583.
[42] L.T.P. Le, A.H.Q. Nguyen, L.M.T. Phan, H.T.T. Ngo, X. Wang, B. Cunningham, E. Valera, R. Bashir, A.W. Taylor-Robinson, C.D. Do, Current smartphone-assisted point-of-care cancer detection: Towards supporting personalized cancer monitoring, TrAC Trends Anal. Chem. 174 (2024) 117681, https://doi.org/10.1016/j.trac.2024.117681.
[43] G. Zhao, R. Jiang, Y. Shi, S. Gao, D. Wang, Z. Li, Y. Zhou, J. Sun, W. Wu, J. Peng, T. Kuang, Y. Rong, J. Yuan, S. Zhu, G. Jin, Y. Wang, W. Lou, Circulating cell-free <scp>DNA</scp> methylation-based multi-omics analysis allows early diagnosis of pancreatic ductal adenocarcinoma, Mol. Oncol. 18 (2024) 2801–2813, https://doi.org/10.1002/1878-0261.13643.
[44] M.H. Maher, W. Treekitkarnmongkol, S. Ghatak, J. Dai, S. Liu, T. Nguyen, D. Y. Duose, M.P. Kim, T.Y. Hu, M.W. Hurd, P.L. Paris, K.S. Kirkwood, A. Maitra, R. Luthra, S. Sen, S. Roy-Chowdhuri, An integrated multi-omics biomarker approach using molecular profiling and microRNAs for evaluation of pancreatic cyst fluid, Cancer Cytopathol. 133 (2025), https://doi.org/10.1002/cncy.70008.
[45] L.E. Kane, G.S. Mellotte, K.C. Conlon, B.M. Ryan, S.G. Maher, Multi-Omic Biomarkers as Potential Tools for the Characterisation of Pancreatic Cystic Lesions and Cancer: Innovative Patient Data Integration, Cancers (Basel) 13 (2021) 769, https://doi.org/10.3390/cancers13040769.
[46] B. Wilcox, J. Blume, K. Swaminathan, P. Williams, M. Khadka, J. Deyarmin, S. Ramaswamy, Y. Kodama, B. Young, C. Belthangady, M. Liu, M. Yang, P. Ma, Abstract 3924: Deep, unbiased multi-omics approach for identification of pancreatic cancer biomarkers from blood, Cancer Res. 82 (2022) 3924, https://doi.org/10.1158/1538-7445.AM2022-3924.
[47] E. Khaledian, P. Prasad, J. Blume, G. Bundalian, C. Chao-Shern, J. Choi, R. Cuaresma, J. Deyarmin, J.H. Jang, M. Khadka, T. Khin, Y. Kodama, A. Kokate, J.-Y. Lee, M. Liu, N. Mudaliar, M. Ramaiah, S. Ramaswamy, P. Spiro, K. Swaminathan, P. Williams, M. Yang, J. Yee, B. Young, R. Zawada, S. Zhang, C. Belthangady, B. Wilcox, P. Ma, Abstract A038: High-dimensional, multi-omics analyses of proteins, metabolites, transcripts, and genes enable biomarker discovery in early- and late-stage pancreatic cancer, Cancer Res. 82 (2022) A038–A, https://doi.org/10.1158/1538-7445.PANCA22-A038.
[48] K.-L. Reese, K. Pantel, D.J. Smit, Multibiomarker panels in liquid biopsy for early detection of pancreatic cancer – a comprehensive review, J. Exp. Clin. Cancer Res. 43 (2024) 250, https://doi.org/10.1186/s13046-024-03166-w.
[49] B. Turanli, E. Yildirim, G. Gulfidan, K.Y. Arga, R. Sinha, Current State of "Omics" Biomarkers in Pancreatic Cancer, J. Pers. Med. 11 (2021) 127, https://doi.org/10.3390/jpm11020127.
[50] M. Taherian, H. Wang, H. Wang, Pancreatic Ductal Adenocarcinoma: Molecular Pathology and Predictive Biomarkers, Cells 11 (2022) 3068, https://doi.org/10.3390/cells11193068.
[51] M. Orth, P. Metzger, S. Gerum, J. Mayerle, G. Schneider, C. Belka, M. Schnurr, K. Lauber, Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches, Radiat. Oncol. 14 (2019) 141, https://doi.org/10.1186/s13014-019-1345-6.
[52] K.E. Poruk, D.Z. Gay, K. Brown, J.D. Mulvihill, K.M. Boucher, C.L. Scaife, M. A. Firpo, S.J. Mulvihill, The Clinical Utility of CA 19-9 in Pancreatic Adenocarcinoma: Diagnostic and Prognostic Updates, Curr. Mol. Med. 13 (2013) 340–351, https://doi.org/10.2174/1566524013805076876.
[53] T. Simon, P. Riemer, A. Jarosch, K. Detjen, A. Di Domenico, F. Bormann, A. Menne, S. Khouja, N. Monjé, L.H. Childs, D. Lenze, U. Leser, F. Rossner, M. Morkel, N. Blüthgen, M. Pavel, D. Horst, D. Capper, I. Marinoni, A. Perren, S. Mamlouk, C. Sers, DNA methylation reveals distinct cells of origin for pancreatic neuroendocrine carcinomas and pancreatic neuroendocrine tumors, Genome Med. 14 (2022) 24, https://doi.org/10.1186/s13073-022-01018-w.
[54] R. Kushima, The updated WHO classification of digestive system tumours—gastric adenocarcinoma and dysplasia, Pathologe 43 (2022) 8–15, https://doi.org/10.1007/s00292-021-01023-7.
[55] B.R. van´ t Veld, W.M. Hackeng, C. Luchini, L.A.A. Brosens, K.M.A. Dreijerink, Clinical Relevance of ATRX/DAXX Gene Mutations and ALT in Functioning Pancreatic Neuroendocrine Tumors, Endocr. Pathol. 36 (2025) 3, https://doi.org/10.1007/s12022-025-09848-1.
[56] P.K. Gorai, P.S. Bharti, S. Kumar, G.H. Rajacharya, S. Bandyopadhyay, S. Pal, R. Dhingra, R. Kumar, F. Nikolajeff, S. Kumar, N. Rani, C1QA and COMP: plasma-based biomarkers for early diagnosis of pancreatic neuroendocrine tumors, Sci. Rep. 13 (2023) 21021, https://doi.org/10.1038/s41598-023-48323-x.
[57] G. Rindi, O. Mete, S. Uccella, O. Basturk, S. La Rosa, L.A.A. Brosens, S. Ezzat, W. W. de Herder, D.S. Klimstra, M. Papotti, S.L. Asa, Overview of the, WHO Classification of Neuroendocrine Neoplasms, Endocr. Pathol. 33 (2022) (2022) 115–154, https://doi.org/10.1007/s12022-022-09708-2.
[58] H. Ishida, A.K. Lam, Pancreatic neuroendocrine neoplasms: Updates on genomic changes in inherited tumour syndromes and sporadic tumours based on WHO classification, Crit. Rev. Oncol. Hematol. 172 (2022) 103648, https://doi.org/10.1016/j.critrevonc.2022.103648.
[59] J.W. Chen, C.M. Heidsma, A.F. Engelsman, E. Kabaktepe, S. van Dieren, M. Falconi, M.G. Besselink, E.J.M. Nieveen van Dijkum, Clinical Prediction Models for Recurrence in Patients with Resectable Grade 1 and 2 Sporadic Non-Functional Pancreatic Neuroendocrine Tumors: A Systematic Review, Cancers (Basel) 15 (2023) 1525, https://doi.org/10.3390/cancers15051525.
[60] Y. Xie, E. Abaydulla, S. Zhang, H. Liu, H. Hang, Q. Li, Y. Qiu, H. Cheng, Preoperative prediction of pancreatic neuroendocrine tumors grade based on computed tomography, magnetic resonance imaging and endoscopic ultrasonography, Abdom. Radiol. (2025), https://doi.org/10.1007/s00261-025-04865-4.
[61] D. Takayanagi, H. Cho, E. Machida, A. Kawamura, A. Takashima, S. Wada, T. Tsunoda, T. Kohno, K. Shiraishi, Update on Epidemiology, Diagnosis, and Biomarkers in Gastroenteropancreatic Neuroendocrine Neoplasms, Cancers (Basel) 14 (2022) 1119, https://doi.org/10.3390/cancers14051119.
[62] A.-F.-P. Sonnen, A.V.D. Verschuur, L.A.A. Brosens, Diagnostic and prognostic biomarkers for pancreatic neuroendocrine neoplasms, Die Pathol. 45 (2024) 74–82, https://doi.org/10.1007/s00292-024-01393-8.
[63] K.M. Dreijerink, W.M. Hackeng, A.D. Singhi, C.M. Heaphy, L.A. Brosens, Clinical implications of cell-of-origin epigenetic characteristics in non-functional pancreatic neuroendocrine tumors, J. Pathol. 256 (2022) 143–148, https://doi.org/10.1002/path.5834.
[64] C.S. Chan, S.V. Laddha, P.W. Lewis, M.S. Koletsky, K. Robzyk, E. Da Silva, P. J. Torres, B.R. Untch, J. Li, P. Bose, T.A. Chan, D.S. Klimstra, C.D. Allis, L.H. Tang, ATRX, DAXX or MEN1 mutant pancreatic neuroendocrine tumors are a distinct alpha-cell signature subgroup, Nat. Commun. 9 (2018) 4158, https://doi.org/10.1038/s41467-018-06498-2.
[65] W. Gu, Y. Chen, H. Zhu, H. Chen, Z. Yang, S. Mo, H. Zhao, L. Chen, T. Nakajima, X. Yu, S. Ji, Y. Gu, J. Chen, W. Tang, Development and validation of CT-based radiomics deep learning signatures to predict lymph node metastasis in non-functional pancreatic neuroendocrine tumors: a multicohort study, EClinicalMedicine 65 (2023) 102269, https://doi.org/10.1016/j.eclinm.2023.102269.
[66] A.D. Singhi, D.S. Klimstra, Well-differentiated pancreatic neuroendocrine tumours (Pan <scp>NET</scp> s) and poorly differentiated pancreatic neuroendocrine carcinomas (Pan <scp>NEC</scp> s): concepts, issues and a practical diagnostic approach to high-grade (G3) cases, Histopathology 72 (2018) 168–177, https://doi.org/10.1111/his.13408.
[67] J.M. Fang, J. Shi, A Clinicopathologic and Molecular Update of Pancreatic Neuroendocrine Neoplasms With a Focus on the New World Health Organization Classification, Arch. Pathol. Lab. Med. 143 (2019) 1317–1326, https://doi.org/10.5858/arpa.2019-0338-RA.
[68] J. Coll. Physicians Surg. Pakistan 32 (2022) 398–400. https://doi.org/10.29271/jcpsp.2022.03.398.
[69] L.F. Calimano-Ramirez, T. Daoud, D.R. Gopireddy, A.C. Morani, R. Waters, K. Gumus, A.R. Klekers, P.R. Bhosale, M.K. Virarkar, Pancreatic acinar cell carcinoma: A comprehensive review, World J. Gastroenterol. 28 (2022) 5827–5844, https://doi.org/10.3748/wjg.v28.i40.5827.
[70] K. Ikezawa, M. Urabe, Y. Kai, R. Takada, H. Akita, S. Nagata, K. Ohkawa, Comprehensive review of pancreatic acinar cell carcinoma: epidemiology, diagnosis, molecular features and treatment, Jpn. J. Clin. Oncol. 54 (2024) 271–281, https://doi.org/10.1093/jjco/hyad176.
[71] J.A. Yonkus, J.R. Bergquist, R. Alva-Ruiz, T. Ivanics, E.B. Habermann, A. M. Abdelrahman, T.E. Grotz, S.P. Cleary, R.L. Smoot, D.M. Nagorney, M. L. Kendrick, T.R. Halfdanarson, M.J. Truty, A national database analysis of acinar cell carcinoma of the pancreas, a histologically, epidemiologically, and biologically distinct entity increasing in incidence, 3-3, Ann. Pancreat. Cancer 4 (2021), https://doi.org/10.21037/apc-21-1.
[72] S. Zhao, J. Wang, H. Liu, S. Liu, L. Sun, Y. Wang, S. Gao, Y. Sun, Analyses of CTNNB1 mutation and expression and clinicopathological characteristics in 179 cases of solid-pseudopapillary neoplasm of the pancreas, J. Hepatobiliary. Pancreat. Sci. 32 (2025) 327–338, https://doi.org/10.1002/jhbp.12123.
[73] C. Fu, X. Li, Y. Wang, C. Wang, H. Jin, K. Liu, H. Xu, Solid pseudopapillary neoplasm of the pancreas: a retrospective study of 195 cases, Front. Oncol. 14 (2024), https://doi.org/10.3389/fonc.2024.1349282.
[74] A.O. Omiyale, Solid pseudopapillary neoplasm of the pancreas, World, J. Hepatol. 13 (2021) 896–903, https://doi.org/10.4254/wjh.v13.i8.896.
[75] S. La Rosa, M. Bongiovanni, Pancreatic Solid Pseudopapillary Neoplasm: Key Pathologic and Genetic Features, Arch. Pathol. Lab. Med. 144 (2020) 829–837, https://doi.org/10.5858/arpa.2019-0473-RA.
[76] E. Rodriguez-Matta, A. Hemmerich, J. Starr, K. Mody, E.A. Severson, G. Colon-Otero, Molecular genetic changes in solid pseudopapillary neoplasms (SPN) of the pancreas, Acta Oncol. (madr) 59 (2020) 1024–1027, https://doi.org/10.1080/0284186X.2020.1792549.
[77] M.E. Barefoot, N. Loyfer, A.J. Kiliti, A.P. McDeed, T. Kaplan, A. Wellstein, Detection of Cell Types Contributing to Cancer From Circulating, Cell-Free Methylated DNA, Front. Genet. 12 (2021), https://doi.org/10.3389/fgene.2021.671057.
[78] J. Wang, X. Han, Y. Sun, DNA methylation signatures in circulating cell-free DNA as biomarkers for the early detection of cancer, Sci. China Life Sci. 60 (2017) 356–362, https://doi.org/10.1007/s11427-016-0253-7.
[79] W. Guo, Y. Hu, W. Wang, Y. Zhou, Z. Yang, H. An, Q. Yang, Y. Lv, C. Lu, X. Zhang, M. Xu, Y. Xia, L. Ji, S. Chen, Assessment of plasma cell-free DNA fragmentation for multi-cancer early detection: An independent clinical validation study, J. Clin. Oncol. 42 (2024) e15037–e, https://doi.org/10.1200/JCO.2024.42.16_suppl.e15037.
[80] M.F. Arisi, E. Dotan, S.V. Fernandez, Circulating Tumor DNA in Precision Oncology and Its Applications in Colorectal Cancer, Int. J. Mol. Sci. 23 (2022) 4441, https://doi.org/10.3390/ijms23084441.

[81] O.B. Alese, N. Cook, A. Ortega-Franco, M.B. Ulanja, L. Tan, J. Tie, Circulating Tumor DNA: An Emerging Tool in Gastrointestinal Cancers, Am. Soc. Clin. Oncol. Educ. b. (2022) 279–298, https://doi.org/10.1200/EDBK_349143.
[82] Y. Bao, D. Zhang, H. Guo, W. Ma, Beyond blood: Advancing the frontiers of liquid biopsy in oncology and personalized medicine, Cancer Sci. 115 (2024) 1060–1072, https://doi.org/10.1111/cas.16097.
[83] K.T. Helzer, M.N. Sharifi, J.M. Sperger, Y. Shi, M. Annala, M.L. Bootsma, S. R. Reese, A. Taylor, K.R. Kaufmann, H.K. Krause, J.L. Schehr, N. Sethakorn, D. Kosoff, C. Kyriakopoulos, M.E. Burkard, N.R. Rydzewski, M. Yu, P.M. Harari, M. Bassetti, G. Blitzer, J. Floberg, M. Sjöström, D.A. Quigley, S.M. Dehm, A. J. Armstrong, H. Beltran, R.R. McKay, F.Y. Feng, R. O'Regan, K.B. Wisinski, H. Emamekhoo, A.W. Wyatt, J.M. Lang, S.G. Zhao, Fragmentomic analysis of circulating tumor DNA-targeted cancer panels, Ann. Oncol. 34 (2023) 813–825, https://doi.org/10.1016/j.annonc.2023.06.001.
[84] M.W. Snyder, M. Kircher, A.J. Hill, R.M. Daza, J. Shendure, Cell-free DNA Comprises an In Vivo Nucleosome Footprint that Informs Its Tissues-Of-Origin, Cell 164 (2016) 57–68, https://doi.org/10.1016/j.cell.2015.11.050.
[85] F. Mouliere, D. Chandrananda, A.M. Piskorz, E.K. Moore, J. Morris, L.B. Ahlborn, R. Mair, T. Goranova, F. Marass, K. Heider, J.C.M. Wan, A. Supernat, I. Hudecova, I. Gounaris, S. Ros, M. Jimenez-Linan, J. Garcia-Corbacho, K. Patel, O. Østrup, S. Murphy, M.D. Eldridge, D. Gale, G.D. Stewart, J. Burge, W.N. Cooper, M.S. van der Heijden, C.E. Massie, C. Watts, P. Corrie, S. Pacey, K.M. Brindle, R.D. Baird, M. Mau-Sørensen, C.A. Parkinson, C.G. Smith, J.D. Brenton, N. Rosenfeld, Enhanced detection of circulating tumor DNA by fragment size analysis, Sci. Transl. Med. 10 (2018), https://doi.org/10.1126/scitranslmed.aat4921.
[86] W.H.A. Tsui, S.C. Ding, P. Jiang, Y.M.D. Lo, Artificial intelligence and machine learning in cell-free-DNA-based diagnostics, Genome Res. 35 (2025) 1–19, https://doi.org/10.1101/gr.278413.123.
[87] J.C.M. Wan, C. Massie, J. Garcia-Corbacho, F. Mouliere, J.D. Brenton, C. Caldas, S. Pacey, R. Baird, N. Rosenfeld, Liquid biopsies come of age: towards implementation of circulating tumour DNA, Nat. Rev. Cancer 17 (2017) 223–238, https://doi.org/10.1038/nrc.2017.7.
[88] P. Liu, F. Yang, L. Zhang, Y. Hu, B. Chen, J. Wang, L. Su, M. Wu, W. Chen, Emerging role of different DNA methyltransferases in the pathogenesis of cancer, Front. Pharmacol. 13 (2022), https://doi.org/10.3389/fphar.2022.958146.
[89] M.C. Liu, G.R. Oxnard, E.A. Klein, C. Swanton, M.V. Seiden, M.C. Liu, G. R. Oxnard, E.A. Klein, D. Smith, D. Richards, T.J. Yeatman, A.L. Cohn, R. Lapham, J. Clement, A.S. Parker, M.K. Tummala, K. McIntyre, M.A. Sekeres, A.H. Bryce, R. Siegel, X. Wang, D.P. Cosgrove, N.R. Abu-Rustum, J. Trent, D.D. Thiel, C. Becerra, M. Agrawal, L.E. Garbo, J.K. Giguere, R.M. Michels, R.P. Harris, S. L. Richey, T.A. McCarthy, D.M. Waterhouse, F.J. Couch, S.T. Wilks, A.K. Krie, R. Balaraman, A. Restrepo, M.W. Meshad, K. Rieger-Christ, T. Sullivan, C.M. Lee, D.R. Greenwald, W. Oh, C.-K. Tsao, N. Fleshner, H.F. Kennecke, M.F. Khalil, D. R. Spigel, A.P. Manhas, B.K. Ulrich, P.A. Kovoor, C. Stokoe, J.G. Courtright, H. A. Yimer, T.G. Larson, C. Swanton, M.V. Seiden, S.R. Cummings, F. Absalan, G. Alexander, B. Allen, H. Amini, A.M. Aravanis, S. Bagaria, L. Bazargan, J. F. Beausang, J. Berman, C. Betts, A. Blocker, J. Bredno, R. Calef, G. Cann, J. Carter, C. Chang, H. Chawla, X. Chen, T.C. Chien, D. Civello, K. Davydov, V. Demas, M. Desai, Z. Dong, S. Fayzullina, A.P. Fields, D. Filippova, P. Freese, E. T. Fung, S. Gnerre, S. Gross, M. Halks-Miller, M.P. Hall, A.-R. Hartman, C. Hou, E. Hubbell, N. Hunkapiller, K. Jagadeesh, A. Jamshidi, R. Jiang, B. Jung, T. Kim, R.D. Klausner, K.N. Kurtzman, M. Lee, W. Lin, J. Lipson, H. Liu, Q. Liu, M. Lopatin, T. Maddala, M.C. Maher, C. Melton, A. Mich, S. Nautiyal, J. Newman, J. Newman, V. Nicula, C. Nicolaou, O. Nikolic, W. Pan, S. Patel, S.A. Prins, R. Rava, N. Ronaghi, O. Sakarya, R.V. Satya, J. Schellenberger, E. Scott, A. J. Sehnert, R. Shaknovich, A. Shanmugam, K.C. Shashidhar, L. Shen, A. Shenoy, S. Shojaee, P. Singh, K.K. Steffen, S. Tang, J.M. Toung, A. Valouev, O. Venn, R. T. Williams, T. Wu, H.H. Xu, C. Yakym, X. Yang, J. Yecies, A.S. Yip, J. Youngren, J. Yue, J. Zhang, L. Zhang, L. (Quan) Zhang, N. Zhang, C. Curtis, D.A. Berry, Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA, Ann. Oncol. 31 (2020) 745–759, https://doi.org/10.1016/j.annonc.2020.02.011.
[90] J.M. Yi, A.A. Guzzetta, V.J. Bailey, S.R. Downing, L. Van Neste, K.B. Chiappinelli, B.P. Keeley, A. Stark, A. Herrera, C. Wolfgang, E.P. Pappou, C.A. Iacobuzio-Donahue, M.G. Goggins, J.G. Herman, T.-H. Wang, S.B. Baylin, N. Ahuja, Novel Methylation Biomarker Panel for the Early Detection of Pancreatic Cancer, Clin. Cancer Res. 19 (2013) 6544–6555, https://doi.org/10.1158/1078-0432.CCR-12-3224.
[91] H. Kim, J. Chu, I.-G. Do, Y.-P. Lee, H.K. Kim, Y. Yang, J. Kwon, K.H. Lee, C. Batochir, E. Jo, K.R. Kim, H.S. Han, Novel diagnostic biomarkers for pancreatic cancer: assessing methylation status with epigenetic-specific peptide nucleic acid and KRAS mutation in cell-free DNA, Front. Oncol. 14 (2024), https://doi.org/10.3389/fonc.2024.1395473.
[92] J.D. Cohen, L. Li, Y. Wang, C. Thoburn, B. Afsari, L. Danilova, C. Douville, A.A. Javed, F. Wong, A. Mattox, R.H. Hruban, C.L. Wolfgang, M.G. Goggins, M. Dal Molin, T.-L. Wang, R. Roden, A.P. Klein, J. Ptak, L. Dobbyn, J. Schaefer, N. Silliman, M. Popoli, J.T. Vogelstein, J.D. Browne, R.E. Schoen, R.E. Brand, J. Tie, P. Gibbs, H.-L. Wong, A.S. Mansfield, J. Jen, S.M. Hanash, M. Falconi, P.J. Allen, S. Zhou, C. Bettegowda, L.A. Diaz, C. Tomasetti, K.W. Kinzler, B. Vogelstein, A.M. Lennon, N. Papadopoulos, Detection and localization of surgically resectable cancers with a multi-analyte blood test, Science (80-.). 359 (2018) 926–930. https://doi.org/10.1126/science.aar3247.
[93] M.P. Hitchins, Methylated circulating tumor DNA biomarkers for the blood-based detection of cancer signals, in: Epigenetics Precis. Med., Elsevier, 2022: pp. 471–512. https://doi.org/10.1016/B978-0-12-823008-4.00001-9.
[94] L. Li, Y. Sun, Circulating tumor DNA methylation detection as biomarker and its application in tumor liquid biopsy: advances and challenges, MedComm 5 (2024), https://doi.org/10.1002/mco2.766.
[95] X. Liu, S. Guo, C. Ma, Y. Li, X. Liu, Z. Zhang, L. Yu, M. Dai, S. Shen, H.M. Wu, Z. Su, Q. He, R. Liu, J. Gang, Z. Liang, Circulating tumor DNA methylation as markers for early detection of pancreatic ductal adenocarcinoma (PDAC), 395-395, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.3_suppl.395.
[96] J.D. Cohen, A.A. Javed, C. Thoburn, F. Wong, J. Tie, P. Gibbs, C.M. Schmidt, M. T. Yip-Schneider, P.J. Allen, M. Schattner, R.E. Brand, A.D. Singhi, G.M. Petersen, S.-M. Hong, S.C. Kim, M. Falconi, C. Doglioni, M.J. Weiss, N. Ahuja, J. He, M. A. Makary, A. Maitra, S.M. Hanash, M. Dal Molin, Y. Wang, L. Li, J. Ptak, L. Dobbyn, J. Schaefer, N. Silliman, M. Popoli, M.G. Goggins, R.H. Hruban, C. L. Wolfgang, A.P. Klein, C. Tomasetti, N. Papadopoulos, K.W. Kinzler, B. Vogelstein, A.M. Lennon, Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers, Proc. Natl. Acad. Sci. 114 (2017) 10202–10207, https://doi.org/10.1073/pnas.1704961114.
[97] M. Brancaccio, F. Natale, G. Falco, T. Angrisano, Cell-Free DNA Methylation: The New Frontiers of Pancreatic Cancer Biomarkers' Discovery, Genes (Basel) 11 (2019) 14, https://doi.org/10.3390/genes11010014.
[98] A.A. Khan, X. Liu, X. Yan, M. Tahir, S. Ali, H. Huang, An overview of genetic mutations and epigenetic signatures in the course of pancreatic cancer progression, Cancer Metastasis Rev. 40 (2021) 245–272, https://doi.org/10.1007/s10555-020-09952-0.
[99] J. Li, S. Hou, Z. Ye, W. Wang, X. Hu, Q. Hang, Long Non-Coding RNAs in Pancreatic Cancer: Biologic Functions, Mechanisms, and Clinical Significance, Cancers (Basel) 14 (2022) 2115, https://doi.org/10.3390/cancers14092115.
[100] Y. Li, M.N. Al Hallak, P.A. Philip, A.S. Azmi, R.M. Mohammad, Non-Coding RNAs in Pancreatic Cancer Diagnostics and Therapy: Focus on lncRNAs, circRNAs, and piRNAs, Cancers (Basel) 13 (2021) 4161, https://doi.org/10.3390/cancers13164161.
[101] J.-F. Peng, Noncoding RNAs and pancreatic cancer, World J. Gastroenterol. 22 (2016) 801, https://doi.org/10.3748/wjg.v22.i2.801.
[102] J. Qin, B. Wen, Y. Liang, W. Yu, H. Li, Histone Modifications and their Role in Colorectal Cancer (Review), Pathol. Oncol. Res. 26 (2020) 2023–2033, https://doi.org/10.1007/s12253-019-00663-8.
[103] Y. Xu, Q. Zhu, Histone Modifications Represent a Key Epigenetic Feature of Epithelial-to-Mesenchyme Transition in Pancreatic Cancer, Int. J. Mol. Sci. 24 (2023) 4820, https://doi.org/10.3390/ijms24054820.
[104] I.M. Dykes, C. Emanueli, Transcriptional and Post-Transcriptional Gene Regulation by Long Non-Coding RNA, Genomics. Proteomics, Bioinformatics 15 (2017) 177–186, https://doi.org/10.1016/j.gpb.2016.12.005.
[105] J.S. Mattick, P.P. Amaral, P. Carninci, S. Carpenter, H.Y. Chang, L.-L. Chen, R. Chen, C. Dean, M.E. Dinger, K.A. Fitzgerald, T.R. Gingeras, M. Guttman, T. Hirose, M. Huarte, R. Johnson, C. Kanduri, P. Kapranov, J.B. Lawrence, J. T. Lee, J.T. Mendell, T.R. Mercer, K.J. Moore, S. Nakagawa, J.L. Rinn, D. L. Spector, I. Ulitsky, Y. Wan, J.E. Wilusz, M. Wu, Long non-coding RNAs: definitions, functions, challenges and recommendations, Nat. Rev. Mol. Cell Biol. 24 (2023) 430–447, https://doi.org/10.1038/s41580-022-00566-8.
[106] A.A. Seyhan, Circulating microRNAs as Potential Biomarkers in Pancreatic Cancer—Advances and Challenges, Int. J. Mol. Sci. 24 (2023) 13340, https://doi.org/10.3390/ijms241713340.
[107] R. Heery, S. Finn, S. Cuffe, S. Gray, Long Non-Coding RNAs: Key Regulators of Epithelial-Mesenchymal Transition, Tumour Drug Resistance and Cancer Stem Cells, Cancers (Basel) 9 (2017) 38, https://doi.org/10.3390/cancers9040038.
[108] Y. Cheng, P. Imanirad, I. Jutooru, E. Hedrick, U.-H. Jin, A. Rodrigues Hoffman, J. Leal de Araujo, B. Morpurgo, A. Golovko, S. Safe, Role of metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) in pancreatic cancer, PLoS One 13 (2018) e0192264, https://doi.org/10.1371/journal.pone.0192264.
[109] L. Lei, J. Chen, J. Huang, J. Lu, S. Pei, S. Ding, L. Kang, R. Xiao, Q. Zeng, Functions and regulatory mechanisms of metastasis-associated lung adenocarcinoma transcript 1, J. Cell. Physiol. 234 (2019) 134–151, https://doi.org/10.1002/jcp.26759.
[110] S.D. Modali, V.I. Parekh, E. Kebebew, S.K. Agarwal, Epigenetic Regulation of the lncRNA MEG3 and Its Target c-MET in Pancreatic Neuroendocrine Tumors, Mol. Endocrinol. 29 (2015) 224–237, https://doi.org/10.1210/me.2014-1304.
[111] N. Ebrahimi, F. Faghihkhorasani, S.S. Fakhr, P.R. Moghaddam, E. Yazdani, Z. Kheradmand, F. Rezaei-Tazangi, S. Adelian, H. Mobarak, M.R. Hamblin, A. R. Aref, Tumor-derived exosomal non-coding RNAs as diagnostic biomarkers in cancer, Cell. Mol. Life Sci. 79 (2022) 572, https://doi.org/10.1007/s00018-022-04552-3.
[112] Y. Li, J. Zhao, S. Yu, Z. Wang, X. He, Y. Su, T. Guo, H. Sheng, J. Chen, Q. Zheng, Y. Li, W. Guo, X. Cai, G. Shi, J. Wu, L. Wang, P. Wang, X. He, S. Huang, Extracellular Vesicles Long RNA Sequencing Reveals Abundant mRNA, circRNA, and lncRNA in Human Blood as Potential Biomarkers for Cancer Diagnosis, Clin. Chem. 65 (2019) 798–808, https://doi.org/10.1373/clinchem.2018.301291.
[113] V.M. Conn, A.M. Chinnaiyan, S.J. Conn, Circular RNA in cancer, Nat. Rev. Cancer 24 (2024) 597–613, https://doi.org/10.1038/s41568-024-00721-7.
[114] S. Toden, A. Goel, Non-coding RNAs as liquid biopsy biomarkers in cancer, Br. J. Cancer 126 (2022) 351–360, https://doi.org/10.1038/s41416-021-01672-8.
[115] S. Perales, C. Torres, C. Jimenez-Luna, J. Prados, J. Martinez-Galan, J.M. Sanchez-Manas, O. Caba, Liquid biopsy approach to pancreatic cancer, World, J. Gastrointest. Oncol. 13 (2021) 1263–1287, https://doi.org/10.4251/wjgo.v13.i10.1263.

[116] Y. Xie, X. Yuan, W. Zhou, A.A. Kosiba, H. Shi, J. Gu, Z. Qin, The circular RNA HIPK3 (circHIPK3) and its regulation in cancer progression: Review, Life Sci. 254 (2020) 117252, https://doi.org/10.1016/j.lfs.2019.117252.
[117] Y. Fu, H. Sun, Biogenesis, cellular effects, and biomarker value of circHIPK3, Cancer Cell Int. 21 (2021) 256, https://doi.org/10.1186/s12935-021-01956-2.
[118] S. Liu, Q. Li, Y. Ma, C. Corpe, J. Wang, Circular RNAs as novel potential biomarkers for pancreatic cancer, J. Cancer 12 (2021) 4604–4615, https://doi.org/10.7150/jca.58640.
[119] S.N.A.B.M. Nashruddin, F.H.M. Salleh, R.M. Yunus, H.B. Zaman, Artificial intelligence—powered electrochemical sensor: Recent advances, challenges, and prospects, Heliyon 10 (2024) e37964, https://doi.org/10.1016/j.heliyon.2024.e37964.
[120] S.S. Wang, J. Xu, K.Y. Ji, C.-I. Hwang, Epigenetic Alterations in Pancreatic Cancer Metastasis, Biomolecules 11 (2021) 1082, https://doi.org/10.3390/biom11081082.
[121] M.T.T. Roalsø, Ø.H. Hald, M. Alexeeva, K. Søreide, Emerging Role of Epigenetic Alterations as Biomarkers and Novel Targets for Treatments in Pancreatic Ductal Adenocarcinoma, Cancers (Basel) 14 (2022) 546, https://doi.org/10.3390/cancers14030546.
[122] A. Sadakierska-Chudy, M. Filip, A Comprehensive View of the Epigenetic Landscape. Part II: Histone Post-translational Modification, Nucleosome Level, and Chromatin Regulation by ncRNAs, Neurotox, Res. 27 (2015) 172–197, https://doi.org/10.1007/s12640-014-9508-6.
[123] G. Millán-Zambrano, A. Burton, A.J. Bannister, R. Schneider, Histone post-translational modifications — cause and consequence of genome function, Nat. Rev. Genet. 23 (2022) 563–580, https://doi.org/10.1038/s41576-022-00468-7.
[124] A. Wood, A. Shilatifard, Posttranslational Modifications of Histones by Methylation, in: 2004: pp. 201–222. https://doi.org/10.1016/S0065-3233(04)67008-2.
[125] L. Gan, Y. Yang, Q. Li, Y. Feng, T. Liu, W. Guo, Epigenetic regulation of cancer progression by EZH2: from biological insights to therapeutic potential, Biomark. Res. 6 (2018) 10, https://doi.org/10.1186/s40364-018-0122-2.
[126] N. Kang, M. Eccleston, P.-L. Clermont, M. Latarani, D.K. Male, Y. Wang, F. Crea, EZH2 Inhibition: A Promising Strategy to Prevent Cancer Immune Editing, Epigenomics 12 (2020) 1457–1476, https://doi.org/10.2217/epi-2020-0186.
[127] C.-Y. Hsu, A.N. Mohammed, A. Hjazi, S. Uthirapathy, J.S. Renuka, A. Singh, S. Thyagarajan, H.M.H. Ray, Enhancer zeste homolog 2 (EZH2) targeting by small interfering RNA (siRNA); recent advances and prospect, Naunyn. Schmiedebergs. Arch. Pharmacol. (2025), https://doi.org/10.1007/s00210-025-03883-9.
[128] U. Oleksiewicz, M. Kuciak, A. Jaworska, D. Adamczak, A. Bisok, J. Mierzejewska, J. Sadowska, P. Czerwinska, A.A. Mackiewicz, The Roles of H3K9me3 Writers, Readers, and Erasers in Cancer Immunotherapy, Int. J. Mol. Sci. 25 (2024) 11466, https://doi.org/10.3390/ijms252111466.
[129] Y. Tang, S. Tang, W. Yang, Z. Zhang, T. Wang, Y. Wu, J. Xu, C. Pilarsky, M. Mazzone, L.-W. Wang, Y. Sun, R. Tian, Y. Tang, Y. Wang, C. Wang, J. Xue, MED12 loss activates endogenous retroelements to sensitise immunotherapy in pancreatic cancer, Gut 73 (2024) 1999–2011, https://doi.org/10.1136/gutjnl-2024-332350.
[130] Y. Wang, H. Nie, X. He, Z. Liao, Y. Zhou, J. Zhou, C. Ou, The emerging role of super enhancer-derived noncoding RNAs in human cancer, Theranostics 10 (2020) 11049–11062, https://doi.org/10.7150/thno.49168.
[131] G. Pisignano, D.C. Michael, T.H. Visal, R. Pirlog, M. Ladomery, G.A. Calin, Going circular: history, present, and future of circRNAs in cancer, Oncogene 42 (2023) 2783–2800, https://doi.org/10.1038/s41388-023-02780-w.
[132] Y. Ma, Y. Di, Q. Li, Q. Zhan, X. He, S. Liu, H. Zou, C. Corpe, L. Chen, J. Wang, LncRNAs as epigenetic regulators of epithelial to mesenchymal transition in pancreatic cancer, Discov. Oncol. 13 (2022) 61, https://doi.org/10.1007/s12672-022-00522-0.
[133] K. Fu, J. Su, Y. Zhou, X. Chen, X. Hu, The role of epigenetic regulation in pancreatic ductal adenocarcinoma progression and drug response: an integrative genomic and pharmacological prognostic prediction model, Front. Pharmacol. 15 (2024), https://doi.org/10.3389/fphar.2024.1498031.
[134] K. Asada, S. Kaneko, K. Takasawa, H. Machino, S. Takahashi, N. Shinkai, R. Shimoyama, M. Komatsu, R. Hamamoto, Integrated Analysis of Whole Genome and Epigenome Data Using Machine Learning Technology: Toward the Establishment of Precision Oncology, Front. Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.666937.
[135] L. Wang, Z. Liu, R. Liang, W. Wang, R. Zhu, J. Li, Z. Xing, S. Weng, X. Han, Y. Sun, Comprehensive machine-learning survival framework develops a consensus model in large-scale multicenter cohorts for pancreatic cancer, Elife 11 (2022), https://doi.org/10.7554/eLife.80150.
[136] Y.H. Choi, T.H. Hong, S.B. Yoon, I.S. Lee, M.A. Lee, H.J. Choi, M.H. Choi, E. S. Jung, Prognostic Implications of Portal Venous Circulating Tumor Cells in Resectable Pancreatic Cancer, Biomedicines 10 (2022) 1289, https://doi.org/10.3390/biomedicines10061289.
[137] M.J. Amaral, R.C. Oliveira, P. Donato, J.G. Tralhão, Pancreatic Cancer Biomarkers: Oncogenic Mutations, Tissue and Liquid Biopsies, and Radiomics—A Review, Dig. Dis. Sci. 68 (2023) 2811–2823, https://doi.org/10.1007/s10620-023-07904-6.
[138] D. Lin, L. Shen, M. Luo, K. Zhang, J. Li, Q. Yang, F. Zhu, D. Zhou, S. Zheng, Y. Chen, J. Zhou, Circulating tumor cells: biology and clinical significance, Signal Transduct. Target. Ther. 6 (2021) 404, https://doi.org/10.1038/s41392-021-00817-8.
[139] P. Paterlini-Brechot, N.L. Benali, Circulating tumor cells (CTC) detection: Clinical impact and future directions, Cancer Lett. 253 (2007) 180–204, https://doi.org/10.1016/j.canlet.2006.12.014.
[140] R. Harouaka, Z. Kang, S.-Y. Zheng, L. Cao, Circulating tumor cells: Advances in isolation and analysis, and challenges for clinical applications, Pharmacol. Ther. 141 (2014) 209–221, https://doi.org/10.1016/j.pharmthera.2013.10.004.
[141] S. Ju, C. Chen, J. Zhang, L. Xu, X. Zhang, Z. Li, Y. Chen, J. Zhou, F. Ji, L. Wang, Detection of circulating tumor cells: opportunities and challenges, Biomark. Res. 10 (2022) 58, https://doi.org/10.1186/s40364-022-00403-2.
[142] T.A. Allen, The Role of Circulating Tumor Cells as a Liquid Biopsy for Cancer: Advances, Biology, Technical Challenges, and Clinical Relevance, Cancers (Basel) 16 (2024) 1377, https://doi.org/10.3390/cancers16071377.
[143] H. Chen, Y. Li, Z. Zhang, S. Wang, Immunomagnetic separation of circulating tumor cells with microfluidic chips and their clinical applications, Biomicrofluidics 14 (2020), https://doi.org/10.1063/5.0005373.
[144] M.A.M. Gijs, F. Lacharme, U. Lehmann, Microfluidic Applications of Magnetic Particles for Biological Analysis and Catalysis, Chem. Rev. 110 (2010) 1518–1563, https://doi.org/10.1021/cr9001929.
[145] K.H. Lee, H. Park, M. Hwang, Immunomagnetic nanoparticle-based assays for detection of biomarkers, Int. J. Nanomedicine (2013) 4543, https://doi.org/10.2147/IJN.S51893.
[146] M.S. Brown, K.E. Muller, D.R. Pattabiraman, Quantifying the Epithelial-to-Mesenchymal Transition (EMT) from Bench to Bedside, Cancers (Basel) 14 (2022) 1138, https://doi.org/10.3390/cancers14051138.
[147] S. Wu, S. Liu, Z. Liu, J. Huang, X. Pu, J. Li, D. Yang, H. Deng, N. Yang, J. Xu, Classification of Circulating Tumor Cells by Epithelial-Mesenchymal Transition Markers, PLoS One 10 (2015) e0123976, https://doi.org/10.1371/journal.pone.0123976.
[148] Q. Huang, Y. Wang, X. Chen, Y. Wang, Z. Li, S. Du, L. Wang, S. Chen, Nanotechnology-Based Strategies for Early Cancer Diagnosis Using Circulating Tumor Cells as a Liquid Biopsy, Nanotheranostics 2 (2018) 21–41, https://doi.org/10.7150/ntno.22091.
[149] J. Yu, G. Gemenetzis, B. Kinny-Köster, J.R. Habib, V.P. Groot, J. Teinor, L. Yin, N. Pu, A. Hasanain, F. van Oosten, A.A. Javed, M.J. Weiss, R.A. Burkhart, W. R. Burns, M. Goggins, J. He, C.L. Wolfgang, Pancreatic circulating tumor cell detection by targeted single-cell next-generation sequencing, Cancer Lett. 493 (2020) 245–253, https://doi.org/10.1016/j.canlet.2020.08.043.
[150] T. Okabe, S. Togo, Y. Fujimoto, J. Watanabe, I. Sumiyoshi, A. Orimo, K. Takahashi, Mesenchymal Characteristics and Predictive Biomarkers on Circulating Tumor Cells for Therapeutic Strategy, Cancers (Basel) 12 (2020) 3588, https://doi.org/10.3390/cancers12123588.
[151] E.M. Trifylli, A.G. Kriebardis, E. Koustas, N. Papadopoulos, S.P. Fortis, V. L. Tzounakas, A.T. Anastasiadi, P. Sarantis, S. Vasileiadi, A. Tsagarakis, G. Aloizos, S. Manolakopoulos, M. Deutsch, A Current Synopsis of the Emerging Role of Extracellular Vesicles and Micro-RNAs in Pancreatic Cancer: A Forward-Looking Plan for Diagnosis and Treatment, Int. J. Mol. Sci. 25 (2024) 3406, https://doi.org/10.3390/ijms25063406.
[152] J.P. Hinestrosa, R. Kurzrock, J.M. Lewis, N.J. Schork, G. Schroeder, A.M. Kamat, A.M. Lowy, R.N. Eskander, O. Perrera, D. Searson, K. Rastegar, J.R. Hughes, V. Ortiz, I. Clark, H.I. Balcer, L. Arakelyan, R. Turner, P.R. Billings, M.J. Adler, S. M. Lippman, R. Krishnan, Early-stage multi-cancer detection using an extracellular vesicle protein-based blood test, Commun. Med. 2 (2022) 29, https://doi.org/10.1038/s43856-022-00088-6.
[153] S. Liu, Y. Liao, H. Hosseinifard, S. Imani, Q. Wen, Diagnostic Role of Extracellular Vesicles in Cancer: A Comprehensive Systematic Review and Meta-Analysis, Front. Cell Dev. Biol. 9 (2021), https://doi.org/10.3389/fcell.2021.705791.
[154] Y. Hong, J. Yang, X. Liu, S. Huang, T. Liang, X. Bai, Deciphering extracellular vesicles protein cargo in pancreatic cancer, Biochim. Biophys. Acta - Rev. Cancer 1879 (2024) 189142, https://doi.org/10.1016/j.bbcan.2024.189142.
[155] J.L. Petrick, A.A. Florio, J. Zen, Y. Wang, A.T. Gewirtz, R.M. Pfeiffer, S. Loftus, J. Inglefield, J. Koshiol, B. Yang, K. Yu, A. Hildesheim, C. Chen, H. Yang, M. Lee, K.A. McGlynn, Biomarkers of gut barrier dysfunction and risk of hepatocellular carcinoma in the <scp>REVEAL-HBV</scp> and <scp>REVEAL-HCV</scp> cohort studies, Int. J. Cancer 153 (2023) 44–53, https://doi.org/10.1002/ijc.34492.
[156] S.A. Melo, L.B. Luecke, C. Kahlert, A.F. Fernandez, S.T. Gammon, J. Kaye, V. S. LeBleu, E.A. Mittendorf, J. Weitz, N. Rahbari, C. Reissfelder, C. Pilarsky, M. F. Fraga, D. Piwnica-Worms, R. Kalluri, Glypican-1 identifies cancer exosomes and detects early pancreatic cancer, Nature 523 (2015) 177–182, https://doi.org/10.1038/nature14581.
[157] H. Kosanam, I. Prassas, C.C. Chrystoja, I. Soleas, A. Chan, A. Dimitromanolakis, I. M. Blasutig, F. Rückert, R. Gruetzmann, C. Pilarsky, M. Maekawa, R. Brand, E. P. Diamandis, Laminin, gamma 2 (LAMC2): A Promising New Putative Pancreatic Cancer Biomarker Identified by Proteomic Analysis of Pancreatic Adenocarcinoma Tissues, Mol. Cell. Proteomics 12 (2013) 2820–2832, https://doi.org/10.1074/mcp.M112.023507.
[158] Y. Okada, N. Takahashi, T. Takayama, A. Goel, LAMC2 promotes cancer progression and gemcitabine resistance through modulation of EMT and ATP-binding cassette transporters in pancreatic ductal adenocarcinoma, Carcinogenesis 42 (2021) 546–556, https://doi.org/10.1093/carcin/bgab011.
[159] T. Yin, L. Xu, B. Gil, N. Merali, M.S. Sokolikova, D.C.A. Gaboriau, D.S.K. Liu, A. N. Muhammad Mustafa, S. Alodan, M. Chen, O. Txoperena, M. Arrastua, J. M. Gomez, N. Ontoso, M. Elicegui, E. Torres, D. Li, C. Mattevi, A.E. Frampton, L. R. Jiao, S. Ramadan, N. Klein, Graphene Sensor Arrays for Rapid and Accurate Detection of Pancreatic Cancer Exosomes in Patients' Blood Plasma Samples, ACS Nano 17 (2023) 14619–14631, https://doi.org/10.1021/acsnano.3c01812.
[160] Y. Zhang, J. Jiao, Y. Wei, D. Wang, C. Yang, Z. Xu, Plasmonic Colorimetric Biosensor for Sensitive Exosome Detection via Enzyme-Induced Etching of Gold

Nanobipyramid@MnO 2 Nanosheet Nanostructures, Anal. Chem. 92 (2020) 15244–15252, https://doi.org/10.1021/acs.analchem.0c04136.
[161] T.Y.S. Le Large, L.L. Meijer, R. Paleckyte, L.N.C. Boyd, B. Kok, T. Wurdinger, T. Schelfhorst, S.R. Piersma, T.V. Pham, N.C.T. van Grieken, B.M. Zonderhuis, F. Daams, H.W.M. van Laarhoven, M.F. Bijlsma, C.R. Jimenez, E. Giovannetti, G. Kazemier, Combined Expression of Plasma Thrombospondin-2 and CA19-9 for Diagnosis of Pancreatic Cancer and Distal Cholangiocarcinoma: A Proteome Approach, e634-e43, Oncologist 25 (2020), https://doi.org/10.1634/theoncologist.2019-0680.
[162] B. Farrow, D. Albo, D.H. Berger, The Role of the Tumor Microenvironment in the Progression of Pancreatic Cancer, J. Surg. Res. 149 (2008) 319–328, https://doi.org/10.1016/j.jss.2007.12.757.
[163] T.P. Radon, N.J. Massat, R. Jones, W. Alrawashdeh, L. Dumartin, D. Ennis, S. W. Duffy, H.M. Kocher, S.P. Pereira, L. Guarner (posthumous), C. Murta-Nascimento, F.X. Real, N. Malats, J. Neoptolemos, E. Costello, W. Greenhalf, N. R. Lemoine, T. Crnogorac-Jurcevic, Identification of a Three-Biomarker Panel in Urine for Early Detection of Pancreatic Adenocarcinoma, Clin. Cancer Res. 21 (2015) 3512–3521, https://doi.org/10.1158/1078-0432.CCR-14-2467.
[164] D. Li, H. Chen, K. Fan, V. Labunov, S. Lazarouk, X. Yue, C. Liu, X. Yang, L. Dong, G. Wang, A supersensitive silicon nanowire array biosensor for quantitating tumor marker ctDNA, Biosens. Bioelectron. 181 (2021) 113147, https://doi.org/10.1016/j.bios.2021.113147.
[165] V.R. Kumar, N.C. Kampan, N.H. Abd Aziz, C.K. Teik, M.N. Shafiee, P.S. Menon, Recent Advances in Surface Plasmon Resonance (SPR) Technology for Detecting Ovarian Cancer Biomarkers, Cancers (Basel) 15 (2023) 5607, https://doi.org/10.3390/cancers15235607.
[166] J. Swierczynski, Role of abnormal lipid metabolism in development, progression, diagnosis and therapy of pancreatic cancer, World J. Gastroenterol. 20 (2014) 2279, https://doi.org/10.3748/wjg.v20.i9.2279.
[167] G. Pascual, B. Majem, S.A. Benitah, Targeting lipid metabolism in cancer metastasis, Biochim. Biophys. Acta - Rev. Cancer 1879 (2024) 189051, https://doi.org/10.1016/j.bbcan.2023.189051.
[168] R.A. Gaiser, A. Pessia, Z. Ateeb, H. Davanian, C. Fernández Moro, H. Alkharaan, K. Healy, S. Ghazi, U. Arnelo, R. Valente, V. Velagapudi, M. Sällberg Chen, M., Del Chiaro, Integrated targeted metabolomic and lipidomic analysis: A novel approach to classifying early cystic precursors to invasive pancreatic cancer, Sci. Rep. 9 (2019) 10208, https://doi.org/10.1038/s41598-019-46634-6.
[169] D. Wolrab, R. Jirásko, E. Cífková, M. Höring, D. Mei, M. Chocholoušková, O. Peterka, J. Idkowiak, T. Hrnčiarová, L. Kuchař, R. Ahrends, R. Brumarová, D. Friedecký, G. Vivo-Truyols, P. Škrha, J. Škrha, R. Kučera, B. Melichar, G. Liebisch, R. Burkhardt, M.R. Wenk, A. Cazenave-Gassiot, P. Karásek, I. Novotný, K. Greplová, R. Hrstka, M. Holčapek, Lipidomic profiling of human serum enables detection of pancreatic cancer, Nat. Commun. 13 (2022) 124, https://doi.org/10.1038/s41467-021-27765-9.
[170] X. Li, Y. Du, W. Jiang, S. Dong, W. Li, H. Tang, J. Yi, W. Zhou, H. Zhang, Integrated transcriptomics, proteomics and metabolomics-based analysis uncover TAM2-associated glycolysis and pyruvate metabolic remodeling in pancreatic cancer, Front. Immunol. 14 (2023), https://doi.org/10.3389/fimmu.2023.1170223.
[171] Y. Fu, T. Zou, X. Shen, P.J. Nelson, J. Li, C. Wu, J. Yang, Y. Zheng, C. Bruns, Y. Zhao, L. Qin, Q. Dong, Lipid metabolism in cancer progression and therapeutic strategies, MedComm 2 (2021) 27–59, https://doi.org/10.1002/mco2.27.
[172] Y. Zhou, L. Tao, J. Qiu, J. Xu, X. Yang, Y. Zhang, X. Tian, X. Guan, X. Cen, Y. Zhao, Tumor biomarkers for diagnosis, prognosis and targeted therapy, Signal Transduct. Target. Ther. 9 (2024) 132, https://doi.org/10.1038/s41392-024-01823-2.
[173] U. Ungkulpasvich, H. Hatakeyama, T. Hirotsu, E. di Luccio, Pancreatic Cancer and Detection Methods, Biomedicines 11 (2023) 2557, https://doi.org/10.3390/biomedicines11092557.
[174] X. Wang, J. Yang, B. Ren, G. Yang, X. Liu, R. Xiao, J. Ren, F. Zhou, L. You, Y. Zhao, Comprehensive multi-omics profiling identifies novel molecular subtypes of pancreatic ductal adenocarcinoma, Genes Dis. 11 (2024) 101143, https://doi.org/10.1016/j.gendis.2023.101143.
[175] F. Vitale, L. Zileri Dal Verme, M. Paratore, M. Negri, E.C. Nista, M.E. Ainora, G. Esposto, I. Mignini, R. Borriello, L. Galasso, S. Alfieri, A. Gasbarrini, M. A. Zocco, A. Nicoletti, The Past, Present, and Future of Biomarkers for the Early Diagnosis of Pancreatic Cancer, Biomedicines 12 (2024) 2840, https://doi.org/10.3390/biomedicines12122840.
[176] B. Yu, S. Shao, W. Ma, Frontiers in pancreatic cancer on biomarkers, microenvironment, and immunotherapy, Cancer Lett. 610 (2025) 217350, https://doi.org/10.1016/j.canlet.2024.217350.
[177] M.V. García-Ortiz, P. Cano-Ramírez, M. Toledano-Fonseca, E. Aranda, A. Rodríguez-Ariza, Diagnosing and monitoring pancreatic cancer through cell-free DNA methylation: progress and prospects, Biomark. Res. 11 (2023) 88, https://doi.org/10.1186/s40364-023-00528-y.
[178] M. Gallo, R.M. Ruggeri, G. Muscogiuri, G. Pizza, A. Faggiano, A. Colao, Diabetes and pancreatic neuroendocrine tumours: Which interplays, if any? Cancer Treat. Rev. 67 (2018) 1–9, https://doi.org/10.1016/j.ctrv.2018.04.013.
[179] R. Mazzilli, V. Zamponi, C. Mancini, B. Giorgini, B. Golisano, N. Mikovic, G. Pecora, F. Russo, M. Martiradonna, P. Paravani, D. Prosperi, A. Faggiano, Neuroendocrine tumors and diabetes mellitus: which treatment and which effect, Endocrine 88 (2025) 36–50, https://doi.org/10.1007/s12020-024-04149-9.
[180] T. Salvatore, R. Marfella, M.R. Rizzo, F.C. Sasso, Pancreatic cancer and diabetes: A two-way relationship in the perspective of diabetologist, S72-S7, Int. J. Surg. 21 (2015), https://doi.org/10.1016/j.ijsu.2015.06.063.
[181] B. Biadgo, M. Abebe, Type 2 Diabetes Mellitus and Its Association with the Risk of Pancreatic Carcinogenesis: A Review, Korean J. Gastroenterol. 67 (2016) 168, https://doi.org/10.4166/kjg.2016.67.4.168.
[182] S.-C. Chang, W.-C.-V. Yang, Hyperglycemia, tumorigenesis, and chronic inflammation, Crit. Rev. Oncol. Hematol. 108 (2016) 146–153, https://doi.org/10.1016/j.critrevonc.2016.11.003.
[183] P. Ramteke, A. Deb, V. Shepal, M.K. Bhat, Hyperglycemia Associated Metabolic and Molecular Alterations in Cancer Risk, Progression, Treatment, and Mortality, Cancers (Basel) 11 (2019) 1402, https://doi.org/10.3390/cancers11091402.
[184] J.-X. Hu, C.-F. Zhao, W.-B. Chen, Q.-C. Liu, Q.-W. Li, Y.-Y. Lin, F. Gao, Pancreatic cancer: A review of epidemiology, trend, and risk factors, World J. Gastroenterol. 27 (2021) 4298–4321, https://doi.org/10.3748/wjg.v27.i27.4298.
[185] J. Wu, L. Tang, F. Zheng, X. Chen, L. Li, A review of the last decade: pancreatic cancer and type 2 diabetes, Arch. Physiol. Biochem. 130 (2024) 660–668, https://doi.org/10.1080/13813455.2023.2252204.
[186] W. Chen, B. Zhou, T.Q. Luong, E. Lustigova, F. Xie, L.M. Matrisian, B.U. Wu, Prediction of pancreatic cancer in patients with new onset hyperglycemia: A modified ENDPAC model, Pancreatology 24 (2024) 1115–1122, https://doi.org/10.1016/j.pan.2024.09.015.
[187] D. Jin, N.U. Khan, W. Gu, H. Lei, A. Goel, T. Chen, Informatics strategies for early detection and risk mitigation in pancreatic cancer patients, Neoplasia 60 (2025) 101129, https://doi.org/10.1016/j.neo.2025.101129.
[188] D. Li, Diabetes and pancreatic cancer, Mol. Carcinog. 51 (2012) 64–74, https://doi.org/10.1002/mc.20771.
[189] S.T. Chari, Detecting Early Pancreatic Cancer: Problems and Prospects, Semin. Oncol. 34 (2007) 284–294, https://doi.org/10.1053/j.seminoncol.2007.05.005.
[190] R. Ruze, J. Song, X. Yin, Y. Chen, R. Xu, C. Wang, Y. Zhao, Mechanisms of obesity- and diabetes mellitus-related pancreatic carcinogenesis: a comprehensive and systematic review, Signal Transduct. Target. Ther. 8 (2023) 139, https://doi.org/10.1038/s41392-023-01376-w.
[191] X. Shi, X. Wang, W. Yao, D. Shi, X. Shao, Z. Lu, Y. Chai, J. Song, W. Tang, X. Wang, Mechanism insights and therapeutic intervention of tumor metastasis: latest developments and perspectives, Signal Transduct. Target. Ther. 9 (2024) 192, https://doi.org/10.1038/s41392-024-01885-2.
[192] N. Vitorakis, A.N. Gargalionis, K.A. Papavassiliou, C. Adamopoulos, A. G. Papavassiliou, Precision Targeting Strategies in Pancreatic Cancer: The Role of Tumor Microenvironment, Cancers (Basel) 16 (2024) 2876, https://doi.org/10.3390/cancers16162876.
[193] E. Vernucci, J. Abrego, V. Gunda, S.K. Shukla, A. Dasgupta, V. Rai, N. Chaika, K. Buettner, A. Illies, F. Yu, A.J. Lazenby, B.J. Swanson, P.K. Singh, Metabolic Alterations in Pancreatic Cancer Progression, Cancers (Basel) 12 (2019) 2, https://doi.org/10.3390/cancers12010002.
[194] S. Fu, S. Xu, S. Zhang, The role of amino acid metabolism alterations in pancreatic cancer: From mechanism to application, Biochim. Biophys. Acta - Rev. Cancer 1878 (2023) 188893, https://doi.org/10.1016/j.bbcan.2023.188893.
[195] H.-L. Gao, W.-Q. Wang, X.-J. Yu, L. Liu, Molecular drivers and cells of origin in pancreatic ductal adenocarcinoma and pancreatic neuroendocrine carcinoma, Exp. Hematol. Oncol. 9 (2020) 28, https://doi.org/10.1186/s40164-020-00184-0.
[196] E. Pelosi, G. Castelli, U. Testa, Pancreatic Cancer: Molecular Characterization, Clonal Evolution and Cancer Stem Cells, Biomedicines 5 (2017) 65, https://doi.org/10.3390/biomedicines5040065.
[197] A. Cacciato Insilla, M. Giordano, D. Campani, Molecular Pathology of Pancreatic Ductal Adenocarcinoma, in: 2022: pp. 130–132. https://doi.org/10.1007/978-3-030-62416-3_5572.
[198] M. Bevere, A. Gkountakos, F.M. Martelli, A. Scarpa, C. Luchini, M. Simbolo, An Insight on Functioning Pancreatic Neuroendocrine Neoplasms, Biomedicines 11 (2023) 303, https://doi.org/10.3390/biomedicines11020303.
[199] A. Viúdez, A. De Jesus-Acosta, F.L. Carvalho, R. Vera, S. Martín-Algarra, N. Ramírez, Pancreatic neuroendocrine tumors: Challenges in an underestimated disease, Crit. Rev. Oncol. Hematol. 101 (2016) 193–206, https://doi.org/10.1016/j.critrevonc.2016.03.013.
[200] H. Yang, W. Li, L. Ren, Y. Yang, Y. Zhang, B. Ge, S. Li, X. Zheng, J. Liu, S. Zhang, G. Du, B. Tang, H. Wang, J. Wang, Progress on diagnostic and prognostic markers of pancreatic cancer, Oncol. Res. 31 (2023) 83–99. https://doi.org/10.32604/or.2023.028905.
[201] J. Belkhouribchia, Artificial intelligence is going to transform the field of endocrinology: an overview, Front. Endocrinol. (lausanne). 16 (2025), https://doi.org/10.3389/fendo.2025.1513929.
[202] F. Giorgini, G. Di Dalmazi, S. Diciotti, Artificial intelligence in endocrinology: a comprehensive review, J. Endocrinol. Invest. 47 (2023) 1067–1082, https://doi.org/10.1007/s40618-023-02235-9.
[203] Y. Kumari, P. Bai, F. Waqar, A.T. Asif, B. Irshad, S. Raj, V. Varagantiwar, M. Kumar, F. Neha, S. Chand, S. Kumar, G. Varrassi, M. Khatri, T. Mohamad, Advancements in the Management of Endocrine System Disorders and Arrhythmias: A Comprehensive Narrative Review, Cureus (2023), https://doi.org/10.7759/cureus.46484.
[204] R.M.A. Bin Qadir, M. Bin Umair, U. Bin Tariq, A. Ahmad, W. Kiran, M.H. Shahid, Unraveling Pancreatic Cancer: Epidemiology, Risk Factors, and Global Trends, Cureus (2024), https://doi.org/10.7759/cureus.72816.
[205] C.J. Cabasag, M. Arnold, M. Rutherford, A. Bardot, J. Ferlay, E. Morgan, A. Little, P. De, E. Dixon, R.R. Woods, N. Saint-Jacques, S. Evans, G. Engholm, M. Elwood, N. Merrett, D. Ransom, D.L. O'Connell, F. Bray, I. Soerjomataram, Pancreatic cancer survival by stage and age in seven high-income countries (ICBP SURVMARK-2): a population-based study, Br. J. Cancer 126 (2022) 1774–1782, https://doi.org/10.1038/s41416-022-01752-3.

[206] M.A. Morales, J.M. Halpern, Guide to Selecting a Biorecognition Element for Biosensors, Bioconjug. Chem. 29 (2018) 3231–3239, https://doi.org/10.1021/acs.bioconjchem.8b00592.
[207] P. Sousa, L. Silva, J.S. Câmara, P. Guedes de Pinho, R. Perestrelo, Integrating OMICS-based platforms and analytical tools for diagnosis and management of pancreatic cancer: a review, Mol. Omi. 21 (2025) 108–121, https://doi.org/10.1039/D4MO00187G.
[208] S. Li, Z. Chen, F. Yang, W. Yue, Emerging two-dimensional materials for analytical lab-on-chip platforms: A review of electrochemical and optical biosensor, Microchem. J. 194 (2023) 109247, https://doi.org/10.1016/j.microc.2023.109247.
[209] S.R.S. Pour, D. Calabria, A. Emamiamin, E. Lazzarini, A. Pace, M. Guardigli, M. Zangheri, M. Mirasoli, Electrochemical vs, Optical Biosensors for Point-of-Care Applications: A Critical Review, Chemosensors 11 (2023) 546, https://doi.org/10.3390/chemosensors11100546.
[210] M.Y. Azab, M.F.O. Hameed, S.S.A. Obayya, Overview of Optical Biosensors for Early Cancer Detection: Fundamentals, Applications and Future Perspectives, Biology (basel). 12 (2023) 232, https://doi.org/10.3390/biology12020232.
[211] F. Mi, C. Hu, Y. Wang, L. Wang, F. Peng, P. Geng, M. Guan, Recent advancements in microfluidic chip biosensor detection of foodborne pathogenic bacteria: a review, Anal. Bioanal. Chem. 414 (2022) 2883–2902, https://doi.org/10.1007/s00216-021-03872-w.
[212] A.C. Carpenter, I.T. Paulsen, T.C. Williams, Blueprints for Biosensors: Design, Limitations, and Applications, Genes (Basel) 9 (2018) 375, https://doi.org/10.3390/genes9080375.
[213] G. Luka, A. Ahmadi, H. Najjaran, E. Alocilja, M. DeRosa, K. Wolthers, A. Malki, H. Aziz, A. Althani, M. Hoorfar, Microfluidics Integrated Biosensors: A Leading Technology towards Lab-on-a-Chip and Sensing Applications, Sensors 15 (2015) 30011–30031, https://doi.org/10.3390/s151229783.
[214] S. Vigneshvar, C.C. Sudhakumari, B. Senthilkumaran, H. Prakash, Recent Advances in Biosensor Technology for Potential Applications – An Overview, Front. Bioeng. Biotechnol. 4 (2016), https://doi.org/10.3389/fbioe.2016.00011.
[215] T.-T. Wang, X.-F. Huang, H. Huang, P. Luo, L.-S. Qing, Nanomaterial-based optical- and electrochemical-biosensors for urine glucose detection: A comprehensive review, Adv. Sens. Energy Mater. 1 (2022) 100016, https://doi.org/10.1016/j.asems.2022.100016.
[216] U. Farahdina, T. Amrillah, M. Mashuri, V.S. Lee, A. Rubiyanto, N. Nasori, Overview of novel nanobiosensors for electrochemical and optical diagnosis of leukemia: Challenge and opportunity, J. Innov. Opt. Health Sci. 17 (2024), https://doi.org/10.1142/S1793545824300039.
[217] M. Hemdan, M.A. Ali, A.S. Doghish, S.S.A. Mageed, I.M. Elazab, M.M. Khalil, M. Mabrouk, D.B. Das, A.S. Amin, Innovations in Biosensor Technologies for Healthcare Diagnostics and Therapeutic Drug Monitoring: Applications, Recent Progress, and Future Research Challenges, Sensors 24 (2024) 5143, https://doi.org/10.3390/s24165143.
[218] L. Fu, H. Karimi-Maleh, Leveraging electrochemical sensors to improve efficiency of cancer detection, World, J. Clin. Oncol. 15 (2024) 360–366, https://doi.org/10.5306/wjco.v15.i3.360.
[219] T.N.L. Pham, S.H. Nguyen, M.T. Tran, A comprehensive review of transduction methods of lectin-based biosensors in biomedical applications, Heliyon 10 (2024) e38371, https://doi.org/10.1016/j.heliyon.2024.e38371.
[220] E.O. Polat, M.M. Cetin, A.F. Tabak, E. Bilget Güven, B.Ö. Uysal, T. Arsan, A. Kabbani, H. Hamed, S.B. Gül, Transducer Technologies for Biosensors and Their Wearable Applications, Biosensors 12 (2022) 385, https://doi.org/10.3390/bios12060385.
[221] W. Rudolf Seitz, Transducer mechanisms for optical biosensors. Part 1: The chemistry of transduction, Comput. Methods Programs Biomed. 30 (1989) 9–19, https://doi.org/10.1016/0169-2607(89)90118-1.
[222] D. Grieshaber, R. MacKenzie, J. Vörös, E. Reimhult, Electrochemical Biosensors - Sensor Principles and Architectures, Sensors 8 (2008) 1400–1458, https://doi.org/10.3390/s80314000.
[223] W. Yang, R.Y. Lai, Integration of two different sensing modes in an electrochemical DNA sensor for approximation of target mismatch location, Electrochem. Commun. 13 (2011) 989–992, https://doi.org/10.1016/j.elecom.2011.06.020.
[224] E. González-Fernández, N. Avlonitis, A.F. Murray, A.R. Mount, M. Bradley, Methylene blue not ferrocene: Optimal reporters for electrochemical detection of protease activity, Biosens. Bioelectron. 84 (2016) 82–88, https://doi.org/10.1016/j.bios.2015.11.088.
[225] E. Heydari-Bafrooei, A.A. Ensafi, Nanomaterials-based biosensing strategies for biomarkers diagnosis, a review, Biosens. Bioelectron. X 13 (2023) 100245, https://doi.org/10.1016/j.biosx.2022.100245.
[226] E.T.S.G. da Silva, D.E.P. Souto, J.T.C. Barragan, J.de F. Giarola, A.C.M. de Moraes, L.T. Kubota, Electrochemical Biosensors in Point-of-Care Devices: Recent Advances and Future Trends, ChemElectroChem 4 (2017) 778–794, https://doi.org/10.1002/celc.201600758.
[227] F. Faridbod, V.K. Gupta, H.A. Zamani, Electrochemical Sensors and Biosensors, Int. J. Electrochem. 2011 (2011) 1–2, https://doi.org/10.4061/2011/352546.
[228] V. Naresh, N. Lee, A Review on Biosensors and Recent Development of Nanostructured Materials-Enabled Biosensors, Sensors 21 (2021) 1109, https://doi.org/10.3390/s21041109.
[229] F. Huang, Y. Zhang, J. Lin, Y. Liu, Biosensors Coupled with Signal Amplification Technology for the Detection of Pathogenic Bacteria: A Review, Biosensors 11 (2021) 190, https://doi.org/10.3390/bios11060190.
[230] D.R. Thévenot, K. Toth, R.A. Durst, G.S. Wilson, Electrochemical biosensors: recommended definitions and classification1International Union of Pure and Applied Chemistry: Physical Chemistry Division, Commission I.7 (Biophysical Chemistry); Analytical Chemistry Division, Commission vol 5 (Electroanalytical, Biosens. Bioelectron. 16 (2001) 121–131, https://doi.org/10.1016/S0956-5663(01)00115-4.
[231] A. Kaushal, N. Kaur, S. Sharma, A. Sharma, D. Kala, H. Prakash, S. Gupta, Current Update on Biomarkers for Detection of Cancer: Comprehensive Analysis, Vaccines 10 (2022) 2138, https://doi.org/10.3390/vaccines10122138.
[232] Introduction: Principles and Concepts, in: 2008: pp. 1–10. https://doi.org/10.1007/978-0-387-75936-4_1.
[233] B.D. Leca-Bouvier, L.J. Blum, Enzyme for Biosensing Applications, in: Recognit. Recept. Biosens., Springer New York, New York, NY, 2010: pp. 177–220. https://doi.org/10.1007/978-1-4419-0919-0_4.
[234] O. Smutok, E. Katz, Biosensors: Electrochemical Devices—General Concepts and Performance, Biosensors 13 (2022) 44, https://doi.org/10.3390/bios13010044.
[235] B. Bucur, C. Purcarea, S. Andreescu, A. Vasilescu, Addressing the Selectivity of Enzyme Biosensors: Solutions and Perspectives, Sensors 21 (2021) 3038, https://doi.org/10.3390/s21093038.
[236] B. Sequeira-Antunes, H.A. Ferreira, Nucleic Acid Aptamer-Based Biosensors: A Review, Biomedicines 11 (2023) 3201, https://doi.org/10.3390/biomedicines11123201.
[237] M. Domsicova, J. Korcekova, A. Poturnayova, A. Breier, New Insights into Aptamers: An Alternative to Antibodies in the Detection of Molecular Biomarkers, Int. J. Mol. Sci. 25 (2024) 6833, https://doi.org/10.3390/ijms25136833.
[238] J. Zhou, J. Rossi, Aptamers as targeted therapeutics: current potential and challenges, Nat. Rev. Drug Discov. 16 (2017) 181–202, https://doi.org/10.1038/nrd.2016.199.
[239] Y. Li, D. Zhang, X. Zeng, C. Liu, Y. Wu, C. Fu, Advances in Aptamer-Based Biosensors for the Detection of Foodborne Mycotoxins, Molecules 29 (2024) 3974, https://doi.org/10.3390/molecules29163974.
[240] E.M. McConnell, J. Nguyen, Y. Li, Aptamer-Based Biosensors for Environmental Monitoring, Front. Chem. 8 (2020), https://doi.org/10.3389/fchem.2020.00434.
[241] A. Curulli, Nanomaterials in Electrochemical Sensing Area: Applications and Challenges in Food Analysis, Molecules 25 (2020) 5759, https://doi.org/10.3390/molecules25235759.
[242] A. Curulli, Functional Nanomaterials Enhancing Electrochemical Biosensors as Smart Tools for Detecting Infectious Viral Diseases, Molecules 28 (2023) 3777, https://doi.org/10.3390/molecules28093777.
[243] X. Liu, L. Huang, K. Qian, Nanomaterial-Based Electrochemical Sensors: Mechanism, Preparation, and Application in Biomedicine, Adv. Nanobiomed Res. 1 (2021), https://doi.org/10.1002/anbr.202000104.
[244] M. Ramya, P. Senthil Kumar, G. Rangasamy, V. Uma shankar, G. Rajesh, K. Nirmala, A. Saravanan, A. Krishnapandi, A recent advancement on the applications of nanomaterials in electrochemical sensors and biosensors, Chemosphere 308 (2022) 136416, https://doi.org/10.1016/j.chemosphere.2022.136416.
[245] M. Ramesh, R. Janani, C. Deepa, L. Rajeshkumar, Nanotechnology-Enabled Biosensors: A Review of Fundamentals, Design Principles, Materials, and Applications, Biosensors 13 (2022) 40, https://doi.org/10.3390/bios13010040.
[246] Z.A. Qureshi, H. Dabash, D. Ponnamma, M.K.G. Abbas, Carbon dots as versatile nanomaterials in sensing and imaging: Efficiency and beyond, Heliyon 10 (2024) e31634, https://doi.org/10.1016/j.heliyon.2024.e31634.
[247] B.D. Malhotra, M.A. Ali, Nanomaterials in Biosensors, in, Nanomater. Biosens., Elsevier (2018) 1–74, https://doi.org/10.1016/B978-0-323-44923-6.00001-7.
[248] A.I. Barbosa, R. Rebelo, R.L. Reis, M. Bhattacharya, V.M. Correlo, Current nanotechnology advances in diagnostic biosensors, Med. DEVICES SENSORS 4 (2021), https://doi.org/10.1002/mds3.10156.
[249] M. Holzinger, A. Le Goff, S. Cosnier, Nanomaterials for biosensing applications: a review, Front. Chem. 2 (2014), https://doi.org/10.3389/fchem.2014.00063.
[250] Q. Ge, Z.-Y. Zhang, S.-N. Li, J.-Q. Ma, Z. Zhao, Liquid biopsy: Comprehensive overview of circulating tumor DNA (Review), Oncol. Lett. 28 (2024) 548, https://doi.org/10.3892/ol.2024.14681.
[251] X. Wen, H. Pu, Q. Liu, Z. Guo, D. Luo, Circulating Tumor DNA—A Novel Biomarker of Tumor Progression and Its Favorable Detection Techniques, Cancers (Basel) 14 (2022) 6025, https://doi.org/10.3390/cancers14246025.
[252] S. Catuogno, C.L. Esposito, C. Quintavalle, L. Cerchia, G. Condorelli, V. De Franciscis, Recent Advance in Biosensors for microRNAs Detection in Cancer, Cancers (Basel) 3 (2011) 1877–1898, https://doi.org/10.3390/cancers3021877.
[253] E. Genco, F. Modena, L. Sarcina, K. Björkström, C. Brunetti, M. Caironi, M. Caputo, V.M. Demartis, C. Di Franco, G. Frusconi, L. Haeberle, P. Larizza, M. T. Mancini, R. Österbacka, W. Reeves, G. Scamarcio, C. Scandurra, M. Wheeler, E. Cantatore, I. Esposito, E. Macchia, F. Torricelli, F.A. Viola, L. Torsi, A Single-Molecule Bioelectronic Portable Array for Early Diagnosis of Pancreatic Cancer Precursors, Adv. Mater. 35 (2023), https://doi.org/10.1002/adma.202304102.
[254] B. Zhang, J. Wang, L. Ping, Y. Zhong, F. Li, Preparation of Graphene Composite and Its Application in the Detection of Tumor Markers, Sci. Adv. Mater. 12 (2020) 1312–1322, https://doi.org/10.1166/sam.2020.3829.
[255] X. Liu, Y. Wang, Y. Du, J. Zhang, Y. Wang, Y. Xue, J. Zhao, L. Ge, L. Yang, F. Li, Laser-induced graphene (LIG)-based electrochemical microfluidic chip for simultaneous analysis of multiplex microRNAs, Chem. Eng. J. 486 (2024) 150233, https://doi.org/10.1016/j.cej.2024.150233.
[256] P. Patel, Biosensors and Biomarkers: Promising Tools for Cancer Diagnosis, Int. J. Biosens. Bioelectron. 3 (2017). https://doi.org/10.15406/ijbsbe.2017.03.00072.
[257] P. Damborský, J. Švitel, J. Katrlík, Optical biosensors, Essays Biochem. 60 (2016) 91–100, https://doi.org/10.1042/EBC20150010.

[258] S. Sarkar, S. Hazra, S. Patra, M. Gogoi, Biosensors for cancer detection: A review, TrAC Trends Anal. Chem. 180 (2024) 117978, https://doi.org/10.1016/j.trac.2024.117978.
[259] D.N. Moorthy, D. Dhinasekaran, P.N.B. Rebecca, A.R. Rajendran, Optical Biosensors for Detection of Cancer Biomarkers: Current and Future Perspectives, J. Biophotonics 17 (2024), https://doi.org/10.1002/jbio.202400243.
[260] B.B. Motsa, R.V. Stahelin, A beginner's guide to surface plasmon resonance, Biochem. (lond) 45 (2023) 18–22, https://doi.org/10.1042/bio_2022_139.
[261] H. Nguyen, J. Park, S. Kang, M. Kim, Surface Plasmon Resonance: A Versatile Technique for Biosensor Applications, Sensors 15 (2015) 10481–10510, https://doi.org/10.3390/s150510481.
[262] L. Li, X. Cao, T. Zhang, Q. Wu, P. Xiang, C. Shen, L. Zou, Q. Li, Recent Developments in Surface-Enhanced Raman Spectroscopy and Its Application in Food Analysis: Alcoholic Beverages as an Example, Foods 11 (2022) 2165, https://doi.org/10.3390/foods11142165.
[263] J. Karlo, S.S. Razi, M.S. Phaneeswar, A. Vijay, S.P. Singh, Metallic Nanoparticles for Surface-Enhanced Raman Scattering Based Biosensing Applications, Photochem 4 (2024) 417–433, https://doi.org/10.3390/photochem4040026.
[264] S.R. Balasubramani, K. Nagappan, L.S. Ewe, K. Viswanathan, W.K. Yew, S. G. Thiraviam, S. Sadana, T.K.D. Samuel, K. Kamalakannan, Recent developments in surface-enhanced Raman spectroscopy in the field of chemical, biochemical and clinical application– a critical review, Int. J. Environ. Anal. Chem. (2024) 1–27, https://doi.org/10.1080/03067319.2024.2339453.
[265] R. Govindaraju, S. Govindaraju, K. Yun, J. Kim, Fluorescent-Based Neurotransmitter Sensors: Present and Future Perspectives, Biosensors 13 (2023) 1008, https://doi.org/10.3390/bios13121008.
[266] S.B. Wagh, V.A. Maslivetc, J.J. La Clair, A. Kornienko, Lessons in Organic Fluorescent Probe Discovery, Chembiochem 22 (2021) 3109–3139, https://doi.org/10.1002/cbic.202100171.
[267] X. Fang, Y. Zheng, Y. Duan, Y. Liu, W. Zhong, Recent Advances in Design of Fluorescence-Based Assays for High-Throughput Screening, Anal. Chem. 91 (2019) 482–504, https://doi.org/10.1021/acs.analchem.8b05303.
[268] R. Nutiu, L.P. Billen, Y. Li, Fluorescence-Signaling Nucleic Acid-Based Sensors, in: Nucleic Acid Switch. Sensors, Springer US, Boston, MA, 2006: pp. 49–72. https://doi.org/10.1007/978-0-387-47257-7_4.
[269] W.F. An, Fluorescence-Based Assays, in: 2009: pp. 97–107. https://doi.org/10.1007/978-1-60327-545-3_7.
[270] Z.A.R. Jawad, I.G. Theodorou, L.R. Jiao, F. Xie, Highly Sensitive Plasmonic Detection of the Pancreatic Cancer Biomarker CA 19-9, Sci. Rep. 7 (2017) 14309, https://doi.org/10.1038/s41598-017-14688-z.
[271] G.K. Joshi, S. Deitz-McElyea, M. Johnson, S. Mali, M. Korc, R. Sardar, Highly Specific Plasmonic Biosensors for Ultrasensitive MicroRNA Detection in Plasma from Pancreatic Cancer Patients, Nano Lett. 14 (2014) 6955–6963, https://doi.org/10.1021/nl503220s.
[272] Y. Pang, C. Wang, L. Lu, C. Wang, Z. Sun, R. Xiao, Dual-SERS biosensor for one-step detection of microRNAs in exosome and residual plasma of blood samples for diagnosing pancreatic cancer, Biosens. Bioelectron. 130 (2019) 204–213, https://doi.org/10.1016/j.bios.2019.01.039.
[273] Z. Liu, Y. Zhou, J. Lu, T. Gong, E. Ibáñez, A. Cifuentes, W. Lu, Microfluidic biosensors for biomarker detection in body fluids: a key approach for early cancer diagnosis, Biomark. Res. 12 (2024) 153, https://doi.org/10.1186/s40364-024-00697-4.
[274] N. Bargahi, S. Ghasemali, S. Jahandar-Lashaki, A. Nazari, Recent advances for cancer detection and treatment by microfluidic technology, review and update, Biol. Proced. Online 24 (2022) 5, https://doi.org/10.1186/s12575-022-00166-y.
[275] J.L. Garcia-Cordero, S.J. Maerkl, Microfluidic systems for cancer diagnostics, Curr. Opin. Biotechnol. 65 (2020) 37–44, https://doi.org/10.1016/j.copbio.2019.11.022.
[276] N. Azizipour, R. Avazpour, D.H. Rosenzweig, M. Sawan, A. Ajji, Evolution of Biochip Technology: A Review from Lab-on-a-Chip to Organ-on-a-Chip, Micromachines 11 (2020) 599, https://doi.org/10.3390/mi11060599.
[277] D. Raju, S. Bathini, S. Badilescu, A. Ghosh, M. Packirisamy, Microfluidic Platforms for the Isolation and Detection of Exosomes: A Brief Review, Micromachines 13 (2022) 730, https://doi.org/10.3390/mi13050730.
[278] G. Li, W. Tang, F. Yang, Cancer Liquid Biopsy Using Integrated Microfluidic Exosome Analysis Platforms, Biotechnol. J. 15 (2020), https://doi.org/10.1002/biot.201900225.
[279] B. Senf, W.-H. Yeo, J.-H. Kim, Recent Advances in Portable Biosensors for Biomarker Detection in Body Fluids, Biosensors 10 (2020) 127, https://doi.org/10.3390/bios10090127.
[280] T. Wasilewski, W. Kamysz, J. Gębicki, AI-Assisted Detection of Biomarkers by Sensors and Biosensors for Early Diagnosis and Monitoring, Biosensors 14 (2024) 356, https://doi.org/10.3390/bios14070356.
[281] P.P. Behera, N. Kumar, M. Kumari, S. Kumar, P.K. Mondal, R.K. Arun, Integrated microfluidic devices for point-of-care detection of bio-analytes and disease, Sensors & Diagnostics 2 (2023) 1437–1459, https://doi.org/10.1039/D3SD00170A.
[282] D.-K. Vo, K.T.L. Trinh, Advances in Wearable Biosensors for Healthcare: Current Trends, Applications, and Future Perspectives, Biosensors 14 (2024) 560, https://doi.org/10.3390/bios14110560.
[283] N.G. Gurudatt, H. Gwak, K.-A. Hyun, S.-E. Jeong, K. Lee, S. Park, M.J. Chung, S.-E. Kim, J.H. Jo, H.-I. Jung, Electrochemical detection and analysis of tumor-derived extracellular vesicles to evaluate malignancy of pancreatic cystic neoplasm using integrated microfluidic device, Biosens. Bioelectron. 226 (2023) 115124, https://doi.org/10.1016/j.bios.2023.115124.
[284] Y. Zhang, X. Tong, L. Yang, R. Yin, Y. Li, D. Zeng, X. Wang, K. Deng, A herringbone mixer based microfluidic device HBEXO-chip for purifying tumor-derived exosomes and establishing miRNA signature in pancreatic cancer, Sensors Actuators B Chem. 332 (2021) 129511, https://doi.org/10.1016/j.snb.2021.129511.
[285] I. Rawashdeh1, M.G. Al-Fandi, Y. Makableh, T. Harahsha, Developing a nano-biosensor for early detection of pancreatic cancer, Sens. Rev. 41 (2021) 93–100, https://doi.org/10.1108/SR-01-2020-0004.
[286] L. Li, T. Wang, Y. Zhong, R. Li, W. Deng, X. Xiao, Y. Xu, J. Zhang, X. Hu, Y. Wang, A review of nanomaterials for biosensing applications, J. Mater. Chem. B 12 (2024) 1168–1193, https://doi.org/10.1039/D3TB02648E.
[287] X. Liang, N. Li, R. Zhang, P. Yin, C. Zhang, N. Yang, K. Liang, B. Kong, Carbon-based SERS biosensor: from substrate design to sensing and bioapplication, NPG Asia Mater. 13 (2021) 8, https://doi.org/10.1038/s41427-020-00278-5.
[288] N.R. Lemoine, Molecular Advances in Pancreatic Cancer, Digestion 58 (1997) 550–556, https://doi.org/10.1159/000201500.
[289] H. Zhang, L. Zhao, J. Jiang, J. Zheng, L. Yang, Y. Li, J. Zhou, T. Liu, J. Xu, W. Lou, W. Yang, L. Tan, W. Liu, Y. Yu, M. Ji, Y. Xu, Y. Lu, X. Li, Z. Liu, R. Tian, C. Hu, S. Zhang, Q. Hu, Y. Deng, H. Ying, S. Zhong, X. Zhang, Y. Wang, H. Wang, J. Bai, X. Li, X. Duan, Multiplexed nanomaterial-assisted laser desorption/ionization for pan-cancer diagnosis and classification, Nat. Commun. 13 (2022) 617, https://doi.org/10.1038/s41467-021-26642-9.
[290] C. Ss, K.-T. Chen, A.-F.-J. Chen, Polydopamine-gold composite-based electrochemical biosensor using dual-amplification strategy for detecting pancreatic cancer-associated microRNA, Biosens. Bioelectron. 173 (2021) 112815, https://doi.org/10.1016/j.bios.2020.112815.
[291] D. Zeng, Z. Wang, Z. Meng, P. Wang, L. San, W. Wang, A. Aldalbahi, L. Li, J. Shen, X. Mi, DNA Tetrahedral Nanostructure-Based Electrochemical miRNA Biosensor for Simultaneous Detection of Multiple miRNAs in Pancreatic Carcinoma, ACS Appl. Mater. Interfaces 9 (2017) 24118–24125, https://doi.org/10.1021/acsami.7b05981.
[292] D. Li, Y. Xu, L. Fan, B. Shen, X. Ding, R. Yuan, X. Li, W. Chen, Target-driven rolling walker based electrochemical biosensor for ultrasensitive detection of circulating tumor DNA using doxorubicin@tetrahedron-Au tags, Biosens. Bioelectron. 148 (2020) 111826, https://doi.org/10.1016/j.bios.2019.111826.
[293] M. Moccia, V. Caratelli, S. Cinti, B. Pede, C. Avitabile, M. Saviano, A.L. Imbriani, D. Moscone, F. Arduini, Paper-based electrochemical peptide nucleic acid (PNA) biosensor for detection of miRNA-492: a pancreatic ductal adenocarcinoma biomarker, Biosens. Bioelectron. 165 (2020) 112371, https://doi.org/10.1016/j.bios.2020.112371.
[294] N.R. Nené, A. Ney, T. Nazarenko, O. Blyuss, H.E. Johnston, H.J. Whitwell, E. Sedlak, A. Gentry-Maharaj, S. Apostolidou, E. Costello, W. Greenhalf, I. Jacobs, U. Menon, J. Hsuan, S.P. Pereira, A. Zaikin, J.F. Timms, Serum biomarker-based early detection of pancreatic ductal adenocarcinomas with ensemble learning, Commun. Med. 3 (2023) 10, https://doi.org/10.1038/s43856-023-00237-5.
[295] İ. Acer, F.O. Bulucu, S. Içer, F. Latifoğlu, Early diagnosis of pancreatic cancer by machine learning methods using urine biomarker combinations, Turkish J. Electr. Eng. Comput. Sci. 31 (2023) 112–125. https://doi.org/10.55730/1300-0632.3974.
[296] J.C. Soares, L.E.O. Iwaki, A.C. Soares, V.C. Rodrigues, M.E. Melendez, J.H.T. G. Fregnani, R.M. Reis, A.L. Carvalho, D.S. Corrêa, O.N. Oliveira, Immunosensor for Pancreatic Cancer Based on Electrospun Nanofibers Coated with Carbon Nanotubes or Gold Nanoparticles, ACS Omega 2 (2017) 6975–6983, https://doi.org/10.1021/acsomega.7b01029.
[297] M. Akin, M. Bekmezci, R. Bayat, Z.K. Coguplugil, F. Sen, F. Karimi, H. Karimi-Maleh, Mobile device integrated graphene oxide quantum dots based electrochemical biosensor design for detection of miR-141 as a pancreatic cancer biomarker, Electrochim. Acta 435 (2022) 141390, https://doi.org/10.1016/j.electacta.2022.141390.
[298] Q. Meng, S. Shi, C. Liang, D. Liang, W. Xu, S. Ji, B. Zhang, Q. Ni, J. Xu, X. Yu, Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis, Onco. Targets. Ther. 10 (2017) 4591–4598, https://doi.org/10.2147/OTT.S145708.
[299] A. Kumar, A. Kumar, S.K. Srivastava, A study on surface plasmon resonance biosensor for the detection of CEA biomarker using 2D materials graphene, Mxene and MoS2, Optik (stuttg). 258 (2022) 168885, https://doi.org/10.1016/j.ijleo.2022.168885.
[300] M. Bhaiyya, D. Panigrahi, P. Rewatkar, H. Haick, Role of Machine Learning Assisted Biosensors in Point-of-Care-Testing For Clinical Decisions, ACS Sensors 9 (2024) 4495–4519, https://doi.org/10.1021/acssensors.4c01582.
[301] L. Chang, J. Liu, J. Zhu, S. Guo, Y. Wang, Z. Zhou, X. Wei, Advancing precision medicine: the transformative role of artificial intelligence in immunogenomics, radiomics, and pathomics for biomarker discovery and immunotherapy optimization, Cancer, Biol. Med. (2025) 1–15. https://doi.org/10.20892/j.issn.2095-3941.2024.0376.
[302] M.M. Baig, C. Hobson, H. GholamHosseini, E. Ullah, S. Afifi, Generative AI in Improving Personalized Patient Care Plans: Opportunities and Barriers Towards Its Wider Adoption, Appl. Sci. 14 (2024) 10899, https://doi.org/10.3390/app142310899.
[303] M.E. Karar, N. El-Fishawy, M. Radad, Automated classification of urine biomarkers to diagnose pancreatic cancer using 1-D convolutional neural networks, J. Biol. Eng. 17 (2023) 28, https://doi.org/10.1186/s13036-023-00340-0.
[304] N.P. Long, K.H. Jung, N.H. Anh, H.H. Yan, T.D. Nghi, S. Park, S.J. Yoon, J.E. Min, H.M. Kim, J.H. Lim, J.M. Kim, J. Lim, S. Lee, S.-S. Hong, S.W. Kwon, An Integrative Data Mining and Omics-Based Translational Model for the

Identification and Validation of Oncogenic Biomarkers of Pancreatic Cancer, Cancers (Basel) 11 (2019) 155, https://doi.org/10.3390/cancers11020155.
[305] J. Chen, L. Fu, R. Xiang, S. Luo, X. Huang, H. Yu, L. Sun, Artificial Intelligence-Assisted Microfluidic Bio-Imaging—From Sensors to Applications: A Review, IEEE Sens. J. 25 (2025) 2056–2072, https://doi.org/10.1109/JSEN.2024.3507081.
[306] R. Vijayakumar Selvarani, P.S.H. Jose, Biomarker Based Detection and Staging of Breast Cancer from Blood Using Raman Spectroscopy and Deep Learning Technique, Trends Sci. 20 (2023) 5425. https://doi.org/10.48048/tis.2023.5425.
[307] F.A. van Delft, M. Schuurbiers, M. Muller, S.A. Burgers, H.H. van Rossum, M. J. IJzerman, H. Koffijberg, M.M. van den Heuvel, Modeling strategies to analyse longitudinal biomarker data: An illustration on predicting immunotherapy non-response in non-small cell lung cancer, Heliyon 8 (2022) e10932, https://doi.org/10.1016/j.heliyon.2022.e10932.
[308] B. Wang, Y. Li, M. Zhou, Y. Han, M. Zhang, Z. Gao, Z. Liu, P. Chen, W. Du, X. Zhang, X. Feng, B.-F. Liu, Smartphone-based platforms implementing microfluidic detection with image-based artificial intelligence, Nat. Commun. 14 (2023) 1341, https://doi.org/10.1038/s41467-023-36017-x.
[309] H. Raji, M. Tayyab, J. Sui, S.R. Mahmoodi, M. Javanmard, Biosensors and machine learning for enhanced detection, stratification, and classification of cells: a review, Biomed. Microdevices 24 (2022) 26, https://doi.org/10.1007/s10544-022-00627-x.
[310] J. Duan, J. Xiong, Y. Li, W. Ding, Deep learning based multimodal biomedical data fusion: An overview and comparative review, Inf. Fusion 112 (2024) 102536, https://doi.org/10.1016/j.inffus.2024.102536.
[311] K. Murugan, K. Gopalakrishnan, K. Sakthivel, S. Subramanian, I.-C. Li, Y.-Y. Lee, T.-W. Chiu, G.-P. Chang-Chien, Review—Machine Learning-Driven Advances in Electrochemical Sensing: A Horizon Scan, J. Electrochem. Soc. 171 (2024) 097503, https://doi.org/10.1149/1945-7111/ad6b4a.
[312] S.S. Arya, S.B. Dias, H.F. Jelinek, L.J. Hadjileontiadis, A.-M. Pappa, The convergence of traditional and digital biomarkers through AI-assisted biosensing: A new era in translational diagnostics? Biosens. Bioelectron. 235 (2023) 115387 https://doi.org/10.1016/j.bios.2023.115387.
[313] K.E. Schackart, J.-Y. Yoon, Machine Learning Enhances the Performance of Bioreceptor-Free Biosensors, Sensors 21 (2021) 5519, https://doi.org/10.3390/s21165519.
[314] C.D. Flynn, D. Chang, Artificial Intelligence in Point-of-Care Biosensing: Challenges and Opportunities, Diagnostics 14 (2024) 1100, https://doi.org/10.3390/diagnostics14111100.
[315] S. Roy, T. Radivojevic, M. Forrer, J.M. Marti, V. Jonnalagadda, T. Backman, W. Morrell, H. Plahar, J. Kim, N. Hillson, H. Garcia Martin, Multiomics Data Collection Visualization, and Utilization for Guiding Metabolic Engineering, Front. Bioeng.Biotechnol. 9 (2021), https://doi.org/10.3389/fbioe.2021.612893.
[316] G. (Vedant, S. Raikar, A.S. Raikar, S.N. Somnache, Advancements in artificial intelligence and machine learning in revolutionising biomarker discovery, Brazilian, J. Pharm. Sci. 59 (2023), https://doi.org/10.1590/s2175-97902023e23146.
[317] L.M. Helleckes, J. Hemmerich, W. Wiechert, E. von Lieres, A. Grünberger, Machine learning in bioprocess development: from promise to practice, Trends Biotechnol. 41 (2023) 817–835, https://doi.org/10.1016/j.tibtech.2022.10.010.
[318] C. Shorten, T.M. Khoshgoftaar, A survey on Image Data Augmentation for Deep Learning, J. Big Data 6 (2019) 60, https://doi.org/10.1186/s40537-019-0197-0.
[319] S. Candemir, X.V. Nguyen, L.R. Folio, L.M. Prevedello, Training Strategies for Radiology Deep Learning Models in Data-limited Scenarios, Radiol. Artif. Intell. 3 (2021), https://doi.org/10.1148/ryai.2021210014.
[320] H. Javed, S. El-Sappagh, T. Abuhmed, Robustness in deep learning models for medical diagnostics: security and adversarial challenges towards robust AI applications, Artif. Intell. Rev. 58 (2024) 12, https://doi.org/10.1007/s10462-024-11005-9.
[321] S. Ng, S. Masarone, D. Watson, M.R. Barnes, The benefits and pitfalls of machine learning for biomarker discovery, Cell Tissue Res. 394 (2023) 17–31, https://doi.org/10.1007/s00441-023-03816-z.
[322] R. Qureshi, M. Irfan, H. Ali, A. Khan, A.S. Nittala, S. Ali, A. Shah, T.M. Gondal, F. Sadak, Z. Shah, M.U. Hadi, S. Khan, Q. Al-Tashi, J. Wu, A. Bermak, T. Alam, Artificial Intelligence and Biosensors in Healthcare and Its Clinical Relevance: A Review, IEEE Access 11 (2023) 61600–61620, https://doi.org/10.1109/ACCESS.2023.3285596.
[323] L. Tong, W. Shi, M. Isgut, Y. Zhong, P. Lais, L. Gloster, J. Sun, A. Swain, F. Giuste, M.D. Wang, Integrating Multi-Omics Data With EHR for Precision Medicine Using Advanced Artificial Intelligence, IEEE Rev. Biomed. Eng. 17 (2024) 80–97, https://doi.org/10.1109/RBME.2023.3324264.
[324] É. Buteau, G. Gagné, W. Bonilla, M. Boukadoum, P. Fortier, B. Gosselin, TinyML for Real-Time Embedded HD-EMG Hand Gesture Recognition with On-Device Fine-Tuning, in 2024 46th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc, IEEE 2024 (2024) 1–6, https://doi.org/10.1109/EMBC53108.2024.10781755.
[325] V. Chugh, A. Basu, A. Kaushik, S. Manshu, A.K.B. Bhansali, Employing nano-enabled artificial intelligence (AI)-based smart technologies for prediction, screening, and detection of cancer, Nanoscale 16 (2024) 5458–5486, https://doi.org/10.1039/D3NR05648A.
[326] W. Li, X. Yang, T. Bai, J. Xu, Z. Qian, Y. Li, Z. Guo, Y. Zhu, Detection of serum EphA2-EVs for pancreatic cancer diagnosis by light initiated chemiluminescent assay, Anal. Methods 14 (2022) 1335–1341, https://doi.org/10.1039/D1AY02083H.
[327] A. Guo, Y. Li, W. Cao, X. Meng, D. Wu, Q. Wei, B. Du, An electrochemical immunosensor for ultrasensitive detection of carbohydrate antigen 199 based on Au@Cu x OS yolk–shell nanostructures with porous shells as labels, Biosens. Bioelectron. 63 (2015) 39–46, https://doi.org/10.1016/j.bios.2014.07.017.
[328] Q. Rong, F. Feng, Z. Ma, Metal ions doped chitosan–poly(acrylic acid) nanospheres: Synthesis and their application in simultaneously electrochemical detection of four markers of pancreatic cancer, Biosens. Bioelectron. 75 (2016) 148–154, https://doi.org/10.1016/j.bios.2015.08.041.
[329] J. Guo, C. Yuan, Q. Yan, Q. Duan, X. Li, G. Yi, An electrochemical biosensor for microRNA-196a detection based on cyclic enzymatic signal amplification and template-free DNA extension reaction with the adsorption of methylene blue, Biosens. Bioelectron. 105 (2018) 103–108, https://doi.org/10.1016/j.bios.2018.01.036.
[330] J. Li, Z. Chen, Y. Xiang, L. Zhou, T. Wang, Z. Zhang, K. Sun, D. Yin, Y. Li, G. Xie, An electrochemical biosensor for double-stranded Wnt7B gene detection based on enzymatic isothermal amplification, Biosens. Bioelectron. 86 (2016) 75–82, https://doi.org/10.1016/j.bios.2016.06.031.
[331] B. Gu, C. Xu, C. Yang, S. Liu, M. Wang, ZnO quantum dot labeled immunosensor for carbohydrate antigen 19-9, Biosens. Bioelectron. 26 (2011) 2720–2723, https://doi.org/10.1016/j.bios.2010.09.031.
[332] F. Dackson Gudagunti, L. Velmanickam, D. Nawarathna, I.T. Lima, Label-Free Biosensing Method for the Detection of a Pancreatic Cancer Biomarker Based on Dielectrophoresis Spectroscopy, Chemosensors 6 (2018) 33, https://doi.org/10.3390/chemosensors6030033.
[333] Y. Yu, Q. Zhang, J. Buscaglia, C.-C. Chang, Y. Liu, Z. Yang, Y. Guo, Y. Wang, K. Levon, M. Rafailovich, Quantitative real-time detection of carcinoembryonic antigen (CEA) from pancreatic cyst fluid using 3-D surface molecular imprinting, Analyst 141 (2016) 4424–4431, https://doi.org/10.1039/C6AN00375C.
[334] H. Xu, Y. Wang, L. Wang, Y. Song, J. Luo, X. Cai, A Label-Free Microelectrode Array Based on One-Step Synthesis of Chitosan–Multi-Walled Carbon Nanotube–Thionine for Ultrasensitive Detection of Carcinoembryonic Antigen, Nanomaterials 6 (2016) 132, https://doi.org/10.3390/nano6070132.
[335] Q. Shu, F. Liao, N. Hong, L. Cheng, Y. Lin, H. Cui, J. Su, G. Ma, G. Wei, Y. Zhong, J. Xiong, H. Fan, A novel DNA sensor of homogeneous electrochemical signal amplification strategy, Microchem. J. 156 (2020) 104777, https://doi.org/10.1016/j.microc.2020.104777.
[336] S. Shin Low, Y. Pan, D. Ji, Y. Li, Y. Lu, Y. He, Q. Chen, Q. Liu, Smartphone-based portable electrochemical biosensing system for detection of circulating microRNA-21 in saliva as a proof-of-concept, Sensors Actuators B Chem. 308 (2020) 127718, https://doi.org/10.1016/j.snb.2020.127718.
[337] M. Kalubowilage, O. Covarrubias-Zambrano, A.P. Malalasekera, S.O. Wendel, H. Wang, A.S. Yapa, L. Chlebanowski, Y. Toledo, R. Ortega, K.E. Janik, T. B. Shrestha, C.T. Culbertson, A. Kasi, S. Williamson, D.L. Troyer, S.H. Bossmann, Early detection of pancreatic cancers in liquid biopsies by ultrasensitive fluorescence nanobiosensors, Nanomedicine Nanotechnology, Biol. Med. 14 (2018) 1823–1832, https://doi.org/10.1016/j.nano.2018.04.020.
[338] T. Kumeria, M.D. Kurkuri, K.R. Diener, L. Parkinson, D. Losic, Label-free reflectometric interference microchip biosensor based on nanoporous alumina for detection of circulating tumour cells, Biosens. Bioelectron. 35 (2012) 167–173, https://doi.org/10.1016/j.bios.2012.02.038.
[339] G.K. Joshi, S. Deitz-McElyea, T. Liyanage, K. Lawrence, S. Mali, R. Sardar, M. Korc, Label-Free Nanoplasmonic-Based Short Noncoding RNA Sensing at Attomolar Concentrations Allows for Quantitative and Highly Specific Assay of MicroRNA-10b in Biological Fluids and Circulating Exosomes, ACS Nano 9 (2015) 11075–11089, https://doi.org/10.1021/acsnano.5b04527.
[340] G. Wang, R.J. Lipert, M. Jain, S. Kaur, S. Chakraboty, M.P. Torres, S.K. Batra, R. E. Brand, M.D. Porter, Detection of the Potential Pancreatic Cancer Marker MUC4 in Serum Using Surface-Enhanced Raman Scattering, Anal. Chem. 83 (2011) 2554–2561, https://doi.org/10.1021/ac102829b.
[341] H. Ito, K. Hasegawa, Y. Hasegawa, S. Kimura, M. Onimaru, T. Ohmori, H. Ikeda, M. Saito, Y. Kitamura, C. Sato, K. Gomi, S. Sakaue, M. Isozaki, M. Matsukawa, H. Inoue, Simple blood test for diagnosis of gastrointestinal and pancreas cancer using surface-enhanced Raman scattering, 32-32, J. Clin. Oncol. 33 (2015), https://doi.org/10.1200/jco.2015.33.3_suppl.32.
[342] N. Banaei, A. Foley, J.M. Houghton, Y. Sun, B. Kim, Multiplex detection of pancreatic cancer biomarkers using a SERS-based immunoassay, Nanotechnology 28 (2017) 455101, https://doi.org/10.1088/1361-6528/aa8e8c.
[343] J. Carmicheal, C. Hayashi, X. Huang, L. Liu, Y. Lu, A. Krasnoslobodtsev, A. Lushnikov, P.G. Kshirsagar, A. Patel, M. Jain, Y.L. Lyubchenko, Y. Lu, S. K. Batra, S. Kaur, Label-free characterization of exosome via surface enhanced Raman spectroscopy for the early detection of pancreatic cancer, Nanomedicine Nanotechnology, Biol. Med. 16 (2019) 88–96, https://doi.org/10.1016/j.nano.2018.11.008.
[344] H. Zhao, Y. Qu, F. Yuan, X. Quan, A visible and label-free colorimetric sensor for miRNA-21 detection based on peroxidase-like activity of graphene/gold-nanoparticle hybrids, Anal. Methods 8 (2016) 2005–2012, https://doi.org/10.1039/C5AY03296B.
[345] L. Xiao, A. Zhu, Q. Xu, Y. Chen, J. Xu, J. Weng, Colorimetric Biosensor for Detection of Cancer Biomarker by Au Nanoparticle-Decorated Bi 2 Se 3 Nanosheets, ACS Appl. Mater. Interfaces 9 (2017) 6931–6940, https://doi.org/10.1021/acsami.6b15750.
[346] A.S.M. Ali, M.S. El-Halawany, S.A. Ibrahim, O. Plückthun, A.S.G. Khalil, G. Mayer, Aptasensor for Quantifying Pancreatic Polypeptide, ACS Omega 4 (2019) 2948–2956, https://doi.org/10.1021/acsomega.8b03131.
[347] K. Baryeh, S. Takalkar, M. Lund, G. Liu, Development of quantitative immunochromatographic assay for rapid and sensitive detection of carbohydrate antigen 19-9 (CA 19-9) in human plasma, J. Pharm. Biomed. Anal. 146 (2017) 285–291, https://doi.org/10.1016/j.jpba.2017.09.004.

[348] X. Gao, H. Xu, M. Baloda, A.S. Gurung, L.-P. Xu, T. Wang, X. Zhang, G. Liu, Visual detection of microRNA with lateral flow nucleic acid biosensor, Biosens. Bioelectron. 54 (2014) 578–584, https://doi.org/10.1016/j.bios.2013.10.055.
[349] W. Zheng, L. Yao, J. Teng, C. Yan, P. Qin, G. Liu, W. Chen, Lateral flow test for visual detection of multiple MicroRNAs, Sensors Actuators B Chem. 264 (2018) 320–326, https://doi.org/10.1016/j.snb.2018.02.159.
[350] Y. Choi, U. Park, H.-J. Koo, J. Park, D.H. Lee, K. Kim, J. Choi, Exosome-mediated diagnosis of pancreatic cancer using lectin-conjugated nanoparticles bound to selective glycans, Biosens. Bioelectron. 177 (2021) 112980, https://doi.org/10.1016/j.bios.2021.112980.
[351] C.-J. Yang, H. Yan, N. Tang, Y. Zou, Y. Al-Hadeethi, X. Xu, H. Dalir, R.T. Chen, Ultra Sensitivity Silicon-Based Photonic Crystal Microcavity Biosensors for Plasma Protein Detection in Patients with Pancreatic Cancer, Micromachines 11 (2020) 282, https://doi.org/10.3390/mi11030282.
[352] G. Ibáñez-Redín, R.H.M. Furuta, D. Wilson, F.M. Shimizu, E.M. Materon, L.M.R. B. Arantes, M.E. Melendez, A.L. Carvalho, R.M. Reis, M.N. Chaur, D. Gonçalves, O.N. Oliveira Jr, Screen-printed interdigitated electrodes modified with nanostructured carbon nano-onion films for detecting the cancer biomarker CA19-9, Mater. Sci. Eng. C 99 (2019) 1502–1508, https://doi.org/10.1016/j.msec.2019.02.065.
[353] A. Thapa, A.C. Soares, J.C. Soares, I.T. Awan, D. Volpati, M.E. Melendez, J.H.T. G. Fregnani, A.L. Carvalho, O.N. Oliveira, Carbon Nanotube Matrix for Highly Sensitive Biosensors To Detect Pancreatic Cancer Biomarker CA19-9, ACS Appl. Mater. Interfaces 9 (2017) 25878–25886, https://doi.org/10.1021/acsami.7b07384.
[354] K. Liang, F. Liu, J. Fan, D. Sun, C. Liu, C.J. Lyon, D.W. Bernard, Y. Li, K. Yokoi, M. H. Katz, E.J. Koay, Z. Zhao, Y. Hu, Nanoplasmonic quantification of tumour-derived extracellular vesicles in plasma microsamples for diagnosis and treatment monitoring, Nat. Biomed. Eng. 1 (2017) 0021, https://doi.org/10.1038/s41551-016-0021.
[355] Q. Dong, X. Jia, Y. Wang, H. Wang, Q. Liu, D. Li, J. Wang, E. Wang, Sensitive and selective detection of Mucin1 in pancreatic cancer using hybridization chain reaction with the assistance of Fe3O4@polydopamine nanocomposites, J. Nanobiotechnology 20 (2022) 94, https://doi.org/10.1186/s12951-022-01289-w.
[356] Z. Xu, M. Peng, Z. Zhang, H. Zeng, R. Shi, X. Ma, L. Wang, B. Liao, Graphene-Assisted Electrochemical Sensor for Detection of Pancreatic Cancer Markers, Front. Chem. 9 (2021), https://doi.org/10.3389/fchem.2021.733371.
[357] H. Xiong, Z. Huang, Q. Lin, B. Yang, F. Yan, B. Liu, H. Chen, J. Kong, Surface Plasmon Coupling Electrochemiluminescence Immunosensor Based on Polymer Dots and AuNPs for Ultrasensitive Detection of Pancreatic Cancer Exosomes, Anal. Chem. 94 (2022) 837–846, https://doi.org/10.1021/acs.analchem.1c03535.
[358] S. Das, M.K. Dey, R. Devireddy, M.R. Gartia, Biomarkers in Cancer Detection, Diagnosis, and Prognosis, Sensors 24 (2023) 37, https://doi.org/10.3390/s24010037.
[359] M. Mishra, R. Ahmed, D.K. Das, D. Das Pramanik, S.K. Dash, A. Pramanik, Recent Advancements in the Application of Circulating Tumor DNA as Biomarkers for Early Detection of Cancers, ACS Biomater, Sci. Eng. 10 (2024) 4740–4756, https://doi.org/10.1021/acsbiomaterials.4c00606.
[360] C.D. Gutierrez Reyes, G. Alejo-Jacuinde, B. Perez Sanchez, J. Chavez Reyes, S. Onigbinde, D. Mogut, I. Hernández-Jasso, D. Calderón-Vallejo, J.L. Quintanar, Y. Mechref, Multi Omics Applications in Biological Systems, Curr. Issues Mol. Biol. 46 (2024) 5777–5793, https://doi.org/10.3390/cimb46060345.
[361] M. Babu, M. Snyder, Multi-Omics Profiling for Health, Mol. Cell. Proteomics 22 (2023) 100561, https://doi.org/10.1016/j.mcpro.2023.100561.
[362] L. Kunovsky, P. Tesarikova, Z. Kala, R. Kroupa, P. Kysela, J. Dolina, J. Trna, The Use of Biomarkers in Early Diagnostics of Pancreatic Cancer, Can. J. Gastroenterol. Hepatol. 2018 (2018) 1–10, https://doi.org/10.1155/2018/5389820.
[363] A. Hafeez, A. Gupta, M.K. Gupta, Biological omics databases and tools, in: Integr. Omi., Elsevier, 2024: pp. 35–53. https://doi.org/10.1016/B978-0-443-16092-9.00003-5.
[364] O. Palmieri, T. Mazza, S. Castellana, A. Panza, T. Latiano, G. Corritore, A. Andriulli, A. Latiano, Inflammatory Bowel Disease Meets Systems Biology: A Multi-Omics Challenge and Frontier, Omi. A J. Integr. Biol. 20 (2016) 692–698, https://doi.org/10.1089/omi.2016.0147.
[365] M.J. Mitchell, R.K. Jain, R. Langer, Engineering and physical sciences in oncology: challenges and opportunities, Nat. Rev. Cancer 17 (2017) 659–675, https://doi.org/10.1038/nrc.2017.83.
[366] A. Edsjö, L. Holmquist, B. Geoerger, F. Nowak, G. Gomon, C. Alix-Panabières, J. Staaf, C. Ploeger, U. Lassen, C. Le Tourneau, J. Lehtiö, P.A. Ott, A. von Deimling, S. Fröhling, E. Voest, F. Klauschen, R. Dienstmann, A. Alshibany, L. L. Siu, A. Stenzinger, Precision cancer medicine: Concepts, current practice, and future developments, J. Intern. Med. 294 (2023) 455–481, https://doi.org/10.1111/joim.13709.
[367] M.G. Hanna, L. Pantanowitz, R. Dash, J.H. Harrison, M. Deebajah, J. Pantanowitz, H.H. Rashidi, Future of Artificial Intelligence—Machine Learning Trends in Pathology and Medicine, Mod. Pathol. 38 (2025) 100705, https://doi.org/10.1016/j.modpat.2025.100705.
[368] Y. Zhang, Y. Hu, N. Jiang, A.K. Yetisen, Wearable artificial intelligence biosensor networks, Biosens. Bioelectron. 219 (2023) 114825, https://doi.org/10.1016/j.bios.2022.114825.
[369] E.S. Lee, Imaging diagnosis of pancreatic cancer: A state-of-the-art review, World J. Gastroenterol. 20 (2014) 7864, https://doi.org/10.3748/wjg.v20.i24.7864.
[370] U.K. Ballehaninna, R.S. Chamberlain, Biomarkers for pancreatic cancer: promising new markers and options beyond CA 19-9, Tumor Biol. 34 (2013) 3279–3292, https://doi.org/10.1007/s13277-013-1033-3.
[371] S. Scarà, P. Bottoni, R. Scatena, CA 19-9: Biochemical and Clinical Aspects, in: 2015: pp. 247–260. https://doi.org/10.1007/978-94-017-7215-0_15.
[372] U.K. Ballehaninna, R.S. Chamberlain, Serum CA 19-9 as a Biomarker for Pancreatic Cancer—A Comprehensive Review, Indian, J. Surg. Oncol. 2 (2011) 88–100, https://doi.org/10.1007/s13193-011-0042-1.
[373] F.A. Greco, W.J. Lennington, D.R. Spigel, J.D. Hainsworth, Molecular Profiling Diagnosis in Unknown Primary Cancer: Accuracy and Ability to Complement Standard Pathology, JNCI J. Natl. Cancer Inst. 105 (2013) 782–790, https://doi.org/10.1093/jnci/djt099.
[374] W. Hartwig, L. Schneider, M.K. Diener, F. Bergmann, M.W. Büchler, J. Werner, Preoperative tissue diagnosis for tumours of the pancreas, J. Br. Surg. 96 (2009) 5–20, https://doi.org/10.1002/bjs.6407.
[375] L. Zhang, S. Sanagapalli, A. Stoita, Challenges in diagnosis of pancreatic cancer, World J. Gastroenterol. 24 (2018) 2047–2060, https://doi.org/10.3748/wjg.v24.i19.2047.
[376] P. Michl, S. Pauls, T.M. Gress, Evidence-based diagnosis and staging of pancreatic cancer, Best Pract. Res. Clin. Gastroenterol. 20 (2006) 227–251, https://doi.org/10.1016/j.bpg.2005.10.005.
[377] R. Vaidyanathan, R.H. Soon, P. Zhang, K. Jiang, C.T. Lim, Cancer Diagnosis: From Tumor to Liquid Biopsy and Beyond, Lab Chip (2018), https://doi.org/10.1039/C8LC00684A.
[378] N. Soda, B.H.A. Rehm, P. Sonar, N.-T. Nguyen, M.J.A. Shiddiky, Advanced liquid biopsy technologies for circulating biomarker detection, J. Mater. Chem. B 7 (2019) 6670–6704, https://doi.org/10.1039/C9TB01490J.
[379] S. Mummareddy, S. Pradhan, A. Narasimhan, A. Natarajan, On Demand Biosensors for Early Diagnosis of Cancer and Immune Checkpoints Blockade Therapy Monitoring from Liquid Biopsy, Biosensors 11 (2021) 500, https://doi.org/10.3390/bios11120500.
[380] V. Yaghoubi Naei, P. Bordhan, F. Mirakhorli, M. Khorrami, J. Shrestha, H. Nazari, A. Kulasinghe, M., Ebrahimi Warkiani, Advances in novel strategies for isolation, characterization, and analysis of CTCs and ctDNA, Ther. Adv. Med. Oncol. 15 (2023), https://doi.org/10.1177/17588359231192401.
[381] S. Singh, P.S. Podder, M.J. Russo, C. Henry, S. Cinti, Correction: Tailored point-of-care biosensors for liquid biopsy in the field of oncology, 5008-5008, Lab Chip 22 (2022), https://doi.org/10.1039/D2LC90111K.
[382] S.A. Soper, K. Brown, A. Ellington, B. Frazier, G. Garcia-Manero, V. Gau, S. I. Gutman, D.F. Hayes, B. Korte, J.L. Landers, D. Larson, F. Ligler, A. Majumdar, M. Mascini, D. Nolte, Z. Rosenzweig, J. Wang, D. Wilson, Point-of-care biosensor systems for cancer diagnostics/prognostics, Biosens. Bioelectron. 21 (2006) 1932–1942, https://doi.org/10.1016/j.bios.2006.01.006.
[383] P.M. Kalligosfyri, E. Lamprou, D.P. Kalogianni, Emerging Sensing Technologies for Liquid Biopsy Applications: Steps Closer to Personalized Medicine, Sensors 24 (2024) 7902, https://doi.org/10.3390/s24247902.
[384] N. Ya, D. Zhang, Y. Wang, Y. Zheng, M. Yang, H. Wu, G. Oudeng, Recent advances of biocompatible optical nanobiosensors in liquid biopsy: towards early non-invasive diagnosis, Nanoscale 16 (2024) 13784–13801, https://doi.org/10.1039/D4NR01719F.
[385] S.A. Spring, S. Goggins, C.G. Frost, Ratiometric Electrochemistry: Improving the Robustness, Reproducibility and Reliability of Biosensors, Molecules 26 (2021) 2130, https://doi.org/10.3390/molecules26082130.
[386] B. Srinivasan, S. Tung, Development and Applications of Portable Biosensors, SLAS Technol. 20 (2015) 365–389, https://doi.org/10.1177/2211068215581349.
[387] N. Bhalla, Y. Pan, Z. Yang, A.F. Payam, Opportunities and Challenges for Biosensors and Nanoscale Analytical Tools for Pandemics: COVID-19, ACS Nano 14 (2020) 7783–7807, https://doi.org/10.1021/acsnano.0c04421.
[388] B. Daurai, A.J. Baruah, M. Gogoi, Recent advances in point-of-care biosensors for pancreatic diseases, TrAC Trends Anal. Chem. 179 (2024) 117867, https://doi.org/10.1016/j.trac.2024.117867.
[389] R. Tenchov, A.K. Sapra, J. Sasso, K. Ralhan, A. Tummala, N. Azoulay, Q.A. Zhou, Biomarkers for Early Cancer Detection: A Landscape View of Recent Advancements, Spotlighting Pancreatic and Liver Cancers, ACS Pharmacol. Transl. Sci. 7 (2024) 586–613, https://doi.org/10.1021/acsptsci.3c00346.
[390] K. Zhang, J. Wang, T. Liu, Y. Luo, X.J. Loh, X. Chen, Machine Learning-Reinforced Noninvasive Biosensors for Healthcare, Adv. Healthc. Mater. 10 (2021), https://doi.org/10.1002/adhm.202100734.
[391] Y. Dai, C.C. Liu, Recent Advances on Electrochemical Biosensing Strategies toward Universal Point-of-Care Systems, Angew, Chemie 131 (2019) 12483–12496, https://doi.org/10.1002/ange.201901879.
[392] M.L. Sin, K.E. Mach, P.K. Wong, J.C. Liao, Advances and challenges in biosensor-based diagnosis of infectious diseases, Expert Rev, Mol. Diagn. 14 (2014) 225–244, https://doi.org/10.1586/14737159.2014.888313.
[393] S. Rasheed, T. Kanwal, N. Ahmad, B. Fatima, M. Najam-ul-Haq, D. Hussain, Advances and challenges in portable optical biosensors for onsite detection and point-of-care diagnostics, TrAC Trends Anal. Chem. 173 (2024) 117640, https://doi.org/10.1016/j.trac.2024.117640.
[394] B.A. Prabowo, P.D. Cabral, P. Freitas, E. Fernandes, The Challenges of Developing Biosensors for Clinical Assessment: A Review, Chemosensors 9 (2021) 299, https://doi.org/10.3390/chemosensors9110299.
[395] M. Liu, Y. Wen, Point-of-care testing for early-stage liver cancer diagnosis and personalized medicine: Biomarkers, current technologies and perspectives, Heliyon 10 (2024) e38444, https://doi.org/10.1016/j.heliyon.2024.e38444.

[396] N. Pouyanfar, S.Z. Harofte, M. Soltani, S. Siavashy, E. Asadian, F. Ghorbani-Bidkorbeh, R. Keçili, C.M. Hussain, Artificial intelligence-based microfluidic platforms for the sensitive detection of environmental pollutants: Recent advances and prospects, Trends Environ. Anal. Chem. 34 (2022) e00160, https://doi.org/10.1016/j.teac.2022.e00160.
[397] X. Ma, G. Guo, X. Wu, Q. Wu, F. Liu, H. Zhang, N. Shi, Y. Guan, Advances in Integration, Wearable Applications, and Artificial Intelligence of Biomedical Microfluidics Systems, Micromachines 14 (2023) 972, https://doi.org/10.3390/mi14050972.
[398] K. Sampath, B. Thirupathi, S.K. Venishetty, D.L. Bharadwaj, S. Kummari, The Development Process of Point-of-Care Sensor-Based Detection Modules for Biomedical Diagnoses, in: Biosens. Pers. Healthc., Springer Nature Singapore, Singapore, 2024: pp. 297–313. https://doi.org/10.1007/978-981-97-5473-1_10.
[399] E. Noviana, T. Ozer, C.S. Carrell, J.S. Link, C. McMahon, I. Jang, C.S. Henry, Microfluidic Paper-Based Analytical Devices: From Design to Applications, Chem. Rev. 121 (2021) 11835–11885, https://doi.org/10.1021/acs.chemrev.0c01335.
[400] A. Nilghaz, L. Guan, W. Tan, W. Shen, Advances of Paper-Based Microfluidics for Diagnostics—The Original Motivation and Current Status, ACS Sensors 1 (2016) 1382–1393, https://doi.org/10.1021/acssensors.6b00578.
[401] R. Uddin, I. Koo, Real-Time Remote Patient Monitoring: A Review of Biosensors Integrated with Multi-Hop IoT Systems via Cloud Connectivity, Appl. Sci. 14 (2024) 1876, https://doi.org/10.3390/app14051876.
[402] S. Dave, A. Dave, S. Radhakrishnan, J. Das, S. Dave, Biosensors for healthcare: an artificial intelligence approach, in: Biosens. Emerg. Re-Emerging Infect. Dis., Elsevier, 2022: pp. 365–383. https://doi.org/10.1016/B978-0-323-88464-8.00008-7.
[403] K.I. Adeyinka, T.I. Adeyinka, Cybersecurity Measures for Protecting Data, in: 2024: pp. 365–414. https://doi.org/10.4018/979-8-3693-9491-5.ch016.
[404] R.K. Talreja, H. Sable, V. Chaudhary, S. Kadian, M. Singh, M. Kumar, J. Kishore, V. Chaudhary, A. Khosla, Review—Challenges in Lab-to-Clinic Translation of 5th /6 th Generation Intelligent Nanomaterial-enabled Biosensors, ECS Sens. Plus 3 (2024) 041602, https://doi.org/10.1149/2754-2726/ad9f7e.
[405] P. Yager, G.J. Domingo, J. Gerdes, Point-of-Care Diagnostics for Global Health, Annu. Rev. Biomed. Eng. 10 (2008) 107–144, https://doi.org/10.1146/annurev.bioeng.10.061807.160524.
[406] R.W. Peeling, P.G. Smith, P.M.M. Bossuyt, A guide for diagnostic evaluations, Nat. Rev. Microbiol. 4 (2006) S2–S6, https://doi.org/10.1038/nrmicro1568.
[407] S.M. Russell, R. de la Rica, Policy Considerations for Mobile Biosensors, ACS Sensors 3 (2018) 1059–1068, https://doi.org/10.1021/acssensors.8b00289.
[408] G. Liu, Grand Challenges in Biosensors and Biomolecular Electronics, Front. Bioeng. Biotechnol. 9 (2021), https://doi.org/10.3389/fbioe.2021.707615.
[409] N. Wongkaew, M. Simsek, C. Griesche, A.J. Baeumner, Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective, Chem. Rev. 119 (2019) 120–194, https://doi.org/10.1021/acs.chemrev.8b00172.
[410] M. Mascini, S. Tombelli, Biosensors for biomarkers in medical diagnostics, Biomarkers 13 (2008) 637–657, https://doi.org/10.1080/13547500802645905.
[411] A. Poschenrieder, M. Thaler, R. Junker, P.B. Luppa, Recent advances in immunodiagnostics based on biosensor technologies—from central laboratory to the point of care, Anal. Bioanal. Chem. 411 (2019) 7607–7621, https://doi.org/10.1007/s00216-019-01915-x.
[412] S. Shrivastava, T.Q. Trung, N.-E. Lee, Recent progress, challenges, and prospects of fully integrated mobile and wearable point-of-care testing systems for self-testing, Chem. Soc. Rev. 49 (2020) 1812–1866, https://doi.org/10.1039/C9CS00319C.
[413] F. Cui, Y. Yue, Y. Zhang, Z. Zhang, H.S. Zhou, Advancing Biosensors with Machine Learning, ACS Sensors 5 (2020) 3346–3364, https://doi.org/10.1021/acssensors.0c01424.
[414] M.G. Hanna, L. Pantanowitz, B. Jackson, O. Palmer, S. Visweswaran, J. Pantanowitz, M. Deebajah, H.H. Rashidi, Ethical and Bias Considerations in Artificial Intelligence/Machine Learning, Mod. Pathol. 38 (2025) 100686, https://doi.org/10.1016/j.modpat.2024.100686.
[415] M.S. Sengar, P. Kumari, N. Sengar, Challenges in the development of nanobiosensors in the diagnosis of cancer, in: Nano Biosens. Non-Invasive Diagnosis Cancer, IOP Publishing, 2024: pp. 13-1-13–21. https://doi.org/10.1088/978-0-7503-6234-4ch13.
[416] A.U. Patel, C.L. Williams, S.N. Hart, C.A. Garcia, T.J.S. Durant, T.C. Cornish, D. S. McClintock, Cybersecurity and Information Assurance for the Clinical Laboratory, J. Appl. Lab. Med. 8 (2023) 145–161, https://doi.org/10.1093/jalm/jfac119.
[417] M.E. Karim, Biosensors: Ethical, Regulatory, and Legal Issues, in: Handb. Cell Biosens., Springer International Publishing, Cham, 2022: pp. 679–705. https://doi.org/10.1007/978-3-030-23217-7_23.
[418] W. Jin, Q. Yang, S. Liu, C. Dong, T. Ren, Sensor-Assisted Next-Generation Diagnostics: Emerging Concepts, Biomarkers, Technologies, and Challenges, in: Miniaturized Biosensing Devices, Springer Nature Singapore, Singapore, 2022: pp. 1–37. https://doi.org/10.1007/978-981-16-9897-2_1.
[419] M. Sekar, R. Sriramprabha, P.K. Sekhar, S. Bhansali, N. Ponpandian, M. Pandiaraj, C. Viswanathan, Review—Towards Wearable Sensor Platforms for the Electrochemical Detection of Cortisol, J. Electrochem. Soc. 167 (2020) 067508, https://doi.org/10.1149/1945-7111/ab7e24.
[420] K.M. Koo, E.J.H. Wee, Y. Wang, M. Trau, Enabling miniaturised personalised diagnostics: from lab-on-a-chip to lab-in-a-drop, Lab Chip 17 (2017) 3200–3220, https://doi.org/10.1039/C7LC00587C.
[421] P. Lakhera, V. Chaudhary, B. Bhardwaj, P. Kumar, S. Kumar, Development and recent advancement in microfluidics for point of care biosensor applications: A review, Biosens. Bioelectron. X 11 (2022) 100218, https://doi.org/10.1016/j.biosx.2022.100218.
[422] M.A. Tainsky, Genomic and proteomic biomarkers for cancer: A multitude of opportunities, Biochim. Biophys. Acta - Rev, Cancer 1796 (2009) 176–193, https://doi.org/10.1016/j.bbcan.2009.04.004.
[423] B. Mohan, V. Mehak, A. Kumar, K. Modi, G. Singh, I.M. Garazade, J. Parikh, A.J. L. Pombeiro, A.A. Solovev, Detecting cancer biomarkers using electrochemical composite nanomaterials tools, Vietnam J. Chem. 63 (2025) 175–194, https://doi.org/10.1002/vjch.202300399.
[424] M.R. Ali, M.S. Bacchu, M.R. Al-Mamun, M.I. Hossain, A. Khaleque, A. Khatun, D. D. Ridoy, M.A.S. Aly, M.Z.H. Khan, Recent Advanced in MXene Research toward Biosensor Development, Crit. Rev. Anal. Chem. 54 (2024) 1381–1398, https://doi.org/10.1080/10408347.2022.2115286.
[425] G. Cutshaw, S. Uthaman, N. Hassan, S. Kothadiya, X. Wen, R. Bardhan, The Emerging Role of Raman Spectroscopy as an Omics Approach for Metabolic Profiling and Biomarker Detection toward Precision Medicine, Chem. Rev. 123 (2023) 8297–8346, https://doi.org/10.1021/acs.chemrev.2c00897.
[426] S. Das, R. Devireddy, M.R. Gartia, Surface Plasmon Resonance (SPR) Sensor for Cancer Biomarker Detection, Biosensors 13 (2023) 396, https://doi.org/10.3390/bios13030396.
[427] N. Bellassai, R. D'Agata, V. Jungbluth, G. Spoto, Surface Plasmon Resonance for Biomarker Detection: Advances in Non-invasive Cancer Diagnosis, Front. Chem. 7 (2019), https://doi.org/10.3389/fchem.2019.00570.
[428] S.M. Marcovina, F. Crea, J. Davignon, J.C. Kaski, W. Koenig, U. Landmesser, P. L. Pieri, J. Schulz-Menger, L.J. Shaw, J. Sobesky, Biochemical and bioimaging markers for risk assessment and diagnosis in major cardiovascular diseases: a road to integration of complementary diagnostic tools, J. Intern. Med. 261 (2007) 214–234, https://doi.org/10.1111/j.1365-2796.2006.01734.x.
[429] M.-F. Dafni, M. Shih, A.Z. Manoel, M.Y.E. Yousif, S. Spathi, C. Harshal, G. Bhatt, S.Y. Chodnekar, N.S. Chune, W. Rasool, T.P. Umar, D.C. Moustakas, R. Achkar, H. Kumar, S. Naz, L.M. Acuña-Chavez, K. Evgenikos, S. Gulraiz, E.S.M. Ali, A. Elaagib, I.H.P. Uggh, Empowering cancer prevention with AI: unlocking new frontiers in prediction, diagnosis, and intervention, Cancer Causes Control 36 (2025) 353–367, https://doi.org/10.1007/s10552-024-01942-9.
[430] D.V. Baker, J. Bernal-Escalante, C. Traaseth, Y. Wang, M.V. Tran, S. Keenan, W. R. Algar, Smartphones as a platform for molecular analysis: concepts, methods, devices and future potential, Lab Chip 25 (2025) 884–955, https://doi.org/10.1039/D4LC00966E.
[431] A. Yadav, K. Yadav, Portable solutions for plant pathogen diagnostics: development, usage, and future potential, Front. Microbiol. 16 (2025), https://doi.org/10.3389/fmicb.2025.1516723.
[432] H. Chai, X. Zhou, Z. Zhang, J. Rao, H. Zhao, Y. Yang, Integrating multi-omics data through deep learning for accurate cancer prognosis prediction, Comput. Biol. Med. 134 (2021) 104481, https://doi.org/10.1016/j.compbiomed.2021.104481.
[433] K. Chaudhary, O.B. Poirion, L. Lu, L.X. Garmire, Deep Learning–Based Multi-Omics Integration Robustly Predicts Survival in Liver Cancer, Clin. Cancer Res. 24 (2018) 1248–1259, https://doi.org/10.1158/1078-0432.CCR-17-0853.
[434] A. Mondello, M. Dal Bo, G. Toffoli, M. Polano, Machine learning in onco-pharmacogenomics: a path to precision medicine with many challenges, Front. Pharmacol. 14 (2024), https://doi.org/10.3389/fphar.2023.1260276.
[435] G. Brezgyte, V. Shah, D. Jach, T. Crnogorac-Jurcevic, Non-Invasive Biomarkers for Earlier Detection of Pancreatic Cancer—A Comprehensive Review, Cancers (Basel) 13 (2021) 2722, https://doi.org/10.3390/cancers13112722.
[436] T. Koltai, Earlier Diagnosis of Pancreatic Cancer: Is It Possible? Cancers (Basel) 15 (2023) 4430, https://doi.org/10.3390/cancers15184430.
[437] B. Huang, H. Huang, S. Zhang, D. Zhang, Q. Shi, J. Liu, J. Guo, Artificial intelligence in pancreatic cancer, Theranostics 12 (2022) 6931–6954, https://doi.org/10.7150/thno.77949.
[438] S. Tripathi, A. Tabari, A. Mansur, H. Dabbara, C.P. Bridge, D. Daye, From Machine Learning to Patient Outcomes: A Comprehensive Review of AI in Pancreatic Cancer, Diagnostics 14 (2024) 174, https://doi.org/10.3390/diagnostics14020174.
[439] P. Sijithra, N. Santhi, N. Ramasamy, A review study on early detection of pancreatic ductal adenocarcinoma using artificial intelligence assisted diagnostic methods, Eur. J. Radiol. 166 (2023) 110972, https://doi.org/10.1016/j.ejrad.2023.110972.
[440] R. Romano, A. Picca, L.H.U. Eusebi, E. Marzetti, R. Calvani, L. Moro, C. Bucci, F. Guerra, Extracellular Vesicles and Pancreatic Cancer: Insights on the Roles of miRNA, lncRNA, and Protein Cargos in Cancer Progression, Cells 10 (2021) 1361, https://doi.org/10.3390/cells10061361.
[441] M. Mittal, A. Kumari, B. Paul, A. Varshney, . B., A. Saini, C. Verma, I. Mani, Challenges and Opportunities of Gene Therapy in Cancer, OBM Genet. 08 (2024) 1–501. https://doi.org/10.21926/obm.genet.2401219.
[442] K. Bera, N. Braman, A. Gupta, V. Velcheti, A. Madabhushi, Predicting cancer outcomes with radiomics and artificial intelligence in radiology, Nat. Rev. Clin. Oncol. 19 (2022) 132–146, https://doi.org/10.1038/s41571-021-00560-7.
[443] D. Lee, C. Lee, K. Han, T. Goo, B. Kim, Y. Han, W. Kwon, S. Lee, J.-Y. Jang, T. Park, Machine learning models for pancreatic cancer diagnosis based on microbiome markers from serum extracellular vesicles, Sci. Rep. 15 (2025) 10995, https://doi.org/10.1038/s41598-025-94183-y.
[444] S.Y. Lee, J.M. Pakela, K. Na, J. Shi, B.J. McKenna, D.M. Simeone, E. Yoon, J. M. Scheiman, M.-A. Mycek, Needle-compatible miniaturized optoelectronic sensor for pancreatic cancer detection, Sci. Adv. 6 (2020), https://doi.org/10.1126/sciadv.abc1746.
[445] S. Hermoso-Durán, N. Fraunhoffer, J. Millastre-Bocos, O. Sanchez-Gracia, P. F. Garrido, S. Vega, Á. Lanas, J. Iovanna, A. Velázquez-Campoy, O. Abian,

Development of a Machine-Learning Model for Diagnosis of Pancreatic Cancer from Serum Samples Analyzed by Thermal Liquid Biopsy, Adv. Intell. Syst. 7 (2025), https://doi.org/10.1002/aisy.202400308.
[446] W. Wang, S. Chen, K.A. Brune, R.H. Hruban, G. Parmigiani, A.P. Klein, PancPRO: Risk Assessment for Individuals With a Family History of Pancreatic Cancer, J. Clin. Oncol. 25 (2007) 1417–1422, https://doi.org/10.1200/JCO.2006.09.2452.
[447] A.P. Klein, Genetic susceptibility to pancreatic cancer, Mol. Carcinog. 51 (2012) 14–24, https://doi.org/10.1002/mc.20855.
[448] K.M. Chan, J.M. Gleadle, M. O'Callaghan, K. Vasilev, M. MacGregor, Prostate cancer detection: a systematic review of urinary biosensors, Prostate Cancer Prostatic Dis. 25 (2022) 39–46, https://doi.org/10.1038/s41391-021-00480-8.
[449] V.R. Umapathy, P.M. Natarajan, B. Swamikannu, J. Moses, S. Jones, M. P. Chandran, M.K. Anbumozhi, Emerging Biosensors for Oral Cancer Detection and Diagnosis—A Review Unravelling Their Role in Past and Present Advancements in the Field of Early Diagnosis, Biosensors 12 (2022) 498, https://doi.org/10.3390/bios12070498.