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Review Articles

Frontiers in pancreatic cancer on biomarkers, microenvironment, and immunotherapy

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ABSTRACT

Pancreatic cancer remains one of the most challenging malignancies to treat due to its late-stage diagnosis, aggressive progression, and high resistance to existing therapies. This review examines the latest advancements in early detection, and therapeutic strategies, with a focus on emerging biomarkers, tumor microenvironment (TME) modulation, and the integration of artificial intelligence (AI) in data analysis. We highlight promising biomarkers, including microRNAs (miRNAs) and circulating tumor DNA (ctDNA), that offer enhanced sensitivity and specificity for early-stage diagnosis when combined with multi-omics panels. A detailed analysis of the TME reveals how components such as cancer-associated fibroblasts (CAFs), immune cells, and the extracellular matrix (ECM) contribute to therapy resistance by creating immunosuppressive barriers. We also discuss therapeutic interventions that target these TME components, aiming to improve drug delivery and overcome immune evasion. Furthermore, AI-driven analyses are explored for their potential to interpret complex multi-omics data, enabling personalized treatment strategies and real-time monitoring of treatment response. We conclude by identifying key areas for future research, including the clinical validation of biomarkers, regulatory frameworks for AI applications, and equitable access to innovative therapies. This comprehensive approach underscores the need for integrated, personalized strategies to improve outcomes in pancreatic cancer.

1. Introduction

Pancreatic cancer remains a highly aggressive malignancy characterized by its aggressive nature, late-stage diagnosis, and poor prognosis with a five-year survival rate of 13 % [1]. Recent data from the American Cancer Society's 2024 report shows a gradual improvement in outcomes, with the five-year survival rate rising by one percentage point for the third year. This poor prognosis is largely due to its typically late-stage diagnosis and its intrinsic resistance to conventional therapies such as chemotherapy and radiation [2]. Advances in understanding the molecular and genetic landscape of pancreatic cancer have identified key mutations, including *KRAS, TP53, CDKN2A,* and *SMAD4,* that drive tumorigenesis [3]. However, significant gaps remain in translating these findings into effective clinical strategies. Current biomarkers, such as CA 19–9, have limited sensitivity and specificity for early detection, underscoring the urgent need for more reliable diagnostic markers [4]. Although emerging technologies like multi-omics and liquid biopsy offer promise, their clinical application faces considerable challenges [5].

To address these challenges, an integrated approach is s required, combining the development of novel biomarkers, comprehensive genomic profiling, and a thorough understanding of the mechanisms underlying therapy resistance [6]. Multi-omics technologies, which simultaneously analyze genomics, transcriptomics, proteomics, and metabolomics, could be employed collaboratively with artificial intelligence (AI) and machine learning tools to create a comprehensive molecular profile of each patient's tumor [7]. These profiles could help refine early detection, predict therapy response, and monitor disease progression in real-time. By leveraging AI-driven tools, clinicians could

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analyze complex datasets to identify patterns and correlations that are not apparent through conventional methods, enabling more personalized and adaptive treatment strategies [8].

The tumor microenvironment (TME) also plays a crucial role in promoting tumor growth and therapy resistance, but its complexity introduces significant challenges in designing effective treatments [9]. For example, cancer-associated fibroblasts (CAFs), a key component of the TME, have been shown to exhibit both tumor-promoting and tumor-suppressing roles depending on the context [10]. In some cases, CAFs support tumor growth by enhancing angiogenesis, modulating immune responses, and facilitating metastasis; in other cases, they produce factors that inhibit cancer cell proliferation and invasion [11]. This dual role complicates the development of targeted therapies and necessitates a nuanced understanding of how different TME components contribute to therapy resistance and response [12]. Combining multi-omics data with TME-targeting strategies could help identify which components to modulate, rather than eradicate, thereby achieving a balance that supports immune activation while minimizing tumor-promoting factors [13].

Disparities in pancreatic cancer outcomes due to socioeconomic, racial, and geographic factors further complicate patient care, underscoring the need for equitable access to emerging therapies [14]. Integrating these elements into a unified framework for pancreatic cancer research and treatment, such as developing adaptive clinical trial designs that incorporate multi-omics and real-time monitoring technologies, could lead to more personalized, effective, and equitable care strategies [15]. This review examines these critical areas, focusing on the development of novel biomarkers, a deeper understanding of the TME, and more effective immunotherapy approaches. We also explore the potential of genomic profiling for personalized treatment, discuss the mechanisms underlying therapy resistance and metastasis, and emphasize the importance of improving patient stratification and addressing health disparities to advance pancreatic cancer care.

2. Advances in biomarkers for early detection

Early detection of pancreatic cancer remains a significant challenge due to the lack of highly sensitive and specific biomarkers [16]. The most commonly used biomarker, CA 19–9, lacks sufficient sensitivity and specificity for detecting early-stage detection as it is typically elevated only in advanced stages of the disease [17,18]. This limitation significantly restricts its utility for early diagnosis. Other biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA 125) suffer from a lack of specificity, as they can be elevated in other cancers or benign conditions [19]. Recent research has made significant progress in identifying novel biomarkers and technologies that offer more reliable methods for early detection [17,20,21].

2.1. Emerging biomarkers and multi-omics approaches

A major advancement in early detection of pancreatic cancer is the development of multi-biomarker panels that combine traditional markers like CA 19–9 with newer markers, such as DNA methylation patterns and microRNAs (miRNAs) [22,23]. Combining CA 19–9 with miRNAs like miR-21, miR-155, and miR-196a has shown significant improvement in diagnostic accuracy, especially in the sensitivity and specificity for detecting early-stage pancreatic cancer [24–26]. Studies have demonstrated that miRNAs are stable and non-invasive indicators of tumor presence, allowing for more accurate detection of early-stage pancreatic cancer. When integrated with next-generation sequencing technologies, these multi-omics approaches enhance biomarker discovery by combining genomic, transcriptomic, proteomic, and metabolomic data, enabling a comprehensive characterization of pancreatic tumors and the identification of novel molecular drivers of the disease [24,27].

In addition to miRNAs, circulating tumor DNA (ctDNA) has gained attention for its role in identifying KRAS and TP53 mutations, both of which are relevant for assessing tumor dynamics and response to treatment [28–30]. ctDNA provides a real-time snapshot of the genetic alterations within a tumor, offering valuable insights into how tumors evolve under treatment [31–33]. For example, ctDNA has been used to track mutations in KRAS and TP53, which are common in pancreatic cancer and contribute to its aggressive nature [7,34,35]. These mutations can be used to assess the effectiveness of therapies, identify resistance mechanisms, and guide treatment adjustments [36,37].

Recent multi-omics studies have revealed novel biomarkers and identified pancreatic cancer subtypes, providing new insights into the molecular mechanisms underlying therapy resistance [34,38]. For instance, a study that integrated genomic and transcriptomic data identified a distinct metabolic subtype of pancreatic cancer that is highly resistant to conventional therapies [39]. These findings underscore the potential of multi-omics analyses in advancing precision medicine and enabling the customization of therapeutic approaches.

2.2. AI-driven data analysis in pancreatic cancer

The integration of AI into data analysis is revolutionizing biomarker discovery, early detection, and monitoring strategies in pancreatic cancer research [40,41]. AI algorithms are particularly effective at analyzing large, complex datasets derived from multi-omics and liquid biopsy technologies, allowing for the identification of subtle patterns that may not be apparent through traditional methods [5,42]. AI has been successfully applied in detecting ctDNA, circulating tumor cells (CTCs), and other molecular markers, significantly enhancing early detection capabilities and improving treatment monitoring [43,44].

Specific examples of AI-driven applications include machine learning models trained on genomic and transcriptomic data to predict pancreatic cancer prognosis. These models analyze genomic profiles, including mutations, gene expression patterns, and pathway alterations, to estimate patient outcomes and identify high-risk subgroups [45,46]. Another promising area is the application of AI in analyzing ctDNA and CTCs, which are crucial for non-invasive monitoring of tumor dynamics [47,48]. AI algorithms can identify specific mutation signatures and changes in ctDNA concentration, allowing for real-time monitoring of treatment response and disease progression [49,50].

Despite these advancements, integrating AI-driven analyses into clinical practice faces several challenges. AI models require large, high-quality datasets to achieve reliable predictive accuracy, and collecting these datasets can be challenging, especially in pancreatic cancer, where patient samples are often limited [8,51,52]. Additionally, there is a risk of data bias, which can lead to inaccurate predictions if the training data is not representative of the broader patient population [7,41,53]. Regulatory challenges also pose obstacles, as clinical validation of AI models requires rigorous testing and adherence to regulatory standards, which can slow the adoption of these technologies [54].

To address these limitations, collaborative data-sharing initiatives among research institutions and standardization efforts are being explored. These initiatives aim to create large, diverse datasets that enhance the generalizability of AI models and reduce data bias [55,56]. Additionally, establishing standardized AI model validation protocols can streamline the clinical translation of AI-driven analyses and ensure that they meet regulatory requirements [57]. As AI continues to evolve, these measures are essential for integrating AI into precision oncology, where it can support personalized treatment decisions and improve patient outcomes in pancreatic cancer [8,58].

Fig. 1 provides a comparative analysis of current and emerging biomarkers, highlighting their sensitivity, specificity, and potential for early detection in pancreatic cancer.

To provide a clearer understanding of the current state of biomarker research in pancreatic cancer, Table 1 summarizes the most widely used and emerging biomarkers, highlighting their current utility, limitations, and potential advancements in early detection strategies.

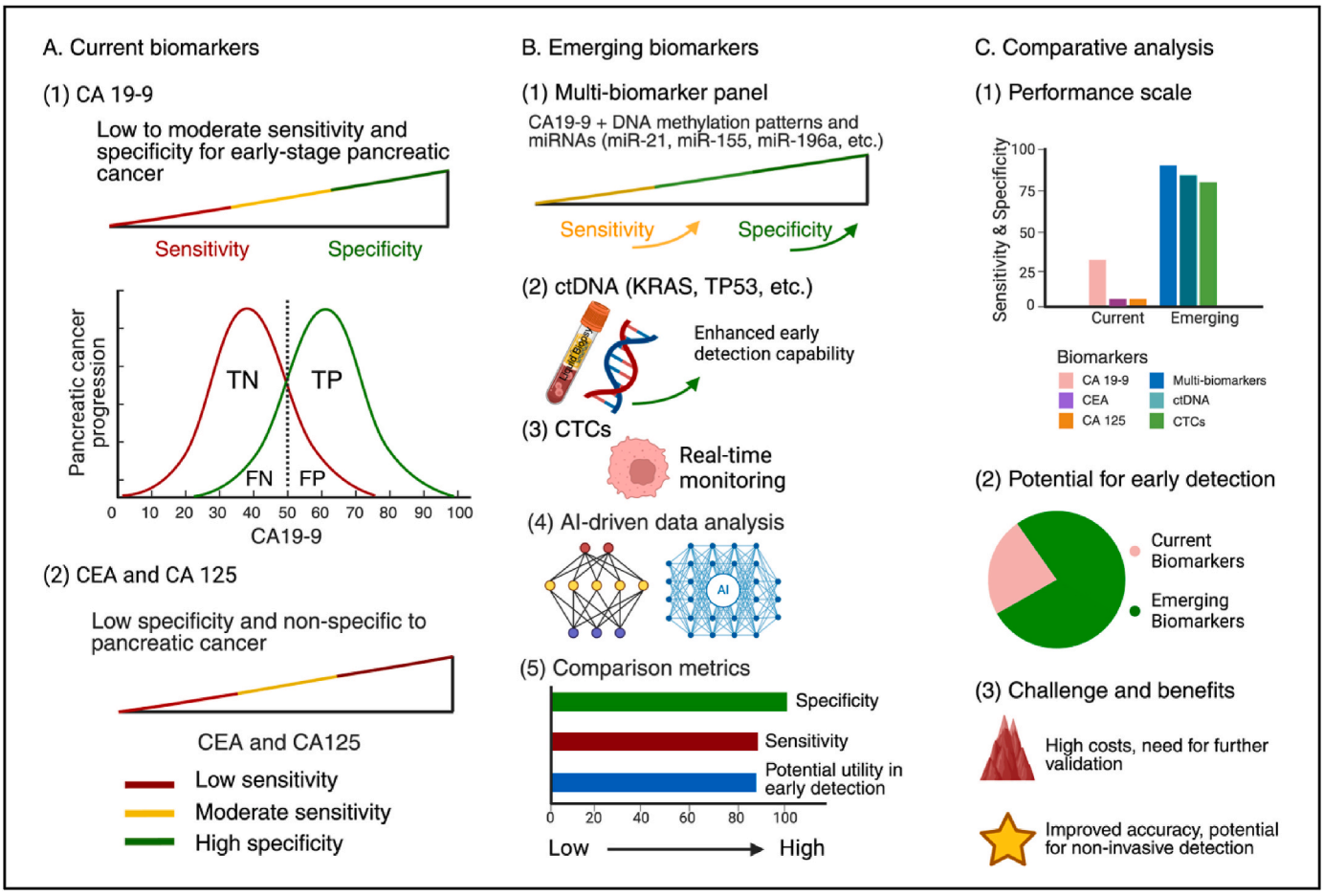

Fig. 1. Comparison of current and emerging biomarkers for early detection of pancreatic cancer. This figure contrasts the current biomarkers (CA 19–9, CEA, CA 125) with emerging options (multi-biomarker panels, ctDNA, and CTCs) for pancreatic cancer detection. It illustrates that current biomarkers have limitations in sensitivity and specificity, particularly for early-stage detection. A. CA 19–9 is typically used for monitoring disease progression rather than diagnose early-stage cancer, while CEA and CA 125 lack specificity needed for accurate early detection. B. Emerging biomarkers offer enhanced sensitivity and specificity, with multi-biomarker panels combining CA 19–9, DNA methylation patterns and microRNA signatures (e.g., miR-21, miR-155, miR-196a). ctDNA detects mutations such as KRAS, TP53, while CTCs enable real-time monitoring through minimally invasive liquid biopsies. C. A comparative analysis using bar and pie charts shows the superior performance of emerging biomarkers in terms of sensitivity, specificity, and potential for early detection. Despite their benefits, challenges, such as high costs and the needs for further validation, balanced against the benefits of improved accuracy and the potential for non-invasive detection methods remain.

2.3. Critical analysis of limitations and future directions

While recent advancements in biomarkers and multi-omics approaches hold promise, several challenges remain. Multi-omics approaches, although powerful, are resource-intensive and require large, well-annotated datasets for meaningful analysis [7,59]. Integrating multi-omics data from diverse platforms can also be technically challenging and prone to variability [59,60]. Similarly, while AI-driven models are promising, they require extensive validation and robust, high-quality datasets for training to ensure accuracy in clinical settings [61]. Biases in these datasets can significantly impact the predictive accuracy of AI models [62].

Future directions in pancreatic cancer biomarker research should focus on validating multi-omics and AI-driven approaches through large-scale clinical trials [63]. Efforts should also be made to integrate these technologies into routine clinical workflows, making them accessible for widespread use [64]. The combination of AI and multi-omics promises significant breakthroughs in personalized medicine, facilitating earlier detection of pancreatic cancer and enabling the tailoring of therapies to individual tumor characteristics [8,65].

3. Mechanisms of therapy resistance and the role of the TME

Pancreatic cancer's intrinsic resistance to conventional therapies is significantly influenced by both genetic mutations and the complex dynamics of the TME [2,66]. The TME in pancreatic cancer is particularly desmoplastic, marked by a dense stromal barrier comprising CAFs, immune cells, extracellular matrix (ECM) components, and hypoxic conditions [67,68]. Together, these elements establish a hostile environment that impedes drug delivery, facilitates immune evasion, and promotes tumor survival [11,69]. Key mutations such as those in KRAS and TP53 activate key survival pathways like phosphatidylinositol 3-kinase/protein kinase B pathway (PI3K/AKT) and mitogen-activated protein kinase (MAPK), which in turn promote the epithelial-mesenchymal transition (EMT), and further enhance these resistance mechanisms [70,71].

3.1. CAFs and resistance mechanisms

CAFs are a dominant component of the pancreatic TME and play a pivotal role in fostering resistance through various mechanisms [72,73]. They secrete growth factors, cytokines, and chemokines that support tumor cell proliferation and survival, while also modulating the ECM to create physical and biochemical barriers against therapeutic agents [74,

Table 1
Current and emerging biomarkers for early detection of pancreatic cancer.

Biomarker	Current use	Limitations	Emerging alternatives
CA 19-9	Most commonly used for diagnostic aid	Low sensitivity and specificity, especially in early-stage disease	miRNA panels in combination with CA 19–9 for enhanced sensitivity
CEA	Diagnostic tool	Low specificity; elevated in non-pancreatic conditions	Use of ctDNA to identify tumor-specific mutations
CA 125	Diagnostic tool for other cancers	Non-specific to pancreatic cancer	Integration with DNA methylation patterns for higher specificity
miRNA (e.g., miR-21, miR-155)	Emerging for early detection	Limited clinical validation; early-stage research	Combined with CA 19–9 to improve early detection
ctDNA (e.g., KRAS, TP53 mutations)	Liquid biopsy to detect mutations	Limited by tumor shedding rates and mutation heterogeneity	Combined with imaging for enhanced detection
CTCs	Monitoring tool for advanced stages	Rare and difficult to capture	Use in combination with other biomarkers like ctDNA for better sensitivity
DNA Methylation Markers (e.g., BMP3, NDRG4)	DNA-based detection	Still in experimental stages, clinical validation needed	Combined with multi-omics approaches for precision
ctDNA	Detection of genetic mutations	Limited by tumor shedding rates	Combined with imaging for better sensitivity
PD-L1	Immunotherapy biomarker for immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1)	Heterogeneous expression; not universally predictive of treatment response	Comprehensive immune profiling for better predictive accuracy

75]. CAFs produce ECM components like collagen and fibronectin, which contribute to the rigidity and density of the tumor stroma, effectively limiting drug penetration [76,77]. Additionally, CAFs promote ECM remodeling through the secretion of matrix metalloproteinases (MMPs), enhancing the invasive potential of cancer cells and supporting metastasis [78,79].

Moreover, CAFs interact with tumor cells and other TME components by releasing signaling molecules such as TGF-β and IL-6, which activate survival pathways (e.g., PI3K/AKT) and drive EMT [67,80]. EMT endows cancer cells with stem-cell-like properties, increasing their resistance to apoptosis and fostering metastatic potential [81]. By creating an immunosuppressive environment, CAFs also recruit immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further enhancing therapy resistance [82,83].

3.2. Immune cells and immunotherapy resistance

Immune cells within the TME are critical mediators of immunotherapy resistance [84,85]. In pancreatic cancer, the TME is often infiltrated by immunosuppressive cells such as Tregs, MDSCs, and tumor-associated macrophages (TAMs), which contribute to immune evasion by secreting cytokines like IL-10, TGF-β, and VEGF [86,87]. These cytokines inhibit the activity of cytotoxic T cells and natural killer (NK) cells [88]. Tregs suppress antitumor immune responses through direct cell-cell interactions and immunosuppressive cytokines, thereby reducing the efficacy of immune checkpoint inhibitors [89].

MDSCs further enhance immune suppression by producing reactive oxygen species (ROS) and nitric oxide, which inhibit T-cell proliferation and promote T-cell apoptosis [83,90]. These immunosuppressive functions are significant barriers to immunotherapy, as they prevent the activation and expansion of effector immune cells [91]. Targeting these immune cells, either by depleting them or inhibiting their functions, has shown promise in preclinical studies as a strategy to enhance immunotherapy efficacy in pancreatic cancer [92,93].

3.3. ECM components and physical barriers

The ECM is a structural component of the TME that plays a dual role in tumor growth and therapy resistance [79,94]. It is rich in collagen, hyaluronan, and fibronectin, which contribute to high interstitial pressure and a dense stroma that limits drug diffusion [95]. This fibrotic stroma acts as a physical barrier, preventing adequate drug penetration and reducing the effectiveness of systemic therapies [78,96]. In addition to its physical properties, the ECM serves as a reservoir for growth factors and cytokines, which are released upon ECM remodeling and promote tumor growth and survival [97,98].

Hyaluronan, a glycosaminoglycan abundant in the ECM of pancreatic tumors, contributes to increased interstitial fluid pressure and hypoxia within the tumor [99]. Targeting ECM components, such as with the enzyme PEGPH20 to degrade hyaluronan, has been explored to reduce stromal density and improve drug delivery [78,100]. However, the depletion of certain ECM components can also have paradoxical effects, as the loss of structural support may lead to increased tumor invasiveness in some cases [78,79]. Therefore, therapeutic strategies targeting the ECM need to be carefully modulated [69,101].

3.4. Key survival pathways: PI3K/AKT and MAPK

Mutations in oncogenes like KRAS and tumor suppressors like TP53 activate survival pathways that play a central role in therapy resistance [36,70]. In pancreatic cancer, KRAS mutations are nearly ubiquitous and lead to the constitutive activation of the MAPK pathway, driving cell proliferation, survival, and metabolic reprogramming [2,101]. The MAPK pathway promotes EMT, which facilitates the acquisition of stem-cell-like characteristics by cancer cells, enhancing their ability to resist apoptosis and survive under adverse conditions, such as hypoxia and nutrient deprivation within the TME [102,103].

The PI3K/AKT pathway, frequently activated through CAF-derived growth factors, supports tumor cell survival, proliferation, and resistance to apoptosis [104,105]. Activation of this pathway also enhances EMT and contributes to a stem-like phenotype that is associated with increased metastatic potential [104]. Both the PI3K/AKT and MAPK pathways provide survival signals that allow cancer cells to evade the cytotoxic effects of chemotherapy and targeted therapies [106,107].

3.5. Therapeutic interventions targeting the TME

Given the TME's role in promoting resistance, several therapeutic strategies aim to modulate the TME and overcome these barriers [77,108,109]. Targeting CAFs and ECM components through stromal modulation is one approach [110]. For example, inhibiting TGF-β or fibroblast activation protein (FAP) to reduce CAF activity and stromal density can enhance drug penetration and reduce immunosuppression [12,111]. However, stromal depletion strategies must be carefully balanced to avoid adverse effects, such as increased tumor aggressiveness [112,113].

Immune checkpoint inhibitors, combined with agents targeting Tregs, MDSCs, or TAMs, show promise for reactivating antitumor immunity within the TME [114,115]. For instance, combining anti-PD-1 or anti-PD-L1 antibodies with agents inhibiting Treg or MDSC function has shown potential to improve the efficacy of immune checkpoint blockade in preclinical studies [116,117].

Finally, combination therapies that target multiple aspects of the TME, including both immune and non-immune components, are

emerging as promising strategies [118–120]. For example, combining immune checkpoint inhibitors with stromal-modulating agents or targeting both CAFs and ECM components in conjunction with conventional chemotherapy can provide a synergistic effect, enhancing drug delivery and antitumor immune responses [121,122]. These approaches are being explored in clinical trials, with the aim of developing effective multimodal therapies that address the unique challenges posed by the TME in pancreatic cancer [2,123,124].

Fig. 2 illustrates the key components of the TME in pancreatic cancer, highlighting the pathways involved in therapy resistance and potential therapeutic strategies targeting these components to improve treatment outcomes.

A. Key components in the TME: Cancer cells with KRAS and TP53 mutations are surrounded by various immune and stromal cells such as CAFs, MDSCs, Tregs, and TAMs, which collectively contribute to an immunosuppressive microenvironment and tumor progression. B. Targets and pathways in treatment resistance: (1) The Hedgehog signaling pathway: targeted by Vismodegib, which inhibits SMO to block GLI transcription factor activation, hindering tumor growth. (2) The hypoxia-induced pathway: low oxygen levels activate HIF1α, driving angiogenesis and drug resistance. (3) The integrin-mediated pathway: integrins interact with ECM components, enhancing cancer cell adhesion, migration, and treatment resistance. C. KRAS/TP53 mutations and EMT activation: mutations in KRAS and TP53 initiate EMT, transforming epithelial cells into mesenchymal cells with increased migratory abilities, loss of cell-cell adhesions, and ECM remodeling, contributing to therapy resistance. D. PI3K/AKT and MAPK pathway activation: KRAS/TP53 mutations also activate survival pathways such as PI3K/AKT and MAPK, promoting tumor cell invasion, angiogenesis, and apoptosis resistance. E. Immune evasion mechanisms in the TME: tumor cells evade immune detection through immune checkpoint pathways (e.g., PD-1/PD-L1, CTLA-4), reduce antigen presentation, and immunosuppressive actions of Tregs, MDSCs, and cytokines, which collectively reduce the efficacy of immune-based therapies. F. Immune checkpoints and potential therapeutic interventions: therapies such as FAP inhibitors and TGF-β inhibitors target CAFs, while immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) aim to restore antitumor immunity. Enzymes like collagenase and PEGPH20 degrade ECM components to improve drug delivery, and colony-stimulating factor 1 receptor (CSF1R) inhibitors target TAMs to reduce immunosuppression. G. Legend: icons represent various cell types and components in the TME, including B cells, CAFs, cytotoxic T cells, and TAMs.

Considering these challenges, various clinical trials have explored combination therapies to enhance the efficacy of immunotherapy in pancreatic cancer. Table 2 provides a comprehensive summary of pivotal clinical studies that focus on combination strategies designed to enhance the efficacy of immunotherapy in pancreatic cancer, presenting key outcomes and identifying potential and areas for further improvement.

4. Overcoming immunotherapy challenges in pancreatic cancer

Immunotherapy has revolutionized cancer treatment, but its efficacy in pancreatic cancer is limited by the unique TME, which is highly immunosuppressive, characterized by a dense stroma and low mutational burden that restrict immune cell infiltration [137,138]. Consequently, treatments like immune checkpoint inhibitors, effective in other cancers, have shown minimal success in pancreatic cancer [137,139]. Similar challenges exist for other immunotherapeutic strategies, such as cancer vaccines and adoptive T cell therapies [108,140].

To overcome these limitations, combination immunotherapy strategies have been explored, but results remain inconsistent [141]. For instance, trials combining immune checkpoint inhibitors with chemotherapy or targeted agents often fail to show significant survival benefits over monotherapy [142]. The Phase III trial of ipilimumab (an anti-CTLA-4 antibody) with gemcitabine showed no survival improvement over gemcitabine alone [143]. Similarly, combining nivolumab (an anti-PD-1 antibody) with nab-paclitaxel and gemcitabine did not demonstrate substantial advantages over chemotherapy alone [5,144].

A strategy to improve these outcomes could involve integrating genomic and molecular profiling with real-time monitoring techniques like liquid biopsies and AI-driven tools [47]. This integration would allow for better patient stratification, enabling the identification of individuals most likely to benefit from specific combinations. For example, liquid biopsies could provide real-time insights into tumor evolution and resistance patterns, while AI tools could analyze complex data to personalize treatment plans dynamically [145].

To systematically implement this strategy in clinical practice, collaborative models between research institutions and healthcare providers are essential [146]. These partnerships could facilitate the rapid translation of genomic data into actionable insights, ensuring that new therapeutic approaches are continuously refined based on real-world outcomes. Future clinical trials should incorporate these technologies to adapt treatments in real time, ultimately enhancing the effectiveness of combination immunotherapy strategies for pancreatic cancer patients [16,147].

5. Personalized therapy through genomic and molecular profiling

Recent advancements in genomic and molecular profiling have significantly improved our understanding of the heterogeneity of pancreatic cancer, revealing distinct molecular subtypes that offer promising avenues for personalized therapies [2,148]. However, translating these findings into clinical practice remains challenging. Subtypes such as “classical” and “basal-like” exhibit unique biological behaviors and therapeutic vulnerabilities [149]. Key mutations in genes like KRAS, TP53, CDKN2A, and SMAD4 are major drivers of tumorigenesis and are associated with patient outcomes [150,151]. Despite these insights providing a foundation for targeted therapies, the lack of effective treatments specifically targeting these mutations limits their clinical application [152].

To address this, a more integrated strategy is needed, combining genomic and molecular profiling with real-time monitoring technologies, such as liquid biopsies and AI-driven tools, to enhance patient stratification, monitor disease progression, and personalize treatment plans [153]. This framework could involve systematically using liquid biopsies to detect ctDNA and RNA, alongside single-cell sequencing, to capture dynamic changes in the tumor profile throughout treatment [154].

AI-driven algorithms can analyze these complex datasets to identify biomarkers predictive of response or resistance to specific therapies, allowing for adaptive, personalized interventions [155]. For example, collaborative models between research institutions and healthcare providers could facilitate the integration of these tools into clinical workflows, ensuring that genomic data and real-time monitoring inform treatment decisions [146,156]. Regular multidisciplinary meetings involving oncologists, pathologists, bioinformaticians, and data scientists could help interpret these data more effectively and refine therapeutic strategies continuously. Fig. 3 illustrates the personalized therapy workflow for pancreatic cancer, highlighting the integration of genomic profiling and real-time monitoring techniques to create tailored treatment plans based on individual patient characteristics.

Furthermore, combining this approach with clinical trials could help stratify patients more accurately based on molecular subtypes, thereby optimizing targeted therapies such as PARP inhibitors for DNA repair defects or HER2 inhibitors for HER2-amplified tumors [157]. Implementing this strategy in a network of cancer centers could allow for shared resources, data, and expertise, ultimately accelerating the development and application of personalized treatments in pancreatic cancer care.

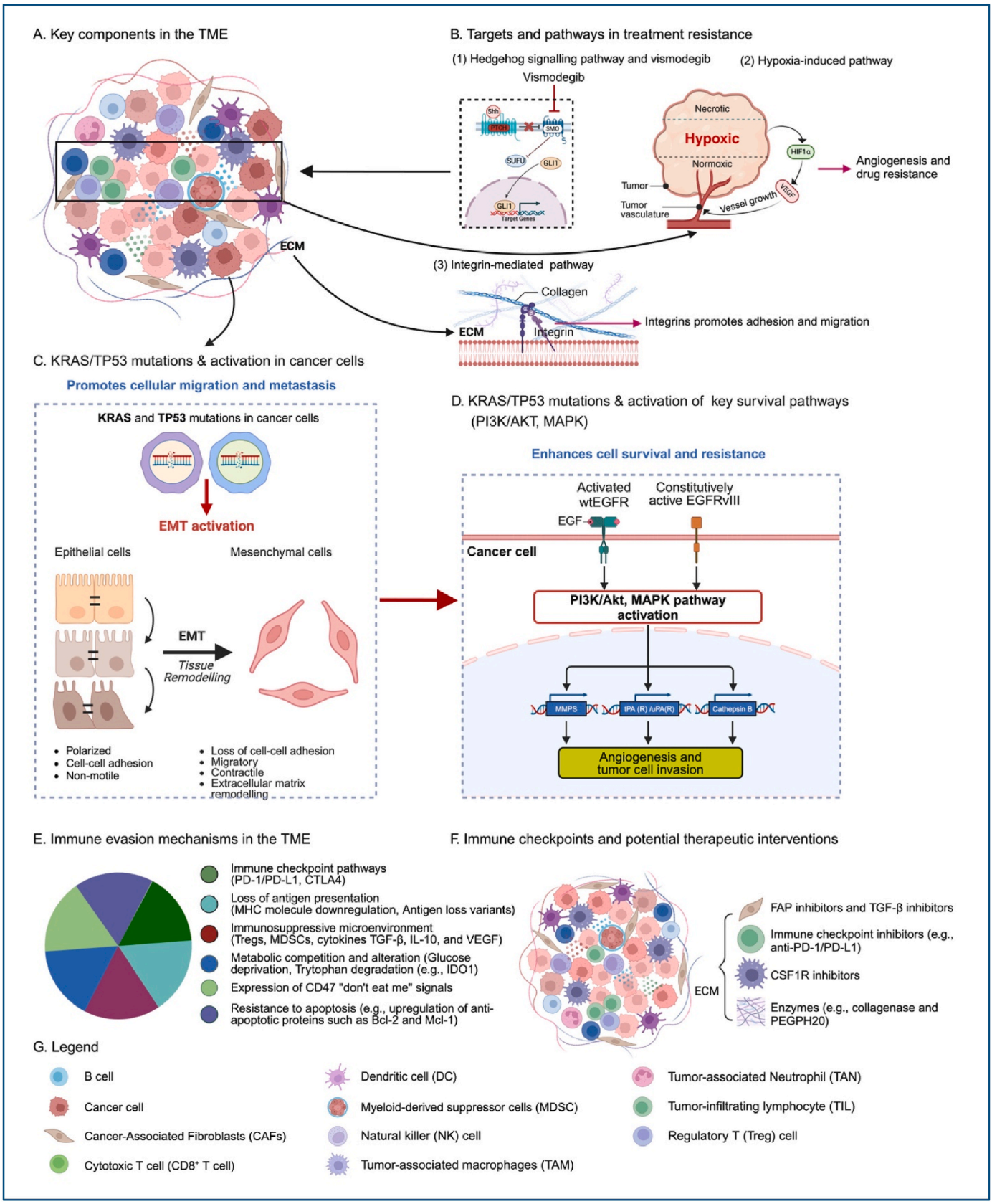

Fig. 2. Mechanisms of therapy resistance and the role of the TME in pancreatic cancer. This figure illustrates the key mechanisms driving therapy resistance in pancreatic cancer, along with potential therapeutic strategies.

Table 2
Clinical studies enhancing immunotherapy efficacy in pancreatic cancer.

Study	Immunotherapy Strategy	Combination Therapy	Clinical Outcome	Phase	References
NCT03884556 NCT02930902	PD-1 Inhibitor (Pembrolizumab)	Combined with CD40 agonist and chemotherapy (Gemcitabine/Nab-paclitaxel)	Improved immune response and partial tumor regression observed in some patients	II	[125,126]
NCT03190265 NCT01896869	CTLA-4 Inhibitor (Ipilimumab)	Combined with GVAX vaccine (granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting allogeneic pancreatic tumor cells)	T-cell activation and prolonged survival in responders	II	[127,128]
NCT02526017 NCT03599362	CSF1R Inhibitor (Cabiralizumab)	Combined with anti-PD-1 therapy (Nivolumab)	Increased infiltration of T-cells in tumors, improved immune checkpoint blockade response	I	[129,130]
NCT03634332	PEGPH20 (targets ECM, hyaluronic acid)	Combined with PD-1 inhibitor and chemotherapy	Enhanced drug delivery and increased efficacy of PD-1 blockade therapy	II	[131,132]
NCT02077881	IDO Inhibitor (Indoximod)	Combined with gemcitabine and Nab-paclitaxel	Improved survival and immune response, reduced immune suppression	I/II	[133,134]
NCT02734160	TGF-β Inhibitor (Galunisertib)	Combined with PD-L1 Inhibitor (Durvalumab)	Reduced immunosuppressive TME, enhanced immune checkpoint inhibitor efficacy	I/II	[135,136]

By fostering collaborations between research and clinical practice, integrating advanced technologies, and standardizing protocols for genomic and molecular profiling, we can move towards more effective and individualized therapies for pancreatic cancer patients [158].

6. Mechanisms driving resistance and metastasis

Pancreatic cancer is resistant to conventional therapies and prone to early metastasis, contributing significantly to its poor prognosis [159]. Developing more effective treatment strategies requires a thorough understanding of the underlying mechanisms driving resistance and metastasis. Resistance arises from genetic, epigenetic, and microenvironmental factors [160]. The dense stromal barrier, composed of CAFs, ECM, and immune cells, obstructs drug delivery and creates a hypoxic environment that supports cancer cell survival [161]. Additionally, cancer cells often exhibit high plasticity through EMT, which enhances resistance to apoptosis and promotes stem cell-like properties [162]. Cancer stem cells (CSCs) further contribute to resistance due to their inherent resilience to chemotherapy and radiation [163]. Moreover, mutations in key signaling pathways, such as KRAS, PI3K/AKT, and MAPK, result in continuous activation of survival and proliferation signals, diminishing the efficacy of treatments [104]. Overexpression of drug efflux pumps, such as those in the ATP-binding cassette (ABC) family, also plays a role by actively removing therapeutic agents from cells [164].

Metastasis, a leading cause of pancreatic cancer mortality, involves several stages, including local invasion, intravasation, survival in the bloodstream, and colonization of distant organs [165]. EMT enhances cancer cell migration and invasion, allowing cells to detach from the primary tumor and enter circulation [162]. The stromal environment supports this process by secreting cytokines and growth factors that promote invasion, while pre-metastatic niches, or microenvironments in distant organs, facilitate the establishment of CTCs as secondary tumors [166]. Additionally, pancreatic cancer cells demonstrate a high affinity for the liver, supported by specific adhesion molecules and chemokine receptors that guide them to this organ [159,165]. Fig. 4 provides an overview of the key mechanisms that drive therapy resistance and metastasis in pancreatic cancer, detailing the genetic mutations, cellular changes, and microenvironmental factors involved in these processes.

To address these challenges, innovative therapeutic strategies are needed that combine targeted agents with immunotherapies or employ new drug delivery systems to penetrate the dense stroma. Combining chemotherapy with agents that inhibit drug efflux pumps or target survival pathways may improve efficacy [167]. Strategies like combining inhibitors of the Hedgehog signaling pathway with immunotherapies could disrupt stromal integrity, enhancing drug delivery while also modifying the immune environment to support anti-tumor activity [168]. Approaches to inhibit EMT or target specific transcription factors may reduce both resistance and the potential for metastasis [169]. Using selective modulators to target subtypes of stromal cells, preventing the formation of pre-metastatic niches, or blocking adhesion molecules that guide tumor cells to distant sites may also be effective. New drug delivery systems, such as nanoparticle-based therapies or stromal-penetrating peptides, could improve the transport of therapeutic agents through the dense stroma, enhancing drug availability to cancer cells [170,171].

Integrating genomic and molecular profiling with real-time monitoring techniques like liquid biopsies and AI-driven tools can help stratify patients based on molecular subtypes and tailor treatments more effectively [172]. This approach would involve creating adaptive clinical trial designs that identify and select patients likely to benefit from specific combinations or new therapeutic strategies. Collaborative models between research institutions and healthcare providers are essential to translating these innovative strategies into clinical practice, ultimately developing more effective therapies to address both resistance and metastasis, thereby improving outcomes for patients with pancreatic cancer.

7. Advancing clinical trials through enhanced patient stratification

To improve the efficacy of clinical trials in pancreatic cancer, precise patient stratification using advanced molecular profiling and AI tools is essential [7,173]. Current trial designs often overlook the disease's heterogeneity, leading to suboptimal outcomes [174]. Stratification based on genetic mutations, molecular subtypes, and other biomarkers is crucial for identifying subgroups most likely to benefit from specific therapies, thereby enhancing trial success and minimizing adverse effects [22].

Many existing trials still employ a "one-size-fits-all" approach, which fails to account for the diverse biological characteristics of pancreatic cancer [173,175]. This can result in ineffective treatments across broader patient populations. Additionally, the lack of comprehensive molecular profiling limits the identification of predictive biomarkers [172]. To address this, integrating multi-omics data (genomic, transcriptomic, proteomic) and AI-driven tools can enhance the identification of relevant patient subgroups by analyzing large datasets more effectively [176]. AI algorithms can help identify patterns that may not be apparent through traditional methods, thus refining patient selection criteria.

Adaptive trial designs that allow modifications based on interim results are recommended to tailor treatments dynamically. These designs can help optimize therapeutic strategies in real-time by incorporating findings such as emerging biomarkers or changes in patient response. For example, trials could start with a broad patient cohort and then stratify patients further based on molecular profiling and AI analysis as the trial progresses [173,177]. This approach would ensure that therapies are better targeted to those who are most likely to benefit,

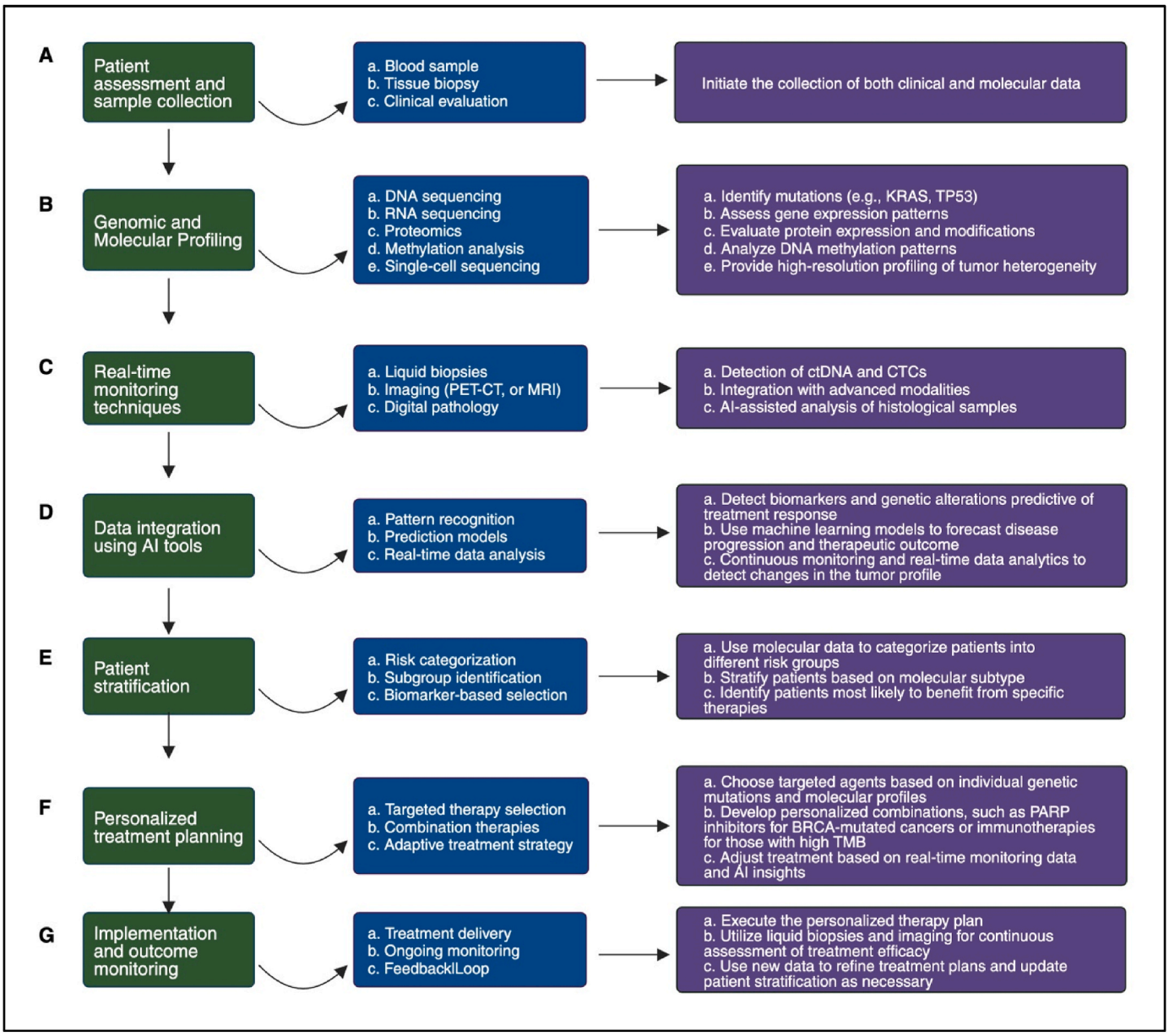

Fig. 3. Personalized therapy workflow in pancreatic cancer using genomic profiling. This diagram outlines the process of developing personalized cancer treatment plans, starting with patient assessment and sample collection (Step A), where blood, tissue, and clinical data are gathered. Step B involves genomic and molecular profiling, using DNA/RNA sequencing, proteomics, and single-cell analysis to characterize tumor features. Real-time monitoring (Step C) employs liquid biopsies, imaging techniques such as PET/CT or MRI, and digital pathology to track tumor changes and identify ctDNA and CTCs. Data integration using AI tools (Step D) enables advanced analysis to predict disease progression and optimize treatment based on patient risk levels and molecular subtypes. Patient stratification (Step E) sorts individuals into groups based on their genetic and molecular profiles to guide targeted therapy choices. In personalized treatment planning (Step F), tailored therapies are selected, and strategies are adjusted as needed. The final step, implementation and outcome monitoring (Step G), focuses on delivering the treatment and continuously evaluating its effectiveness to refine plans for optimal patient outcomes.

improving both the efficacy and safety of new treatments.

To further enhance trial inclusivity, efforts should focus on recruiting a diverse patient population, including those with rare molecular subtypes, advanced disease stages, or from various racial and ethnic backgrounds [178]. This would ensure new therapies are effective across different demographic groups and mitigate potential biases in treatment responses.

Integrating real-time monitoring techniques, such as liquid biopsies, into clinical trials can provide continuous data on treatment response and resistance, enabling timely adjustments to therapeutic strategies [179]. Collaborative models between research institutions and healthcare providers would facilitate the application of these advanced methodologies in clinical practice [180]. By adopting these approaches, clinical trials can become more efficient and inclusive, ultimately leading to meaningful results that improve patient outcomes.

8. Reducing health disparities

Health disparities profoundly affect pancreatic cancer outcomes, leading to unequal burdens among different populations due to socioeconomic, racial, and geographic factors [158,181]. These disparities result in variations in access to care, treatment options, and survival rates, contributing to significant differences in prognosis and overall outcomes across demographic groups [182]. For example, recent studies

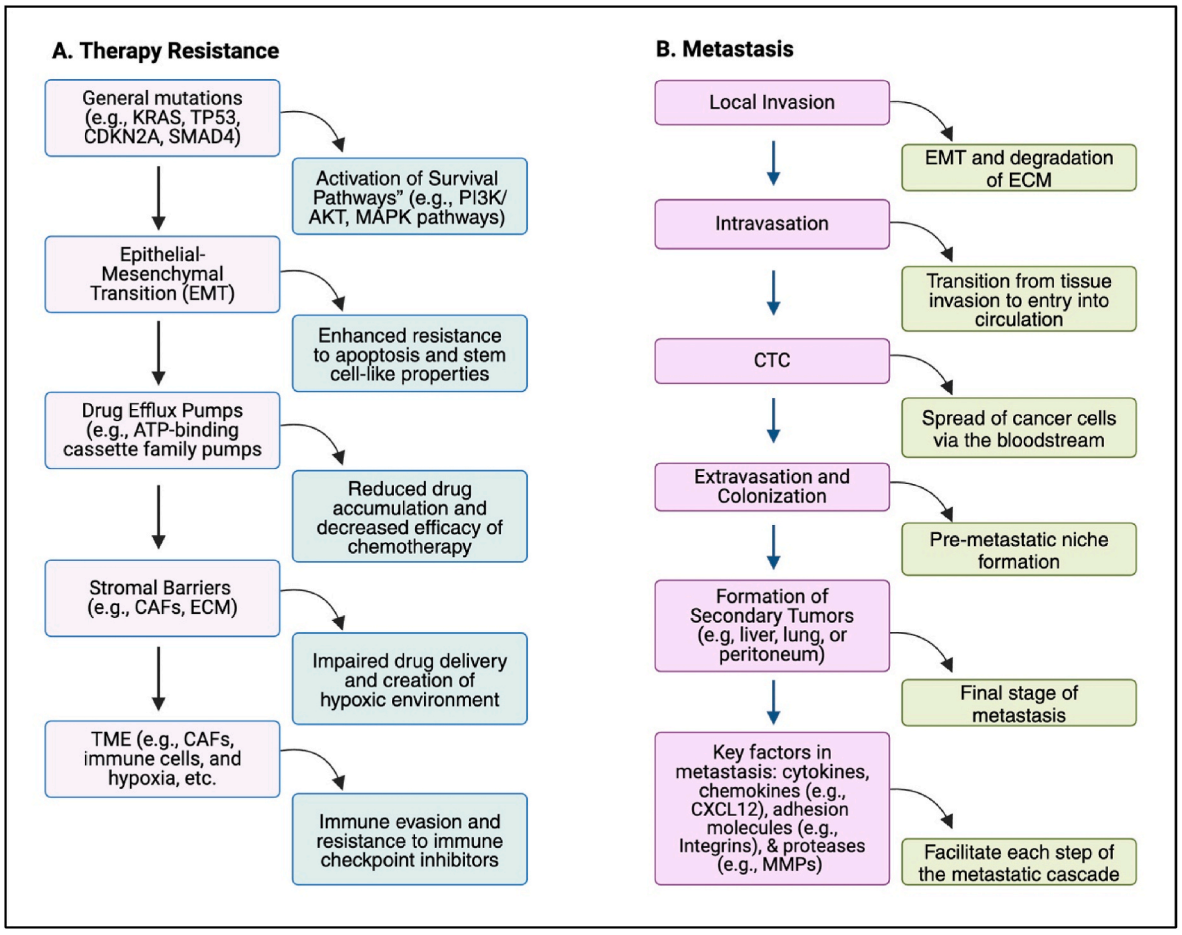

Fig. 4. Mechanisms driving resistance and metastasis in pancreatic cancer. This figure illustrates the fundamental mechanisms contributing to therapy resistance and metastasis in pancreatic cancer. Panel A displays the progression of resistance mechanisms, starting with genetic mutations (e.g., KRAS, TP53, CDKN2A, SMAD4) that activate survival pathways (e.g., PI3K/AKT, MAPK). These mutations drive EMT, increasing apoptosis resistance and promoting stem cell-like properties. Drug efflux pumps (like ATP-binding cassette family pumps) reduce drug accumulation, while stromal barriers (e.g., CAFs and ECM) limit drug delivery and create a hypoxic environment. The TME fosters immune evasion and resistance to immune checkpoint inhibitors. Panel B details the steps of metastasis, beginning with local invasion facilitated by EMT and ECM degradation. This is followed by intravasation (the entry of cancer cells into the bloodstream), the spread of CTCs, and extravasation (exit from the bloodstream). The formation of pre-metastatic niches in distant organs supports colonization and growth of secondary tumors. Key factors in metastasis include cytokines, chemokines, adhesion molecules, and proteases aiding each step of the metastatic cascade.

have shown that African American and Hispanic patients have higher incidence rates of pancreatic cancer and are more often diagnosed at advanced stages than white patients, leading to reduced chances of receiving potentially curative surgical resection and timely treatments, ultimately contributing to higher mortality rates in these groups [183].

Several recent reports highlight that these disparities are driven by a complex interplay of socioeconomic, racial, and geographic factors [184]. Individuals from lower-income backgrounds frequently lack adequate health insurance, access to specialized care, and financial resources to cover the costs of treatment, which results in delayed diagnosis and fewer treatment options [185]. Minority populations, especially African Americans, face additional structural barriers, including implicit bias within the healthcare system, lower referral rates to specialized centers, and reduced access to advanced treatments and clinical trials [186]. Geographic factors further exacerbate these issues, as patients in rural or underserved areas often face significant challenges due to a lack of nearby oncologists, long travel distances to treatment facilities, and limited opportunities to participate in clinical trials [187].

To address these disparities, a multifaceted approach is essential, involving both systemic changes and targeted interventions. Efforts to improve access to early detection and treatment for underserved populations are crucial. Expanding health insurance coverage, increasing funding for community health centers, and enhancing the availability of screening services in low-resource areas are key strategies [188]. Additionally, healthcare providers should receive training to recognize and mitigate implicit bias, improve communication with minority and low-income patients, and ensure equitable care and referral practices across all demographics [189].

Recent initiatives also emphasize the need to increase the diversity of clinical trial participants [190]. Strategies include targeted outreach to minority communities, reducing logistical barriers to participation, and making clinical trials more accessible to diverse populations. Moreover, the use of telemedicine has proven effective in bridging geographic gaps by providing specialized care to patients in remote areas, enabling them to access consultations, follow-ups, and some treatments without the need to travel long distances to major cancer centers [191].

Overall, eliminating health disparities in pancreatic cancer requires comprehensive and coordinated efforts to ensure equitable care for all patients, regardless of background or location. By implementing these strategies, healthcare systems can improve access to high-quality care and optimize outcomes for all individuals affected by this challenging disease [158,192].

9. Conclusions and future directions

Pancreatic cancer remains a challenging malignancy to treat, with

high mortality rates attributed to late-stage diagnosis, rapid progression, and resistance to existing therapies [2,193]. Recent advancements emphasize the potential of integrating sensitive biomarkers, a refined understanding of the TME, and personalized immunotherapy tailored to the unique biology of pancreatic cancer [15,194]. However, substantial challenges must be overcome to translate these advances into improved patient outcomes [172].

Further research should prioritize the clinical validation of promising biomarkers, such as miRNAs and ctDNA, to enhance early detection and enable precise prognostic assessment [195,196]. Multi-biomarker panels combining these markers with CA 19–9, show potential in improving diagnostic accuracy for early-stage pancreatic cancer and require large-scale validation studies for real-world applicability [23,172,197].

Equally important is advancing AI and multi-omics integration in clinical workflows, which holds promise for more personalized approaches to pancreatic cancer care [8]. Overcoming limitations through regulatory frameworks, standardized protocols, and collaborative data-sharing initiatives will be essential for the reliability and clinical utility of AI models in precision oncology [198,199].

Expanding research on TME-targeted therapies, especially strategies combining TME modulation with immunotherapy, is critical to overcoming therapy resistance [9,200]. Targeting CAFs, immune-suppressive cells, and ECM components in synergy with immune checkpoint inhibitors offers potential therapeutic advantages and should be further explored in clinical trials [201].

Ensuring equitable access to advanced diagnostics, immunotherapy, and clinical trials is essential to address healthcare disparities in pancreatic cancer treatment [202,203]. Combining accessibility with innovations in personalized medicine has the potential to transform care for all patients.

In summary, a multifaceted approach focusing on biomarker validation, AI-driven precision medicine, TME modulation, and equitable access is vital for advancing pancreatic cancer treatment. Continued innovation, grounded in evidence-based research, provides a clear roadmap to enhance care standards and improve survival in this formidable disease.

Abbreviations	
AI	artificial intelligence
CAF	cancer-associated fibroblast
CSC	cancer stem cell
CTC	circulating tumor cell
CSF1R	colony-stimulating factor 1 receptor
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte associated protein 4
ECM	extracellular matrix
EMT	epithelial-mesenchymal transition
HIF	hypoxia-inducible factor
KRAS	kirsten rat sarcoma viral oncogene homolog
MAPK	mitogen-activated protein kinase
MDSC	myeloid-derived suppressor cell
PI3K/AKT	phosphatidylinositol 3-kinase/protein kinase B pathway
SMO	smoothened
TAM	tumor-associated macrophage
TME	tumor microenvironment
Treg	regulatory T cell

CRediT authorship contribution statement

Baofa Yu: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Shengwen Shao:** Writing – original draft, Visualization. **Wenxue Ma:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, 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.

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