Received: 2 July 2025 | Revised: 14 August 2025 | Accepted: 20 August 2025

DOI: 10.3322/caac.70035

REVIEW ARTICLE

Advances in pancreatic cancer early diagnosis, prevention, and treatment: The past, the present, and the future

Alessandro Mannucci MD[1,2] | **Ajay Goel PhD**[1,3]

[1]Department of Molecular Diagnostics and Experimental Therapeutics, Beckman Research Institute at City of Hope, Monrovia, California, USA

[2]Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy

[3]City of Hope Comprehensive Cancer Center, Duarte, California, USA

Correspondence

Ajay Goel, Department of Molecular Diagnostics and Experimental Therapeutics, City of Hope Beckman Research Institute, 1218 S. Fifth Avenue, Suite 226, Duarte, CA 92010, USA.
Email: ajgoel@coh.org

Funding information

National Cancer Institute and the National Institute of Health, Grant/Award Numbers: CA202797, CA214254, CA271243

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a dismal prognosis, largely because of late-stage diagnosis and therapeutic resistance. PDAC incidence has been rising, with modifiable and non-modifiable risk factors contributing to disease development. Chronic pancreatitis, diabetes mellitus, smoking, obesity, and familial predisposition have been implicated in PDAC pathogenesis. Early clinical manifestations are vague and insidious; therefore, PDAC is often diagnosed at an advanced stage, limiting curative treatment options. Efforts to improve early detection have focused on serum biomarkers (e.g., carbohydrate antigen 19-9), imaging modalities, and liquid biopsies. Endoscopic ultrasound and magnetic resonance imaging have demonstrated potential in identifying early-stage disease in certain high-risk populations. Surgical resection remains the only potentially curative option, but only 15%–20% of patients have resectable disease at diagnosis. Neoadjuvant chemotherapy has emerged as a promising strategy to improve resectability and survival outcomes. For patients with locally advanced or metastatic PDAC, combination chemotherapy regimens such as FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin), NALIRIFOX (5-fluorouracil, oxaliplatin, liposomal irinotecan, and leucovorin), and combined gemcitabine/nanoparticle albumen-bound paclitaxel offer survival benefits, although toxicity remains a concern, especially for platinum-based therapies. Several breakthroughs in molecular profiling have led to the development of targeted therapies, including sotorasib and olaparib. Immunotherapy has shown limited success in PDAC due to its immunosuppressive tumor microenvironment. However, novel combination approaches are under investigation, including quadruplet therapy, immune checkpoint inhibitors with oncolytic viruses, stromal-targeting agents, and personalized neoantigen vaccines. Key priorities for future research include identifying reliable biomarkers for early detection, refining patient selection for targeted therapies, and developing innovative strategies to overcome treatment resistance.

KEYWORDS

early detection, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX), gemcitabine, pancreatic ductal adenocarcinoma (PDAC), screening, surveillance, treatment

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2025 The Author(s). CA: A Cancer Journal for Clinicians published by Wiley Periodicals LLC on behalf of American Cancer Society.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains a significant public health challenge worldwide. Its insidious onset, often presenting with nonspecific symptoms at advanced stages, hinders early detection and limits curative treatment options. Despite advances in systemic therapies, including targeted therapies in select molecular subgroups, the 5-year survival rate remains low. This review discusses the current understanding of PDAC's pathobiology, diagnostic and screening approaches, and therapeutic strategies, highlighting the urgent need for innovative approaches to improve survival.

EPIDEMIOLOGY WITH INCREASING INCIDENCE

In the United States, approximately 67,000 new cases of PDAC were diagnosed in 2024, with an annual incidence increase of 1.1%.[1] Mortality rates have continued to rise since the 1930s, a trend partially attributable to the obesity epidemic.[2,3] Consequently, PDAC has become the third most lethal solid malignancy in the United States, following lung and colorectal cancer, and is projected to become the second-leading cause of cancer-related deaths in the United States by 2030.

Globally, PDAC ranks 12th in terms of incidence but sixth in mortality, accounting for 2.6% of all cancer cases and 4.8% of cancer deaths worldwide.[4] Although disease-specific lethality has remained relatively stable in many regions, the relative burden of PDAC has grown because of declining mortality from more common cancers, such as lung, colorectal, prostate, breast, and stomach cancers. According to GLOBOCAN estimates, the age-standardized incidence rate of PDAC is higher for men than for women, with a lifetime risk of developing the disease of 0.64% and 0.44%, respectively.[4] Lifetime mortality is similarly high—0.56% for men and 0.38% for women—yielding a mortality-to-incidence ratio that reflects the diagnostic and therapeutic challenges associated with this malignancy.[4–6]

Although PDAC accounts for 5% of all cancer-related deaths worldwide, incidence and mortality rates are disproportionately higher in high-income countries compared with low-income countries (1.72 vs. 0.21 and 1.60 vs. 0.20, respectively).[7] The highest incidence rates are observed in Europe, North America, and Australia/New Zealand, whereas lower rates are reported in Asia, Africa, and Latin America.[4,8]

In the United States, although incidence rates of several common cancers are declining,[9] PDAC continues to rise, particularly among younger adults (younger than 50 years). A Surveillance, Epidemiology, and End Results-based analysis identified a generational shift, with Generation X (born 1965–1980) experiencing significantly larger per-capita increases in PDAC incidence compared with earlier generations (born 1908–1964), suggesting that incidence in the United States may remain elevated for decades.[10] This trend is especially pronounced among Hispanic individuals, with a 34.9% increase in women and a 14.1% increase in men, and in nearly all racial and ethnic groups: non-Hispanic Whites (+1.3% per year), non-Hispanic Blacks (+0.7% per year), non-Hispanic Asians/Pacific Islanders (+0.6% per year), non-Hispanic American Indians (+2.6% per year), and Hispanics (+0.6% per year).[10] Particularly evident is the rise among women in Generation X, who have a 39% higher incidence rate compared with their Baby Boomer parents (incidence rate ratio, 1.39; 95% confidence interval [CI], 1.07–1.80).[10]

PANCREATIC CANCER RISK FACTORS

The single most significant nongenetic demographic risk factor for PDAC is age, with 80% of cases occurring in individuals aged 60–80 years. Other nonmodifiable risk factors—male biological sex, Jewish ancestry, and Black race—confer a modest increase in risk.[11] In contrast, modifiable risk factors, particularly smoking, obesity, and metabolic disease, carry greater clinical relevance. Because PDAC screening remains ineffective in the asymptomatic general population,[12] primary prevention through risk factor modification remains critical.

Cigarette smoking is the strongest modifiable risk factor, responsible for approximately 25% of all PDAC cases.[13] Current smokers face a relative risk between 2 and 5, with a clear, strong dose–response relationship between the amount smoked and the risk.[14] Smoking interacts synergistically with other risk factors, including diabetes, family history, or a history of pancreatitis.[15] For example, individuals with both diabetes and a history of smoking are at significantly higher risk than those with either factor alone. Individuals with diabetes—regardless of smoking status—have a higher risk of PDAC (hazard ratio [HR], 1.67), which rises further in the presence of smoking (HR, 2.77). Former smokers, although partially protected, still carry an increased risk compared with never-smokers. More specifically, among individuals with prediabetes who had quit smoking, the risk remained elevated (HR, 1.31), with an even higher risk observed in those with diabetes (HR, 1.83). Even individuals without diabetes who had quit smoking retained a slightly increased risk (HR, 1.12) relative to never-smokers without diabetes.[16] Similarly, in individuals with a family history of PDAC, smoking further amplifies the risk by 3.7-fold. Notably, smoking has been shown to accelerate disease onset by 10–20 years,[13,17,18] and it remains an independent risk factor even in families with a strong clustering of PDAC cases.[18] Perhaps most importantly, smoking status has been linked to worse overall survival outcomes,[19] underscoring the complex interplay between smoking, smoking cessation, PDAC development, and disease lethality. Conversely, passive smoking does not appear to significantly influence PDAC risk.[20]

The relationship between diabetes and PDAC is complex and bidirectional, with each condition potentially influencing the development of the other, so the direction of causality remains unclear. Diabetes is a common comorbidity in individuals with PDAC, occurring in up to 50% of PDAC cases (compared with 15% in patients with other cancers and 10% in the general population[21,22]); and, in greater than 75% of cases, its diagnosis precedes that of PDAC by less than 24 months. Moreover, long-standing type 2 diabetes modestly

increases PDAC risk, but new-onset diabetes—especially in individuals older than 50 years—may be an early manifestation of underlying malignancy. Approximately 1% of individuals in this group will develop PDAC within 3 years.[23] Because of this bidirectional relationship, referred to as *dual causality*,[24] new-onset diabetes has gained significant attention as a potential early indicator of imminent PDAC development.[24–26]

Because diabetes is frequently associated with obesity—both well recognized risk factors for PDAC[27]—the influence of antidiabetic medications in modulating PDAC risk has become a focus of active investigation. Sulfonylureas (insulin secretagogues) have been associated with a modest increase in PDAC risk, whereas thiazolidinediones have not shown a similar effect. Metformin, a peripheral insulin sensitizer, has attracted attention for its potential protective properties, with a meta-analysis estimating a 27% risk reduction among metformin users (risk ratio, 0.73; 95% CI, 0.56–0.96).[28] However, the overall evidence remains inconclusive, and a causal relationship has yet to be established. Additional metabolic factors may influence PDAC risk. Lower levels of high-density lipoprotein cholesterol have been associated with an increased PDAC risk, particularly in individuals younger than 60 years. Concerns were previously raised about a potential link between PDAC and glucagon-like peptide-1 receptor agonists[29] because of suspected adverse effects on the exocrine pancreas.[30] Nevertheless, meta-analyses and clinical trials have consistently not corroborated such risk.[31–34] A population-based study with a 9-year follow-up further reinforced the safety of glucagon-like peptide-1 receptor agonists, finding no compelling evidence of increased PDAC incidence.[35]

Finally, several occupational and environmental exposures—including red and processed meat, fried foods, dyes, pigments, and industrial solvents—have been investigated as potential risk factors for PDAC. However, the available evidence linking these exposures to pancreatic carcinogenesis remains weak and inconclusive.[33–46] In contrast, excessive alcohol consumption (typically defined as greater than three drinks per day) has been associated with a modest increase in PDAC risk. Chronic pancreatitis, which is frequently linked to alcohol consumption and smoking, carries a substantially higher risk of developing PDAC. Of growing concern is the rising incidence of PDAC in younger individuals,[47–49] a trend potentially linked to rising rates of obesity and diabetes.[2,3] Notably, the strength of these associations tends to diminish with advancing age,[50] suggesting a complex interaction between timing of exposure, duration, and an individual's susceptibility.

Finally, approximately 5%–10% of PDAC cases occur in individuals with a first-degree or second-degree blood relative affected by PDAC,[17,51,52] and this proportion increases to 38% when third-degree and more distant relatives are included.[53] This familial clustering may reflect the contribution of inherited pathogenic variants in cancer susceptibility genes as well as shared environmental exposures and epigenetic influences.[54] Studies estimate that up to 15% of PDAC cases may be attributable to inherited predisposition,[55–58] with twin studies suggesting a role for low-penetrance recessive traits.[59] When familial clustering of PDAC is observed within a family, two primary explanations may account for this phenomenon (Figure 1A). First, a germline pathogenic variant in a cancer susceptibility gene may be present, which constitutes a clinical entity known as *hereditary pancreatic cancer* (HPC). To maximize the identification of individuals with these genetic predispositions, the National Comprehensive Cancer Network guidelines recommend comprehensive germline genetic testing for all patients newly diagnosed with PDAC.[60–70] Beyond purely Mendelian inheritance patterns, *familial pancreatic cancer* (FPC) is another clinical entity characterized by a familial predisposition to PDAC (Figure 1A). FPC is defined as PDAC clustering in families without an identifiable germline pathogenic variant, suggesting polygenic or environmental influences that place immediate relatives at a higher risk of developing PDAC. Regardless of the genetic basis (Figure 1B), individuals with a strong family history of PDAC have an increased lifetime risk of developing the disease, particularly when additional risk factors like smoking are present.[61,71–83] Consequently, smoking cessation should be strongly encouraged in this population.[13]

GENETIC, MOLECULAR, AND HISTOLOGIC CHARACTERISTICS OF PDAC

PDAC arises through a multistep process driven by the accumulation of genetic alterations in pancreatic ductal epithelial cells (Figure 2). The most common precursors of PDAC are *pancreatic intraepithelial neoplasias* (PanINs), which are surprisingly highly prevalent in the general population, with an estimated 13 PanINs per cubic centimeter of normal adult pancreas.[84] A key early event in PanIN progression is the acquisition of activating mutations in the *KRAS* oncogene that drive cellular proliferation and set the stage for malignant transformation. Notably, PanINs often arise independently, as demonstrated by the observation that spatially continuous PanINs may harbor distinct *KRAS* mutations, a finding consistent with a polyclonal origin.[84] This raises the intriguing question of why only a subset of PanINs progress to malignancy despite their abundance. Although most PDACs originate from PanINs, the malignant potential of an individual PanIN is likely lower than that of cystic premalignant lesions—including *intraductal papillary mucinous neoplasms* (IPMNs) and *mucinous cystic neoplasms* (MCNs).[84] PanINs need to accumulate additional genetic alterations, including inactivating mutations in key tumor suppressor genes, such as *CDKN2A*, *TP53*, and *SMAD4*, for malignant transformation,[85,86] by disrupting critical cellular regulatory mechanisms.[87] In addition, a subset of PDACs exhibit mutations in chromatin remodeling genes, particularly those of the SWI/SNF complex, further contributing to tumorigenesis.[88] The interplay between genetic and epigenetic alterations[85] is central to PDAC progression.[89] Advancements in molecular pathology have led to the

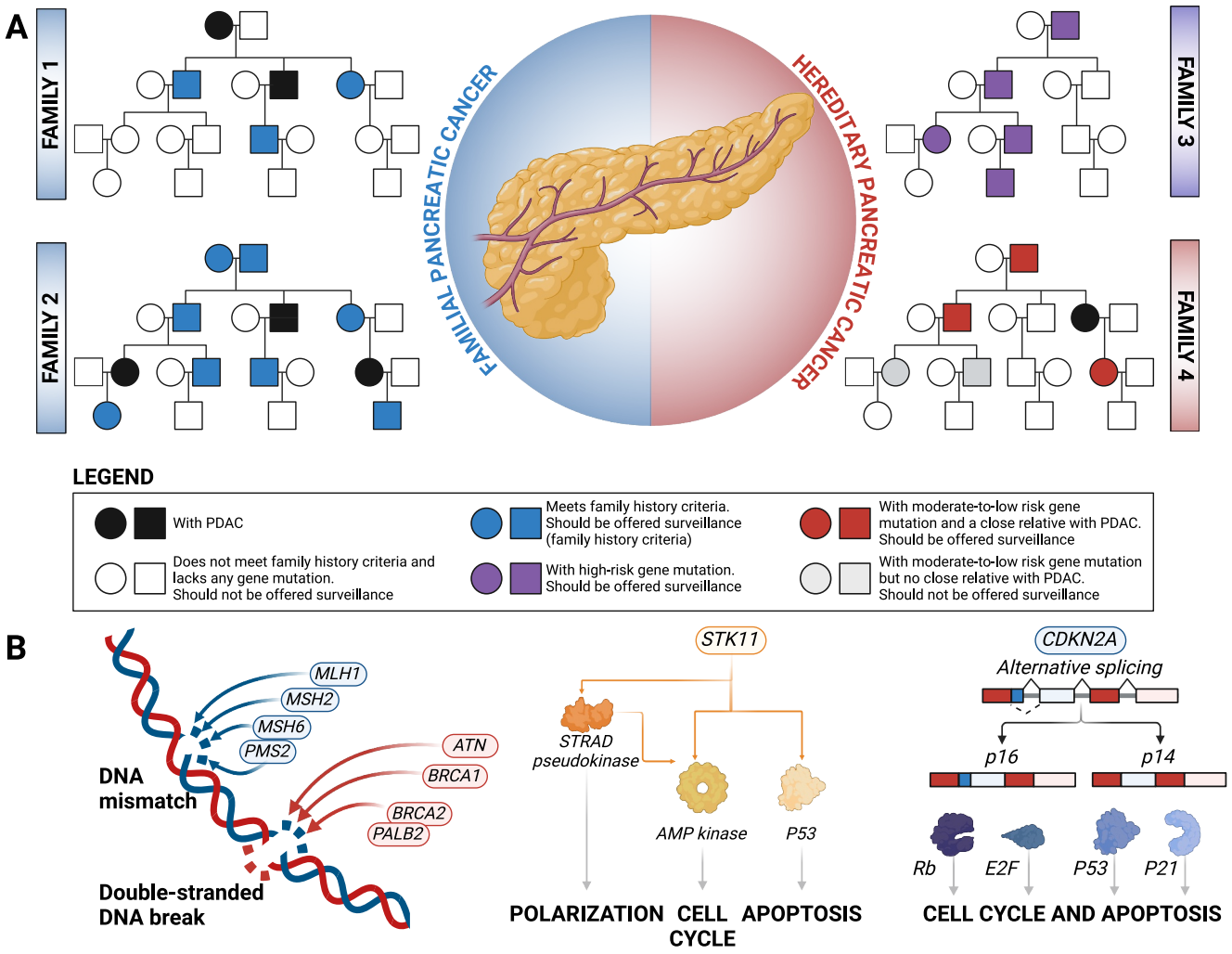


FIGURE 1 Familial and hereditary pancreatic cancer. (A) The criteria for pancreatic cancer surveillance are based on family history (right-hand side of the figure) and genetic predisposition (left-hand side of the figure). Individuals with a family history of pancreatic cancer (at least two affected relatives who are first-degree relatives to each other, of whom at least one is a first-degree relative to the individual considered for surveillance [family 1], or at least three affected relatives on the same side of the family, of whom at least one is a first-degree relative to the individual considered for surveillance [family 2]), those with a germline pathogenic variant in a high-risk gene (*STK11* or *CDKN2A*), regardless of family history (family 3), or those with both a germline pathogenic variant in a low-to-moderate risk gene (*BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6*) and with at least one first-degree blood relative affected by PDAC (family 4) may qualify for surveillance. (B) The biologic mechanisms of genes involved in hereditary pancreatic cancer. PDAC indicates pancreatic ductal adenocarcinoma.

classification of PDAC into distinct molecular subtypes based on gene expression profiles. PDAC is broadly divided into *basal-like* and *classical* subtypes, each with distinct biologic behaviors and therapeutic implications.[85,90] The basal-like subtype is characterized by a more aggressive phenotype, poorer prognosis, and resistance to standard therapies.[91,92] In contrast, the classical subtype exhibits a more differentiated phenotype, which may correlate with better responses to treatment.[93–95]

Beyond genetic alterations, the tumor microenvironment plays a crucial role in progression, invasion, and metastasis. The tumor microenvironment consists of a heterogeneous cellular network, including cancer cells, immune cells, fibroblasts, and extracellular matrix components, which collectively create an immunosuppressive niche that enables PDAC cells to evade immune surveillance.[96,97] Key immunosuppressive components include myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, and regulatory T cells,[96,98] which actively suppress antitumor immune responses.[96] In addition, the dense extracellular matrix, which is rich in hyaluronan, acts as a physical and biochemical barrier, limiting cell infiltration and fostering tumor cell survival.[98] This hostile microenvironment not only promotes tumor progression but also contributes to resistance to conventional therapy. Given the highly immunosuppressive nature of the PDAC microenvironment, efforts are underway to develop immunotherapeutic strategies aimed at enhancing antitumor immunity, including immune checkpoint inhibitors, adoptive cell therapy, and cancer vaccines, to stimulate the immune system and target PDAC cells.[85,96,97]

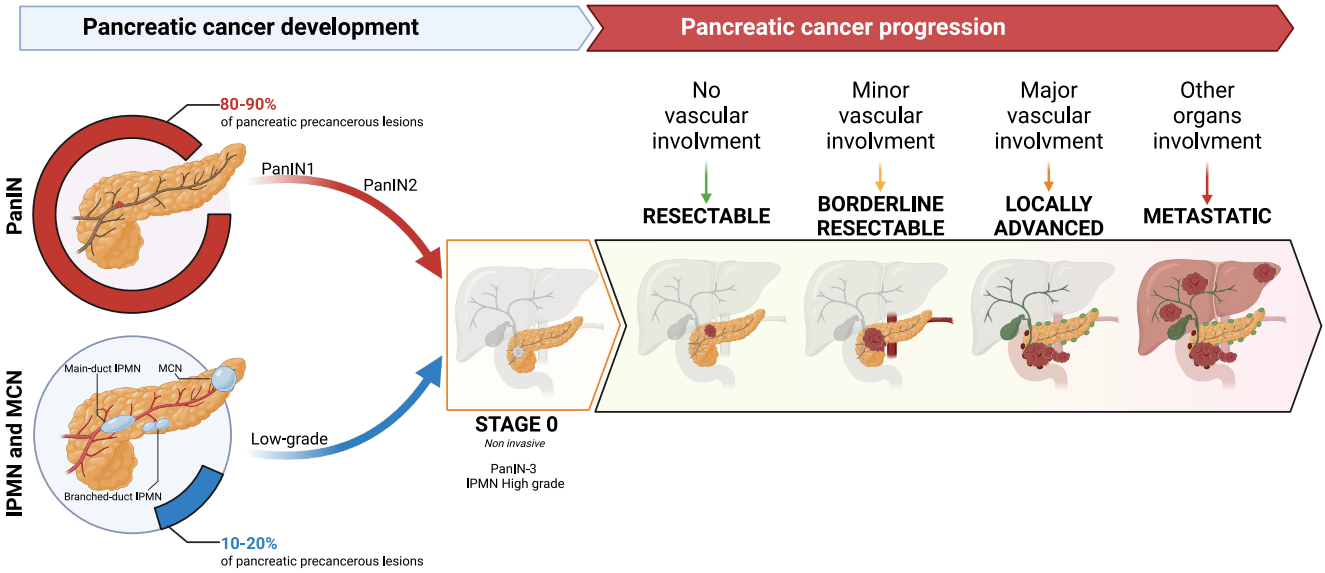


FIGURE 2 Pancreatic cancer pathogenesis and progression. Pancreatic cancer often originates from pancreatic intraepithelial neoplasia (PanIN). However, PanINs are typically not visible on imaging studies. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are more commonly detected premalignant lesions. These lesions can progress to malignancy over 15–20 years. The resectability of pancreatic cancer depends on its relationship with major arterial (the celiac axis, the superior mesenteric artery, and the common hepatic artery) and venous (the superior mesenteric vein and the portal vein) vessels. Tumors with minimal or no involvement of these vessels are considered resectable. Borderline resectable tumors have some degree of vascular involvement, making complete resection more challenging. Locally advanced tumors have extensive vascular involvement, rendering them unresectable.

SCREENING, SURVEILLANCE, AND EARLY DETECTION STRATEGIES

The primary goals of any screening program are early cancer detection, reduced cancer mortality, and a favorable benefit-to-harm ratio. However, PDAC presents significant challenges in meeting these three criteria. The low incidence of PDAC in the general population and the modest impact of environmental and nutritional risk factors suggest that large numbers of individuals would need to be screened to identify a relatively small number of cases, rendering such a strategy inefficient.[99] In addition, screening strategies for PDAC remain limited, with available tests either lacking sufficient sensitivity and specificity (Figure 3) or being prohibitively expensive for widespread use in the general population (magnetic resonance imaging-based and endoscopic ultrasound [EUS]-based surveillance).

Although the US Preventive Services Task Force does not recommend routine screening for asymptomatic individuals,[12] there is growing recognition that early detection strategies can significantly affect PDAC mortality.[99] Several societies, including PRECEDE (Pancreatic Cancer Early Detection), the Cancer of the Pancreas Screening Study, the American Gastroenterology Association (AGA), the American Society of Gastrointestinal Endoscopy, the European Society of Gastrointestinal Endoscopy), the European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis, and the National Comprehensive Cancer Network, have endorsed early detection strategies for high-risk individuals.[5,99–104] However, surveillance strategies heavily rely on expensive and labor-intensive radiologic and endoscopic approaches. As research on biomarker-based screening advances, less invasive and cost-effective approaches are emerging. Various initiatives, such as the Pancreatic Detection Consortium, the UK Early Detection Initiative for Pancreatic Cancer, ADEPTS (Accelerated Diagnosis in Neuroendocrine and Pancreatic Tumors), DETECT (examining differences in hormone and glucose excursions after a mixed meal test), EUROPAC (European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis), METAPAC (from the German Clinical Trials Registry), GENESEEQ (Geneseeq Technology Inc.), and PANDA (pancreatic cancer detection with artificial intelligence), are actively exploring these novel screening strategies, which hold the potential to revolutionize PDAC early detection and improve patient outcomes (Table 1).[108,110–128]

Surveillance in individuals with a family history of PDAC or with a germline pathogenic variant

Implementing a practical screening test necessitates the identification of a target high-risk population.[81,129] Individuals who meet specific criteria based on family history (FPC; Figure 1A, left) or genetic predisposition (HPC; Figure 1A, right) are the primary candidates for surveillance, as recommended by guidelines.[66,100,130]

More specifically, FPC is diagnosed when multiple first-degree or second-degree relatives have had PDAC yet no identifiable germline pathogenic variant has been found (Figure 1A). This familial clustering may be caused by low-penetrance genetic variants, undiscovered susceptibility genes, or shared environmental and

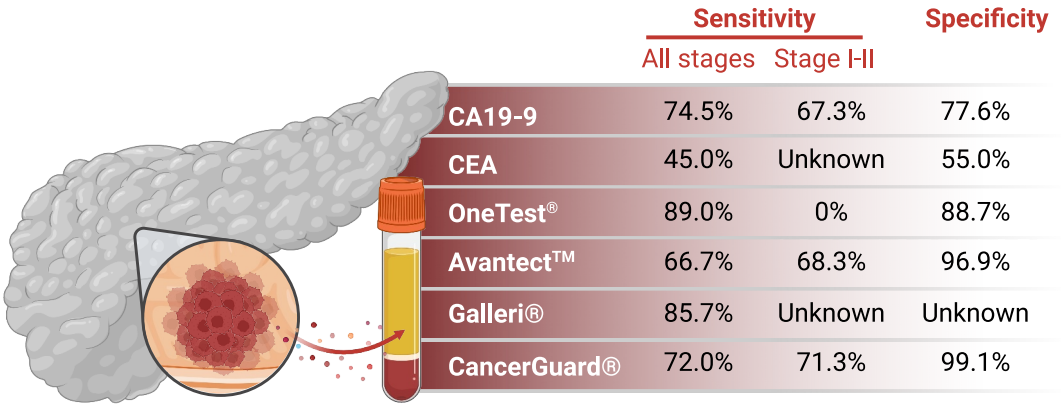


FIGURE 3 Commercially available blood test for pancreatic cancer. CA 19-9 indicates carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

TABLE 1 Selected early detection strategies currently under development.

Study name	Strategy
UK-EDI[105]	Will explore the link between new-onset diabetes and pancreatic cancer
ADEPTS (formerly TRANSBIL)[106]	Blood and urine analysis (proteomics)
DETECT[107]	Examine differences in hormone and glucose excursions after a mixed meal test
EUROPAC[77]	European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis
METAPAC[108]	Blood analysis (metabolomics)
PANDA[109]	Computed tomography-based radiomics
PANXEON[110]	Blood analysis (cell-free and exosome-based transcriptomics)
GENESEEQ[111]	Blood analysis (cell-free DNA fragmentomics)

epigenetic factors. The presence of multiple affected family members significantly increases the risk of PDAC for immediate relatives, qualifying them for surveillance. HPC is defined by the presence of a germline pathogenic variant in a PDAC susceptibility gene. To maximize the identification of hereditary cancer syndromes (Figure 1B), the National Comprehensive Cancer Network recommends comprehensive germline genetic testing for all patients newly diagnosed with PDAC,[66] ideally using a multigene panel approach.[64] Since the implementation of these guidelines, approximately 5%–10% of patients have been identified as carriers of germline pathogenic variants in DNA repair genes, most notably *BRCA1*, *BRCA2*, *PALB2*, and *ATM*, and in Peutz–Jeghers syndrome–associated genes.[64,65,67,68] Additional clinically significant germline pathogenic variants have been reported in mismatch repair genes.[70] Furthermore, whereas chronic pancreatitis is largely multifactorial, pathogenic variants in the *PRSS1*, *SPINK1*, *CTRC*, *CFTR*, and *CASR* genes have been implicated in hereditary pancreatitis, predisposing carriers to PDAC.[60–63]

Surveillance strategies for individuals with FPC and HPC rely on EUS or magnetic resonance imaging. Numerous studies have demonstrated that annual pancreatic surveillance improves survival rates among high-risk individuals who participate in surveillance programs.[61,71–83] The Cancer of the Pancreas Screening Study CAPS5 study demonstrated that surveillance enables early detection, with nearly 80% of cases diagnosed at stage I in surveilled individuals, compared with 85% diagnosed at stage IV among those not under surveillance.[131] This dramatic shift toward earlier stage diagnoses significantly improves patient outcomes because these cancers are resectable in >90% of cases, with 5-year survival rates exceeding 60%.[74,131,132] One meta-analysis reinforced these findings, reporting that 2% of the 1550 individuals enrolled in 16 surveillance programs were diagnosed with PDAC or a high-grade precursor lesion.[133] However, the most significant benefit appears to be among individuals with pathogenic germline variants, particularly *CDKN2A* carriers, who account for the majority of cancers detected through surveillance. The efficacy of surveillance in FPC families without a confirmed pathogenic germline variant remains unclear.[71,77,134] Despite its advantages, PDAC surveillance is not without limitations. Some studies have documented interval cancers developing between scheduled examinations and missed diagnoses because of imaging limitations.[135] Continued research is essential to refine screening strategies, improve imaging modalities, enhance diagnostic precision, and reduce costs.

Surveillance for cystic precursor lesions

Mucinous cysts are recognized as precursors to a significant proportion of PDACs, potentially accounting for 15% of all cases. Because PanINs—the most common noncystic precursors—are virtually invisible on cross-sectional imaging, mucinous cysts represent the only premalignant lesions that can be reliably identified.[129,136] Their detection provides an opportunity for preventive interventions and early cancer detection. Imaging studies estimate that the prevalence of pancreatic cysts ranges from 2% to 15%,

whereas autopsy series suggest that up to 50% of individuals harbor such lesions.[137–140] With the widespread adoption of imaging, detection rates have increased.[141,142] However, PDAC remains a relatively rare diagnosis, and this discrepancy in prevalence underscores a key point: most of these cysts are benign, only a subset possesses malignant potential, and fewer still will progress to PDAC.[143–148] The overall malignancy risk is estimated at 0.5%–1.5%, with an annual progression risk of 0.5%.[141,149]

Premalignant cysts are typically mucinous (MCNs and IPMNs).[150] MCNs, characterized by an ovarian-like stroma, predominantly affect women in their 40s through 60s[151]; present as unilocular, thick-walled cysts, primarily in the pancreatic tail; and lack communication with the main pancreatic duct.[152] Peripheral (eggshell) calcifications are pathognomonic of MCNs, but uncommon,[153] and the risk of advanced neoplasia in MCNs is 30%–40%.[152] IPMNs are the most common premalignant mucinous cysts, affect men and women equally, and are more prevalent after age 50 years.[154,155] They arise from ductal epithelial cells and are classified as main-duct, branch-duct, or mixed-type IPMNs. Main-duct IPMNs cause diffuse or segmental pancreatic duct dilatation,[156] with endoscopic examination revealing a *fish-mouth papilla* extruding mucin. Branch-duct IPMNs, which can be solitary or multifocal, are clustered cystic lesions,[157] with 21%–40% presenting as multifocal disease.

The management of pancreatic cysts must be individualized based on the lesion's characteristics and risk profile.[158] IPMNs are often asymptomatic, and their malignant potential varies.[159,160] In the absence of worrisome features or high-risk stigmata, stable cysts require reassurance and less frequent surveillance. Low-risk cysts, such as small branch-duct IPMNs, pose a minimal risk of malignancy.[161] Intermediate-risk cysts have a low risk of current malignancy but a moderate risk of future transformation.[161] High-risk cysts, which often are mucinous, carry a significant risk of advanced neoplasia and often require surgical evaluation.[161] For intermediate-risk and high-risk mucinous cysts,[162] EUS plays a crucial role in risk stratification and tissue sampling[163] because of its accuracy in detecting ductal communication and mural nodules.[164] When cyst characterization remains uncertain, EUS can be further enhanced with intravenous contrast,[165] fine-needle aspiration, cyst fluid analysis, and cytology[166]; or intracystic biopsy using microforceps[167] can aid in differential diagnosis.

After a definitive or presumptive diagnosis, management options include surgical intervention, surveillance, or no further action.[161] Decision making considers malignancy risk, patient health, and additional PDAC risk factors.[78] International guidelines differ markedly in philosophy and trade-offs. The AGA favors avoiding unnecessary surgery and tolerating a higher risk of missed malignancy,[158] whereas the International Association of Pancreatology[168] and European[147] guidelines prioritize sensitivity, accepting more resections of benign lesions. Comparative data[169] show that the latter two detect more advanced neoplasia in IPMNs[147,168] than AGA criteria,[158] but at the cost of substantially more potentially avoidable surgeries—underscoring the need to balance cancer detection with the morbidity of overtreatment. High-risk cysts typically warrant surgical resection in patients with acceptable operative risk.[79] Intermediate-risk cysts require specialized assessment, often at a tertiary care center with a multidisciplinary team.[151] Low-risk cysts are typically managed with surveillance, starting with semiannual follow-ups and then shifting to annual monitoring if stable. Cyst stability is defined as an increase <20% in the greatest dimension or <2.5 mm yearly growth. A growing body of evidence suggests that the risk of pancreatic cancer-related mortality for a patient older than 75 years and whose IPMN has remained stable for 5 or more years is comparable to that of the general population.[170] Therefore, cessation may be considered for low-risk cysts that have remained stable for several years.[170,171] Under these circumstances, regular reassessment is essential because changes in patient health may necessitate adjustments to the surveillance plan.[172] Finally, whereas current risk assessment relies primarily on imaging, next-generation sequencing of cyst fluid has emerged as a promising adjunct that can improve IPMN risk stratification, refine diagnostic accuracy, and better distinguish truly high-risk cysts from those that are biologically trivial.[173,174]

Finally, although IPMNs provide a potential window for early intervention, and surgical management of these lesions has increased over time, PDAC mortality has remained essentially unchanged over the decades.[175] This sobering statistic emphasizes that, although surgery is important, it alone cannot reduce PDAC mortality, highlighting the critical need for advances in systemic therapies, early detection, and interception strategies to improve patient outcomes and ultimately alter PDAC epidemiology.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The median age at PDAC diagnosis is 71 years, with a slight male predominance. Most patients present with advanced disease, limiting curative treatment options.[7,8,10,176,177] Early stage PDAC often presents with vague or nonspecific symptoms, making early diagnosis challenging.[178]

Clinical presentation

Symptoms like jaundice, cachexia, and obstructive gastrointestinal symptoms typically indicate advanced disease. Although these symptoms are typical of PDAC, their presence often suggests that the opportunity for early diagnosis has been missed. Occasionally, presenting symptoms may relate to local dysfunction at the site of metastatic disease (Figure 4).[179] A prospective cohort study of 391 individuals aged 40 years or older identified no significant differences in initial symptoms between those diagnosed with versus without PDAC, including common symptoms such as decreased appetite (28% vs. 31%, respectively), indigestion (27% vs. 39%, respectively), and changes in bowel habits (27% vs. 22%,

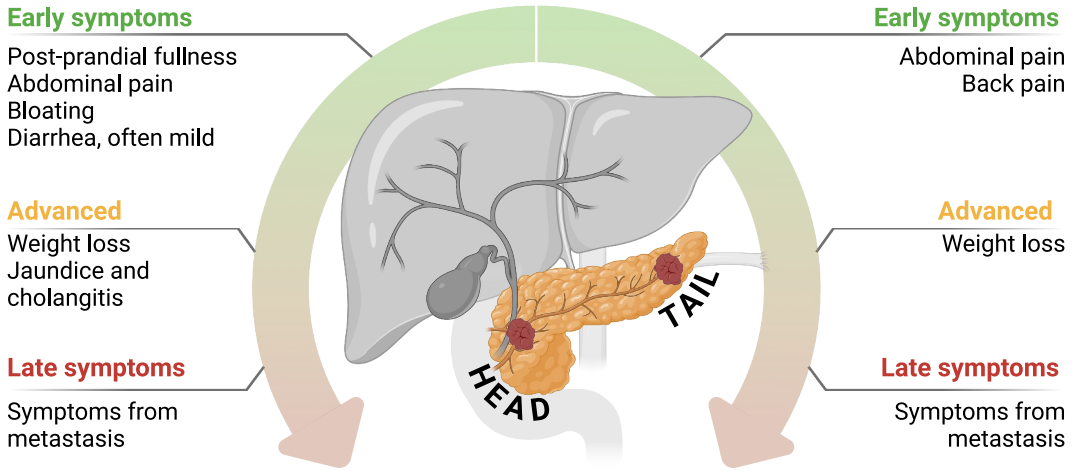


FIGURE 4 Presenting symptoms of pancreatic cancer by stage. Patients with early stage pancreatic cancer often present with nonspecific symptoms, making early detection challenging. As the disease progresses, more specific symptoms, such as jaundice, weight loss, and pain, may develop. However, these symptoms typically indicate advanced disease, limiting curative treatment options.

respectively).[180] Head-of-pancreas tumors, accounting for 70% of cases, often present with biliary obstruction, leading to symptoms such as jaundice, weight loss, and fatigue. Exocrine pancreatic insufficiency may be present in 25% of patients, too. Body and tail tumors may present with more nonspecific symptoms, like abdominal or back pain.[181] New-onset or worsening diabetes may indicate underlying PDAC.[5] Rarely, PDAC may initially manifest as acute pancreatitis.

Staging

Imaging is central to the diagnosis, staging, and management of PDAC.[182] Computed tomography is the primary imaging modality, providing crucial information on tumor size, location, and vascular involvement. Magnetic resonance imaging and magnetic resonance cholangiopancreatography offer additional insights and are particularly useful for detecting liver metastases and poorly defined lesions; whereas positron emission tomography/computed tomography may help differentiate benign from malignant lesions, although its specificity is limited by inflammatory and infectious conditions.[183] EUS is valuable for assessing vascular invasion and, most importantly, obtaining tissue samples for definitive histologic diagnosis; whereas endoscopic retrograde cholangiopancreatography primarily serves a therapeutic role in managing biliary obstruction. Serum carbohydrate antigen 19-9 (CA 19-9) remains the most well established biomarker for monitoring PDAC progression and treatment response, although it is not suitable for screening.[109] Emerging biomarkers, such as circulating tumor DNA, exosomes, and circulating tumor cells, show promise for early detection and disease monitoring, but further validation is needed.[184] For clinical decision making, PDAC is typically characterized as resectable, borderline resectable, and locally advanced based on vascular involvement,[185] the diagnostic criteria of which are discussed in the section below.

PANCREATIC CANCER SURGERY

Surgical resection, combined with systemic therapy, remains the only potentially curative treatment modality for PDAC.[186] However, because of strict resectability criteria, only 15%–20% of patients are eligible for surgery at diagnosis (Table 2 and Figure 2). PDAC without distant metastases is broadly categorized as resectable, borderline resectable, and locally advanced based on the extent of tumor involvement with major vasculature structures, including the superior mesenteric artery, coeliac artery, proper hepatic artery, superior mesenteric vein, and aorta.[188] For resectable PDAC, upfront surgery has remained the standard approach, followed by adjuvant chemotherapy, although trials are demonstrating a survival advantage with neoadjuvant therapies. For borderline resectable and locally advanced cases, upfront surgery is often suboptimal because of the high risk of positive-margin (R1) resections and the frequent presence of micrometastatic disease, which is undetectable on standard imaging[189,190] but often becomes apparent postoperatively.[191,192] To address this, there has been a growing adoption of preoperative therapy—termed *neoadjuvant chemotherapy* for borderline resectable and *induction therapy* for locally advanced PDAC—to improve resectability rates and eliminate micrometastases before surgery.[193–195] A systematic review of 11,713 patients who received treatment with preoperative therapy reported resection rates of 61% in borderline resectable PDAC and 22% in locally advanced PDAC.[196]

Traditionally, anatomic staging—based on tumor contact with major vasculature—has been the primary determinant of resectability.[197] However, emerging evidence supports a multifactorial approach, incorporating biologic (e.g., CA 19-9 levels, regional lymph node involvement) and conditional (e.g., patient performance status) factors.[198] This evolving paradigm is reflected in guidelines from organizations such as the American Society of Clinical Oncology, which advocate for a personalized assessment of resectability beyond vascular involvement alone.[199,200] The 2018 consensus

TABLE 2 Pancreatic cancer resectability criteria.[187]

Criteria	Resectable (all criteria must be met)	Borderline resectable (any one criterion)	Locally advanced (any one criterion)
A Superior mesenteric vein	No tumor contact, or contact <180 degrees, without occlusion	Tumor contact/invasion >180 degrees or occlusion (*not exceeding the inferior border of the duodenum*)	Tumor contact/invasion >180 degrees or occlusion exceeding the inferior border of the duodenum
A Portal vein			
A Superior mesenteric artery	No tumor contact/invasion	Tumor contact/invasion <180 degrees (*but without stenosis/deformity*)	Tumor contact/invasion >180 degrees
A Celiac artery	No tumor contact/invasion	Tumor contact/invasion <180 degrees (*but without stenosis/deformity*)	Tumor contact/invasion >180 degrees
A Common hepatic artery	No tumor contact/invasion	Tumor contact/invasion (*but without contact/invasion of the proper hepatic artery and/or the celiac artery*)	Tumor contact/invasion with contact/invasion of the proper hepatic artery and/or the celiac artery
A Aorta	No tumor contact/invasion	No tumor contact/invasion	Tumor contact/invasion
B CA 19-9 level	<500 U/mL	>500 U/mL	>500 U/mL
B Regional lymph nodes	No regional lymph node metastasis diagnosed by biopsy or PET-CT	Regional lymph node metastasis diagnosed by biopsy or PET-CT	NA
C Conditional (or clinical)	Performance status, 0–1	Performance status, 2	NA

Abbreviations: A, anatomic criteria; B, biologic criteria; C, conditional criteria; CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; NA, not available; PET, positron emission tomography.

statement introduced a classification system in which a tumor may be considered borderline resectable based on anatomic, biologic, or conditional criteria. For instance, CA 19-9 levels exceeding 500 U/mL or the presence of regional lymph node metastases may designate a tumor as biologically borderline resectable, even in the absence of major vascular involvement.[187] In fact, patients with anatomically resectable but biologically borderline resectable PDAC exhibit worse survival outcomes, highlighting the prognostic significance of these parameters.[201,202] Similarly, locally advanced PDAC represents a spectrum of vascular involvement, necessitating subclassification systems—such as the Johns Hopkins locally advanced pancreatic cancer stratification (LAPC-1, LAPC-2, LAPC-3 scores).[203–207] Nomograms integrating anatomic, biologic, and conditional variables are increasingly used to predict resectability, response to therapy, and survival outcomes. Given the high rate of undetected micrometastases, staging laparoscopy may be considered before initiating systemic therapy or before surgery,[208,209] particularly in high-risk patients (e.g., elevated CA 19-9, large primary tumors, lymphadenopathy, or severe symptoms).[210] However, the use of staging laparoscopy has been declining, particularly in the United States, reflecting shifts in clinical practice.[211] Nevertheless, data also suggest that staging laparoscopy can reduce the time to initiation of systemic chemotherapy in patients who would otherwise undergo nontherapeutic laparotomy and may be associated with improved survival outcomes.[212,213]

For tumors in the pancreatic head, the standard procedure remains pancreaticoduodenectomy (Whipple procedure), which involves en-bloc resection of the pancreatic head, duodenum, gallbladder, and bile duct. Distal pancreatectomy is performed for tumors in the body or tail, whereas total pancreatectomy is reserved for extensive disease requiring complete gland removal. Portomesenteric venous resections are standard practice in high-volume centers, with reported major morbidity of ≤28% and mortality of ≤4%.[214] However, venous resections encompass a broad spectrum of techniques, each with distinct risks and technical demands.[215,216] Advances in preoperative therapy have also altered surgical approaches to arterial involvement, with select tumors now amenable to arterial divestment—a technique involving periadventitial or subadventitial dissection to separate the cancer from critical arteries.[217] Nonetheless, this approach should be limited to experienced centers given the complexity of decision making, potential arterial injury, and the need for arterial resection in select cases.[218,219] Despite advancements in surgical techniques, PDAC resection remains associated with significant morbidity, including pancreatic fistula, delayed gastric emptying, hemorrhage, and infection.[220]

To reduce postoperative complication rates, minimally invasive approaches, including laparoscopic and robotic surgery, are increasingly being adopted,[221] offering potential benefits, such as faster recovery and reduced perioperative complications. Landmark trials, including LEOPARD and DIPLOMA, have demonstrated that, for distal pancreatectomy, a minimally invasive approach reduces blood loss and results in faster (or at least comparable) functional recovery.[222–224] For pancreatoduodenectomy, however, laparoscopic approaches remain more controversial, partly because of the steep learning curve[225] and partly because of conflicting reports suggesting higher morbidity rates.[226–230] With the advent of robotic

pancreatoduodenectomy, renewed interest in minimally invasive approaches[231,232] has led to two landmark 2024 studies[233,234] demonstrating that robotic pancreatoduodenectomy is safe even in complex cases and, in some instances, may improve surgical outcomes.[235,236] Given the high recurrence rate, adjuvant systemic chemotherapy is standard after surgery to improve long-term survival outcomes. The ongoing integration of preoperative therapy, refined staging criteria, and individualized treatment strategies represents a paradigm shift in PDAC management, aiming to optimize both surgical outcomes and overall survival in this challenging malignancy.

ADVANCES IN SYSTEMIC THERAPY

The history of systemic therapy for PDAC has been fraught with numerous failed attempts to extend patient survival. Since 2000, extensive clinical investigation—including 481 phase 1 trials and 85 phase 3 trials for metastatic PDAC—has resulted in only five new drug approvals, and the median overall survival remains less than 1 year.[237] Although 5-year overall survival rates have improved from 4% in the 1990s to 13% in the 2020s, this increase is attributed in part to the increased incidental detection of pancreatic neuroendocrine tumors, which are more indolent and biologically distant from PDAC.[238] For the vast majority of patients diagnosed with metastatic PDAC, the 5-year overall survival rate remains below 10%, and two primary systemic chemotherapy regimens have demonstrated efficacy: multiagent 5-fluorouracil (5-FU)-based chemotherapy, such as folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX), modified FOLFIRINOX (mFOLFIRINOX), gemcitabine-based chemotherapy, including gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel; GnP; Figure 5).

Adjuvant therapy

More than one half of all PDACs recur within 12 months of curative-intent resection.[239,240] Several factors, including preoperative CA 19-9 levels, nodal status, tumor grade, tumor size, and, most importantly, the administration of adjuvant therapy, are associated with recurrence risk.[239] Although adjuvant therapy is standard practice, its effect on survival has long been debated, with conflicting results from early clinical trials (Table 3).[192,239,240,245,247,254–256]

Two landmark trials established adjuvant chemotherapy as a survival-enhancing strategy (European Study Group for Pancreatic Cancer trial 1 [ESPAC-1] for 5-FU and Charitie Onkologie trial 001

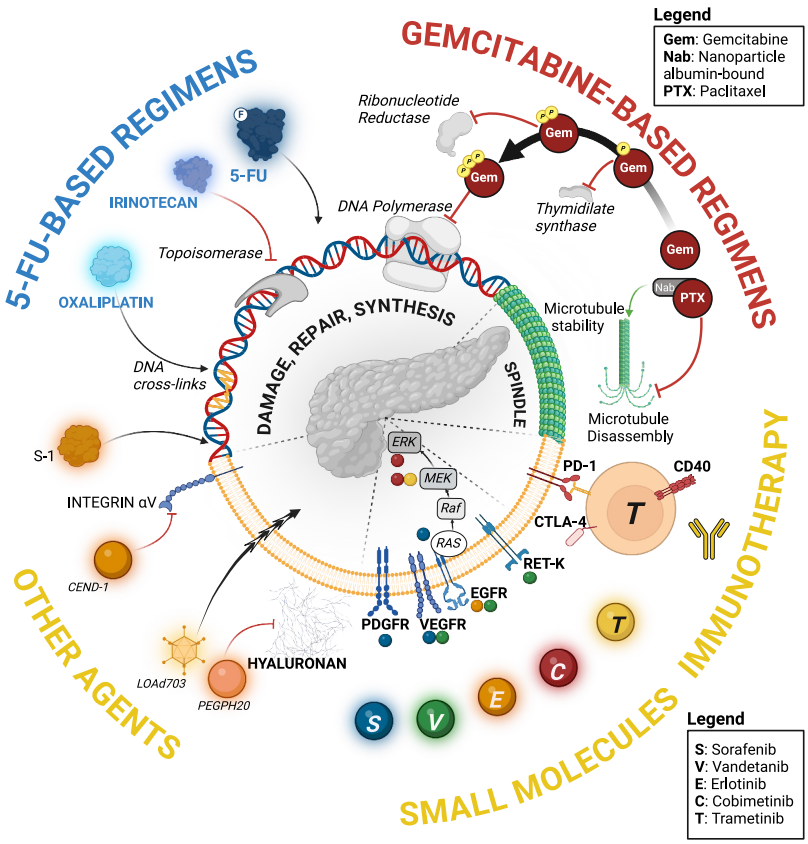


FIGURE 5 Molecular mechanisms and therapies in pancreatic cancer. 5-FU (in blue) forms the backbone of many triplet therapy regimens, whereas gemcitabine (in red) is a cornerstone of doublet therapy with nanoparticle albumen-bound paclitaxel. Other agents, in yellow, remain currently under investigation for their potential therapeutic benefits. 5-FU indicates 5-fluorouracil.

TABLE 3 Adjuvant chemotherapy trials.

Trial (reference, year)	Study regimen	Comparator regimen	Sample size	Disease-free survival	Overall survival
ESPAC (Neoptolemos 2004[241])	Fluorouracil	Observation	289	Not reported	20.1 vs. 15.5 months, $p = .05$
ESPAC (Neoptolemos 2004[241])	Radiation plus fluorouracil	Observation	289	Not reported	15.9 vs. 17.9 months, $p = .05$
CapRI (Knaebel 2005[242])	Chemoradiotherapy followed by 5-fluorouracil and IFNa2b	5-fluorouracil + folinic acid	110	Not reported	32.1 vs. 28.5 months, $p > .05$
CHONKO-001 (Oettle 20137, 2007[243,244])	Gemcitabine	Observation	368	13.4 vs. 6.7 months, $p < .001$	22.8 vs. 20.2 months, $p = .01$
JSAP-02 (Ueno 2009[245])	Gemcitabine	Observation	118	11.0 vs. 5.0 months, $p = .01$	23.0 vs. 23.6 months, $p = .19$
ESPAC-3 (Neoptolemous 2010[246])	5-fluorouracil + folinic acid	Gemcitabine	1088	14.1 vs. 14.3 months, $p = .53$	23.0 vs. 23.6 months, $p = .39$
JASPAC-01 (Uesaka 2016[247])	S-1[a]	Gemcitabine	385	22.9 vs. 11.3 months, $p < .0001$	46.5 vs. 25.5 months, $p < .0001$
CHONKO-005 (Sinn 2017[248])	Gemcitabine + erlotinib	Gemcitabine	436	11.4 vs. 11.4 months; $p = .26$	24.5 vs. 26.5 months, $p = .61$
RTOG-0848 (Abrams 2020[249])	Gemcitabine + erlotinib	Gemcitabine	163	12.4 vs. 12.7 months, $p = .58$	29.9 vs. 28.1 months, $p = .62$
ESPAC-4 (Neoptolemos 2017[192])	Gemcitabine + capecitabine	Gemcitabine	732	13.1 vs. 13.9 months, $p = .082$	28.0 vs. 25.5 months, $p = .032$
PRODIGE-24 (Conroy 2018[191])	mFOLFIRINOX	Gemcitabine	493	21.6 vs. 12.8 months, $p < .001$	54.4 vs. 35.0 months, $p = .003$
CHONKO-006 (Sinn 2020[250])	Gemcitabine + sorafenib	Gemcitabine	122	8.5 vs. 9.4 months, $p = .730$	17.6 vs. 17.5 months, $p = .481$
PRODIGE-24 (Conroy 2022[251])	mFOLFIRINOX	Gemcitabine	493	21.4 vs. 12.8 months, $p < .001$	53.5 vs. 35.5 months, $p < .001$
APACT (Tempero 2023[252]	Gemcitabine + nab-paclitaxel	Gemcitabine	866	19.4 vs. 18.8 months, $p = .18$	41.8 vs. 37.7 months, $p = .0091$
ESPAC-4 (Palmer 2024[253])	Gemcitabine + capecitabine	Gemcitabine	732	21.3 vs. 18.3 months, $p = .053$	31.6 vs. 28.4 months, $p = .031$

Abbreviations: IFNa2b, interferon a2b; mFOLFIRINOX, modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; RTOG, radiation therapy oncology group.

[a]S-1, also known as tegafur/gimeracil/oteracil, is an oral drug composed of a 5-fluororacil prodrug (tegafur) and two 5-fluororacil–enhancer drugs (gimeracil and oteracil).

[CHONKO-001] for gemcitabine). The ESPAC trial was the first to report an overall survival benefit with adjuvant 5-FU compared with observation alone.[241] The phase 3 CHONKO-001 trial later confirmed that a 6-month course of gemcitabine improved overall survival compared with observation alone (hazard ratio [HR], 0.76; $p = .01$), translating to a 10.3% absolute increase in 5-year survival and 4.5% in 10-year survival.[243,244]

Building upon these findings, subsequent trials sought to enhance efficacy by incorporating additional agents to gemcitabine. The addition of targeted therapies to gemcitabine, including erlotinib (CHONKO-005 and Radiation Therapy Oncology Group 04848) and sorafenib (CHONKO-006), failed to demonstrate overall survival benefits.[248–250] However, the APACT trial reported an overall survival benefit with GnP over gemcitabine monotherapy (HR, 0.8; $p = .0091$), but its effect on disease-free survival was less pronounced (HR, 0.88; $p = .18$).[252,257]

Comparative studies between 5-FU–based and gemcitabine-based adjuvant therapies provided further insights. First, the ESPAC-3 trial found no significant survival difference between gemcitabine and 5-FU/folinic acid, although gemcitabine was better tolerated.[246] Importantly, ESPAC-3 identified completion of all six cycles of adjuvant therapy—rather than early initiation within 12 weeks—as an independent prognostic factor for survival, underscoring the importance of adequate postoperative recovery before therapy initiation.[258] The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer 01 (JASPAC-01_ trial later demonstrated the

superiority of S-1 (an oral fluoropyrimidine) over gemcitabine (overall survival: HR. 0.57; $p < .0001$).[247] The ESPAC-4 trial established the overall survival benefit of gemcitabine plus capecitabine over gemcitabine alone (HR, 0.82; $p = .032$),[192] a benefit sustained beyond 100 months of follow-up.[253] Then, the PRODIGE trial established mFOLFIRINOX as superior to gemcitabine (overall survival: HR, 0.64), albeit with higher toxicity risks (75.9% vs. 52.9%).[191] This survival advantage persisted in the 5-year follow-up.[251] Based on these findings, adjuvant treatment guidelines suggest mFOLFIRINOX for fit patients and GnP for more frail individuals. Nevertheless, emerging studies suggest that sensitivity to gemcitabine may be determined from resected tumor specimens, potentially guiding regimen selection.[259]

IPMN-derived PDACs differ substantially from PanIN-derived PDACs[260] in both biology[261] and postoperative survival.[262] This distinction has prompted discussions on whether adjuvant therapy should be tailored based on tumor origin.[263] A pooled analysis of over 1000 patients from 16 centers concluded that adjuvant chemotherapy provided no survival benefit in node-negative, IPMN-derived PDAC ($p > .05$), whereas node-positive patients, particularly those with elevated CA 19-9, derived the most benefit.[264]

Adjuvant radiation therapy is generally not recommended.[265] Multiple studies, including those by the ESPAC group, have demonstrated that adjuvant chemoradiation may negatively affect survival.[241,266]

Management of recurrent PDAC after surgery

Most patients who undergo surgery for PDAC experience disease recurrence within 2 years.[267] Potential treatment options include re-resection, chemoradiotherapy, and stereotactic body radiation therapy. Although re-resection offers the potential for cure, it is associated with significant morbidity and mortality. In contrast, chemoradiotherapy and stereotactic body radiation therapy are less invasive options and have lower rates of major complications. The combination of radiation therapy with immunotherapy (pembrolizumab and trametinib) is an option for patients with *KRAS*-mutated, PD-L1-positive PDAC who have experienced local recurrence after surgery and adjuvant mFOLFIRINOX.[255] This combination therapy significantly improved survival compared with radiation therapy plus gemcitabine (HR, 0.69; $p = .021$). A subsequent study explored the effect of higher radiation doses (60–65 or >65 grays), but overall survival was not improved.

Neoadjuvant chemotherapy for resectable and borderline resectable pancreatic cancer

The morbidity associated with pancreatic surgery has fueled interest in shifting the administration of chemotherapy from the adjuvant to the neoadjuvant setting for both resectable and borderline resectable PDAC (Table 4).[268,269,282–284] The rationale is 2-fold: to improve resectability by downsizing tumors and to select patients most likely to benefit from surgery.[285]

Initial support for neoadjuvant therapy emerged from a single-arm trial (PREP-01), which evaluated gemcitabine plus S-1, demonstrating promising survival outcomes.[283] Likewise, a single-arm study on neoadjuvant mFOLFIRINOX reported a high rate of progression-free survival (67% at 1 year) and an association between undetectable circulating tumor DNA levels postsurgery and improved survival (HR, 11.7; $p = .02$).[286] Another study confirmed that neoadjuvant chemotherapy can lead to a pathologic complete response in 4.8% of patients, which is associated with improved overall survival (HR, 0.46; $p < .001$).[287]

The PACT-15 trial, a landmark phase 2/3 study, first demonstrated the superiority of perioperative PEXG (three cycles before and three cycles after surgery) over upfront surgery followed by gemcitabine or PEXG, with markedly improved recurrence-free survival at 1 year (66% vs. 50% and 23%, respectively).[269] Further validation came from the PREP-02 study, which reported that neoadjuvant gemcitabine plus S-1 improved overall survival versus upfront surgery with adjuvant S-1 in resectable PDAC.[270] This was extended by the PREOPANC-1 trial, which included both resectable and borderline resectable PDAC. Patients receiving neoadjuvant chemoradiotherapy had longer progression-free and overall survival compared with those undergoing upfront surgery.[273,274] However, the contribution of radiotherapy to this benefit was questioned by the A021501 phase 2 trial, which compared mFOLFIRINOX with or without hypofractionated radiotherapy in borderline resectable PDAC. The study indicated no survival advantage with the addition of radiotherapy, suggesting that the primary benefit of neoadjuvant treatment stems from systemic chemotherapy.[275] The ESPAC-5 trial, focusing exclusively on borderline resectable PDAC, compared three neoadjuvant regimens versus upfront surgery and confirmed the survival advantage of neoadjuvant therapy for both progression-free and overall survival outcomes (HR, 0.53; $p = .016$).[276] Finally, in the setting of unresectable PDAC, the CHONKO-007 trial demonstrated that, among patients without disease progression after 3 months of induction chemotherapy, chemoradiotherapy—compared with continued chemotherapy alone—did not increase the overall conversion rate to resectable disease. However, in those who subsequently underwent surgery, negative resection (R0) rates were higher.[281]

Such wealth of evidence in favor of the neoadjuvant approach led to the formulation of the first studies that compared different neoadjuvant therapy options, including the Southwest Oncology Group SWOG-S1505 trial (mFOLFIRINOX vs. GnP for resectable PDAC) and the CSGO-HBP-015 trial (GnP vs. gemcitabine plus S-1 for resectable and borderline resectable PDAC),[271,272,279] which reported no statistically significant difference in overall survival between regimens. However, the CASSANDRA phase 3 trial, which compared neoadjuvant cisplatin, nab-paclitaxel, gemcitabine, and capecitabine (PAXG) versus mFOLFIRINOX in patients with stage I–III PDAC demonstrated a significant improvement in median event-free survival (16 vs. 10.2 months) and 3-year event-free survival for

TABLE 4 Neoadjuvant chemotherapy trials.

Trial (reference, year)	Study regimen	Comparator regimen	Stage	Sample size	Progression-free survival	Overall survival
Germany (Golcher 2015,[268] Reni 2018[269])	CRT▶ SRG ▶GEM	SRG ▶ GEM	R	66	8.7 vs. 8.4 months, $p = .95$	17.4 vs. 14.4 months, $p = .96$
PACT-15 (Reni 2018[269])	PEXG ▶ SRG ▶PEXG	SRG ▶ GEM or SRG ▶ PEXG	R	88	16.9 vs. 4.7 months 16.9 vs. 12.4 months	39.8 vs. 20.4 months 39.8 vs. 26.4 months
PREP-02 (Motoi 2019[270])	GEM–S-1 ▶ SRG ▶S-1	SRG ▶ S-1	R	362	Not reported	36.7 vs. 26.7 months $p = .015$
SWOG S1505 (Sohal 2021,[271] Ahmad 2020[271])	mFOLFIRINOX ▶ SRG ▶ mFOLFIRINOX	GnP ▶ SRG ▶GnP	R	102	Not reported	25.5 vs. 16.7 months, $p = .15$
PREOPANC-1 (Versteijne 2020, 2022[273,274])	CRT▶ SRG	SRG	R/BR	246	8.1 vs. 7.7 months, $p = .001$	15.7 vs. 14.3 months, $p = .025$
A021501 (Katz 2022[275])	mFOLFIRINOX + RT ▶ SRG[b]	mFOLFIRINOX ▶ SRG	BR	126	10.2 vs. 15.0 months, p = NA	17.1 vs. 29.8 months, p = NA
ESPAC-5 (Ghaneh 2023[276])	CT▶ SRG[a]	SRG	BR	90	8.9 vs. NE months, $p = .028$	10.7 vs. NE months, $p = .004$
NEONAX (Seufferlein 2023[277])	GnP ▶ SRG ▶ GnP	SRG ▶GnP		118	11.5 vs. 5.9 months, $p > .05$	25.2 vs. 16.7 months, $p > .05$
NORPACT (Labori 2024[278])	FOLFIRINOX▶ SRG	SRG	R	140	11.9 vs. 16.2 months, $p = .22$	25.1 vs. 38.5 months, $p = .05$
CSGO-HBP-015 (Yamada 2024[279])	GnP▶ SRG	GEM–S-1▶ SRG	R/BR	100	14.0 vs. 9.0 months, $p = .048$	42 vs. 22 months, $p = .255$
CASSANDRA (Reni 2025[280])	PAXG ▶ SRG	mFOLFIRINOX▶ SRG	R/BR	260	16.0 vs. 10.2 months, $p = .003$	Not reported
CONKO-007 (Fietkau 2025[281])	CT ▶ CRT ▶ SRG	CT ▶ CT ▶ SRG	NR	525	Not reported	18 vs. 9 months, $p = .57$

Abbreviations: BR, borderline resectable; CT, chemotherapy; CRT, chemoradiotherapy; GEM, gemcitabine; GnP, gemcitabine and nanoparticle albumin-bound paclitaxel; mFOLFIRINOX, modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; NA, not available; NE, not evaluable; NR, nonresectable; PAXG, cisplatin, nanoparticle albumin-bound paclitaxel, gemcitabine, and capecitabine; PEXG, cisplatin, epirubicin, gemcitabine, and capecitabine; R, resectable; S-1, tegaful/gimeracil/oteracil; SRG, surgery.

[a]Three alternative neoadjuvant strategies were tested: (1) gemcitabine plus capecitabine; (2) folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; and (3) chemoradiation. All patients included in this study had borderline resectable pancreatic ductal adenocarcinoma.

[b]The radiotherapy regimen was a hypofractionated radiation therapy.

PAXG (31% vs. 13%; HR, 0.64; $p = .003$),[280] supporting the adoption of PAXG in the neoadjuvant setting.

However, not all trials concluded that a neoadjuvant approach produces a survival benefit.[277,278] The NEONAX study did not demonstrate a statistically significant improvement in overall survival among 118 patients with resectable PDAC who were randomly assigned to perioperative GnP versus upfront surgery with adjuvant GnP.[277] The NORPACT trial compared upfront surgery followed by adjuvant FOLFIRINOX versus neoadjuvant FOLFIRINOX followed by surgery in patients with resectable or borderline resectable PDAC. The upfront surgery group had a higher 18-month survival rate, raising questions about the overall impact of neoadjuvant FOLFIRINOX on survival.[278] In an intention-to-treat analysis of 140 enrolled patients, those undergoing upfront surgery had a greater likelihood of survival (HR, 1.52).[278] Notably, patients in the neoadjuvant arm of NORPACT received a median of only two chemotherapy cycles, a regimen that does not reflect standard clinical practice and may have contributed to the lack of observed survival benefit.[278]

As the field shifts from adjuvant to neoadjuvant therapy, numerous clinical questions emerge regarding their optimal integration. For instance, it remains unclear whether adjuvant therapy after neoadjuvant treatment confers additional benefit, how the number of neoadjuvant cycles influences the need for and duration of adjuvant treatment, and which regimens are most effective in the post-neoadjuvant setting. These questions are the focus of much ongoing investigation.

Systemic therapy for metastatic pancreatic cancer

Historically, gemcitabine and fluoropyrimidines were the primary treatment options for metastatic PDAC.[288] The landmark 1997 study established that gemcitabine was superior to 5-FU, demonstrating improved quality of life, pain control, and weight gain.[288] However, its efficacy was arguably modest, with a median overall survival benefit of just 1 month.[288] Nevertheless, gemcitabine monotherapy

remained the standard first-line treatment for about 15 years.[288] Combination therapies emerged in the late 2000s, but with limited success. In 2007, gemcitabine plus erlotinib showed an overall survival improvement of just 10 days, likely reaching statistical significance because of the trial's large sample size rather than a clinically meaningful benefit.[289] In 2009, the combination of gemcitabine and capecitabine demonstrated superior median progression-free survival compared with gemcitabine alone, but without a significant impact on overall survival.[290] These findings led to the continued exploration of combination regimens in subsequent clinical trials. After 25 years of research, only seven drugs have been approved for metastatic PDAC: gemcitabine, erlotinib, nab-paclitaxel, nanoliposomal irinotecan, oxaliplatin, 5-FU, and olaparib.[237] Yet, even in the context of clinical trials, the median overall survival for patients with metastatic PDAC remains less than 1 year.[291–302] Furthermore, real-world data suggest survival outcomes outside clinical trials are even worse. Studies highlight an efficacy-effectiveness gap for FOLFIRINOX, with median overall survival estimated at 8 months in routine clinical practice compared with 11 months in trials.[303] A Dutch study analyzing real-world data observed that the 5-year survival rates in 2014–2018 improved by just 1% compared with the rates in 1989–1993, despite the introduction of FOLFIRINOX.[304] In fact, PDAC mortality rates have continued to rise since 2000, whereas the mortality from all other major cancers has declined by approximately 2% per year in the same period. Furthermore, unlike breast, lung, or colorectal cancers, in which survival rates vary significantly between high-income and low-income countries, PDAC outcomes remain equally poor worldwide.[305] These sobering statistics underscore a harsh reality: access to novel, high-cost treatments has had minimal impact on population-level outcomes. This should serve as a call to action—clinicians must remain proactive in the fight against PDAC. The sections below outline the key trials that shaped treatment paradigms, those that advanced the field, and those that failed to meet expectations.

The first clinical trials to establish the superiority of combination therapy over single-agent treatment were the pivotal PRODIGE-4 (FOLFIRINOX) and MPACT (GnP) trials, both of which set a new standard of care for metastatic PDAC (Table 5).[288–290,296,302,306–314] In 2011, the PRODIGE-4 trial demonstrated that FOLFIRINOX was superior to gemcitabine monotherapy, improving both overall survival and progression-free survival (HR, 0.57 and 0.47, respectively), albeit with increased toxicity (HR, 0.47).[306] That trial marked the introduction of FOLFIRINOX among the first-line therapy options for metastatic PDAC.[315–317] In 2013, after a dose-finding trial,[318] the phase 3 MPACT trial demonstrated the efficacy of GnP over gemcitabine alone, with improved overall survival (HR, 0.72) and progression-free survival (HR, 0.69),[307,319] even in patients with high CA 19-9 levels, a group known to have a worse prognosis.[319] The favorable toxicity profile of this regimen, especially in elderly and frail patients,[320] contributed to its widespread adoption.[315–317] Subsequent studies further validated and optimized the GnP regimen. Notably, one trial demonstrated higher metabolic response rates (PET avidity) with GnP compared with gemcitabine alone.[321] However, the median overall survival associated with GnP was still less than 12 months, thus alternative combinations were explored. The AFUGEM-GERCOR trial assessed nab-paclitaxel plus leucovorin/5-FU versus GnP, reporting promising results (50% progression-free survival at 4 months) and leading to an ongoing phase 3 trial.[322] Efforts to refine GnP dosing have also been pursued. The FIRGEMAX study explored an alternating regimen of GnP and FOLFIRINOX, observing higher response rates (40.3% vs. 26.7%) and improved 6-month progression-free survival (45.2% vs. 23.3%) compared with continuous GnP therapy.[311] Similarly, the ALPACA trial explored a dose-reduction strategy (alternating GnP with gemcitabine monotherapy vs. uninterrupted GnP), demonstrating no difference in overall survival but improved tolerability.[323]

Because of the poor prognosis of PDAC and the scarcity of effective chemotherapy lines, relatively few trials compared second-line chemotherapy lines after first-line failure (Table 6).[294,302,324–332] Notable studies include PANCREOX, NAPOLI-1, and CONKO-003.[302,325,326] In addition, GEMPAX evaluated gemcitabine with or without paclitaxel in 211 patients with metastatic PDAC who had progressed after first-line FOLFIRINOX. Although progression-free survival and overall response rates improved, the trial did not demonstrate an overall survival benefit.[332]

One distinct subgroup of patients is those with oligometastatic PDAC.[333] The EXTEND trial assessed the effect of metastasis-directed stereotactic ablative radiotherapy alongside chemotherapy. After a median follow-up of 17 months, patients receiving the combination therapy had significantly longer progression-free survival (HR, 0.43; $p = .030$).[310]

Although metastatic PDAC has been the primary focus of clinical trials, locally advanced disease presents unique therapeutic opportunities, particularly the potential for conversion to a resectable stage. Historically, clinical trials often grouped locally advanced and metastatic PDAC together, leading to the assumption that treatment strategies for metastatic disease could be applicable to locally advanced cases. However, key differences exist, particularly given the potential to convert a locally advanced disease to a resectable stage.[334–344] The LAPACT trial, emanating from the MPACT trial, demonstrated that neoadjuvant GnP could achieve tumor downstaging, enabling surgical resection in approximately 16% of patients with locally advanced PDAC.[341] The NEOLAP trial compared two neoadjuvant regimens—GnP versus GnP followed by FOLFIRINOX—observing similar resectability rates (approximately 30%) with both approaches.[340] A few studies investigated whether add-on therapies for GnP could improve clinical outcomes in patients with locally advanced PDAC. A Japanese phase 2 trial investigated a neoadjuvant triplet therapy (GnP plus S-1), reporting a remarkably high resectability rate (96%) and an impressive 5-year overall survival rate of 44.6% in borderline resectable PDAC with arterial contact.[345] The PANOVA-3 study, instead, demonstrated that the addition of tumor treating fields to GnP (noninvasive therapy using low-intensity electric fields[346]) improved both overall survival (HR, 0.82; $p = .039$) and distant progression-free survival (HR, 0.74;

TABLE 5 Metastatic chemotherapy trials, first-line treatment.

Trial: Reference	Study regimen	Comparator regimen	Sample size	Progression-free survival	Overall survival
Burris 1997[288]	Gemcitabine	5-fluorouracil	126	2.33 vs. 0.92 months, $p = .0002$	5.65 vs. 4.41 months, $p = .0025$
Moore 2007[289]	Gemcitabine + erlotinib	Gemcitabine	569	3.75 vs. 3.55 months, $p = .004$	6.24 vs. 5.91 months, $p = .038$
Cunningham 2009[290]	Gemcitabine + capecitabine	Gemcitabine	533	5.3 vs. 3.87 months, $p = .004$	7.1 vs. 6.2 months, $p = .08$
PRODIGE4: Conroy 2011[306]	FOLFIRINOX	Gemcitabine	342	6.4 vs. 3.3 months, $p < .001$	11.1 vs. 6.8 months, $p < .001$
MPACT: Von Hoff 2013[307]	Gemcitabine + albumin-bound paclitaxel	Gemcitabine	861	5.5 vs. 3.7 months, $p < .001$	8.5 vs. 6.7 months, $p < .001$
NAPOLI-I: Wang-Gillam 2016[302]	5-fluorouracil + leucovorin + nanoliposomal irinotecan	5-fluorouracil + leucovorin	417	2.3 vs. 1.4 months, $p = .0002$	6.1 vs. 4.2 months, $p = .012$
POLO: Golan 2019[296, a]	Olaparib	Placebo	154	7.4 vs. 3.8 months, $p = .004$	18.9 vs. 18.1 months, $p = .68$
POLO: Kindler 2022[308, a]	Olaparib	Placebo	154	6.7 vs. 3.7 months, $p = .0004$	19.0 vs. 19.2 months, $p = .3487$
O'Reilly 2020[309, b]	Gemcitabine + cisplatin + veliparib	Gemcitabine + cisplatin	50	10.1 vs. 9.7 months, $p = .73$	15.5 vs. 16.4 months, $p = .6$
EXTEND: Ludmir 2024[310, c]	Metastatic-directed therapy + systemic therapy	Systemic therapy	40	10.3 vs. 2.5 months, $p = .03$	12 vs. 10 months, $p = .20$
FRIGEMAX: Rinaldi 2020[311]	*Alternating* FOLFIRI.3 and gemcitabine + nab-paclitaxel	Gemcitabine + nab-paclitaxel	127	6.1 vs. 4.2 months, $p < .05$	11.8 vs. 11.2 months, $p > .05$
AVENGER 500: Philip 2024[312]	Modified FFX + demivistat	Modified FFX	528	7.8 vs. 8 months, $p = .94$	11.1 vs. 11.7, $p = .655$
NAPOLI-3: Wainberg 2023[313]	NALIRIFOX	Gemcitabine + nab-paclitaxel	770	7.4 vs. 5.6 months, $p = .0001$	11.1 vs. 9.2 months, $p = .04$
GENERATE: Ohba 2023[314]	Gemcitabine + nab-paclitaxel	FOLFIRINOX	426	Not reported	17.1 vs. 14.0 months, $p < .01$

Abbreviations: FFX, 5-fluorouarcil, oxaliplatin, irinotecan, and leucovorin; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; FOLFIRI.3, folinic acid, 5-fluorouracil, and irinotecan; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; NALIRIFOX, 5-fluorouracil, oxaliplatin, liposomal irinotecan, and leucovorin.

[a]Only *path_BRCA1/2* germline cases. Patients who demonstrated lack of disease progression after 4 months of platinum-based therapy were randomly assigned (3:2) to maintenance therapy with olaparib versus placebo.

[b]Only path_BRCA1/2/PALB2 germline cases.

[c]Oligometastatic PDAC only.

$p = .022$).[347] These findings underscore the evolving role of therapy and the ongoing efforts to transform locally advanced PDAC into a surgically treatable disease.

5-FU–based or gemcitabine-based therapy

The decision between GnP and FOLFIRINOX as first-line therapy for metastatic PDAC remains complex and should involve active patient participation. Although both regimens are effective, their differences in toxicity and intensity make treatment selection highly individualized—with GnP often regarded as more tolerable. In contrast, FOLFIRINOX is more aggressive but potentially more effective in fit patients. A pivotal development in this debate came with the NAPOLI 3 trial, which introduced combined 5-FU, oxaliplatin, liposomal irinotecan, and leucovorin (NALIRIFOX) as a new treatment option.[313] This regimen demonstrated a modest survival advantage over GnP (HR, 0.83; $p = .036$) and has been proposed as a new standard of care.[313] However, an important caveat is that NALIRIFOX was never compared with FOLFIRINOX. This trial would have been crucial to determining whether liposomal irinotecan indeed provides an advantage over standard irinotecan.

TABLE 6 Metastatic chemotherapy trials, second-line treatment.

Trial (reference, year)	First-line therapy failure	Study regimen	Comparator regimen	Sample size	Progression-free survival	Overall survival
CONKO-003 (Oettle 2014[325])	Gemcitabine-based	Oxaliplatin, folinic acid, and fluorouracil	Folinic acid	168	2.9 vs. 2.0 months $p = .019$	5.9 vs. 3.3 months, $p = .010$
PANCREOX (Gill 2016[326])	Gemcitabine-based	mFOLFOX6	Fluorouracil and leucovorin	108	3.1 vs. 2.9 months; $p = .99$	6.1 vs. 9.9 months, $p = .02$
NAPOLI-1 (Wang-Gillam 2016[302])	Gemcitabine-based	Nanoliposomal irinotecan with fluorouracil and folinic acid	Nanoliposomal irinotecan	236	3.1 vs. 1.5 months, $p = .0001$	6.2 vs. 4.2 months, $p = .039$
JANUS-1 (Hurwitz 2018[327])	Any prior line	Ruxolitinib + capecitabine	Capecitabine	321	1.4 vs. 1.5 months, $p = .667$	3.0 vs. 3.1 months, $p = .409$
JANUS-2 (Hurwitz 2018[327])	Any prior line	Ruxolitinib + capecitabine	Capecitabine	86	1.6 vs. 2.0 months, $p = .720$	3.6 vs. 5.0 months, $p = .942$
GRAPE (Ioka 2019[328])	Gemcitabine-based	S-1 plus leucovorin	S-1	603	3.9 vs. 2.8 months, $p = .009$	7.6 vs. 7.9 months, $p = .756$
ECLIPSE (Le 2019[329])	Two or more prior lines	Cy/GVAX + CRS-207 or CRS-207	Physician choice		2.3 vs. 2.1 months, $p = .0253$ 2.1 vs. 2.1 months, $p = .7385$	3.7 vs. 4.6 months, $p = .8148$ 5.4 vs. 4.6 months, $p = .3160$
MPACA-3 (Go 2021[330])	Gemcitabine-based	mFOLFIRINOX	S-1	80	5.2 vs. 2.2 months, $p < .001$	9.2 vs. 4.9 months, $p = .002$
SEQUOIA (Hecht 2021[331])	Gemcitabine-based	FOLFOX + pegilodecakin	FOLFOX	567	2.1 vs. 2.1 months, $p > .8144$	5.8 vs. 6.3 months, $p > .6565$
CodeBreaK 100 (Strickler 2023[294])	Any prior line	Sotorasib	No comparator (Single arm)	38	4.0 months (95% CI, 2.8–5.6 months)	6.9 months (95% CI, 5.0–9.1 months)
GEMPAX (De La Fouchardiere 2024[332])	FOLFIRINOX	Gemcitabine and nab-paclitaxel	Gemcitabine	211	3.1 vs. 2.0 months, $p = .0067$	6.4 vs. 5.9 months, $p = .4095$

Abbreviations: CI, confidence interval; CRS-207, live, attenuated Listeria monocytogenes expressing mesothelin; Cy, cyclophosphamide; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; GVAX, granulocyte-macrophage colony–stimulating factor-secreting allogeneic pancreatic tumor cells; mFOLFOX6, modified 5-fluorouracil, leucovorin, and oxaliplatin; mFOLFIRINOX, modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; S-1, tegafur/gimeracil/oteracil.

Without such a comparison, it remains unclear whether the survival benefit is because of the liposomal formulation or the inclusion of irinotecan—a key question given the significantly high cost of liposomal irinotecan. In addition, the survival associated with GnP has improved over time, unlike FOLFIRINOX, which has consistently produced an overall survival of approximately 11 months in trials spanning more than a decade (NAPOLI-3 [2024]. 11.1 months; PRODIGE-4 [2011], 11.1 months). In fact, in 2023, the GENERATE trial reported a median overall survival of 17.1 months for patients receiving GnP compared with 14.0 months for those receiving FOLFIRINOX.[314] Overall, a meta-analysis of 79 randomized controlled trials spanning 22,168 patients concluded that NALIRIFOX and FOLFIRINOX should be the preferred options for fit patients, whereas GnP remains a good alternative for patients who cannot tolerate triplet therapy.[348] Beyond these comparisons, four other drug combinations are under investigation. The PACT-19 trial assessed a regimen of cisplatin, nab-paclitaxel, capecitabine, and gemcitabine, suggesting a potential benefit in 6-month progression-free survival compared with GnP, although it was limited by a small sample size.[349]

Where is immunotherapy in PDAC?

Despite significant advances in chemotherapy, the role of immunotherapy in PDAC remains an area of active investigation. However, whereas checkpoint inhibitors and immune-modulating agents have revolutionized treatment in other malignancies, as demonstrated by the KEYNOTE-158 study,[350] their efficacy of immune-modulating agents in PDAC has been limited, mainly because of the tumor's immunosuppressive microenvironment and its ability to evade immune responses by regulating the interferon cascade.[351] The PRINCE trial assessed various combinations of gemcitabine, nab-paclitaxel, nivolumab, and sotigalimab: GnP plus nivolumab demonstrated some improvement in overall survival, but GnP plus sotigalimab conferred no significant benefit.[352] The subsequent PRINCE-2 trial met its primary 1-year overall survival end point for GnP plus nivolumab (57.7%), but not for GnP plus sotigalimab (48.1%) or GnP plus sotigalimab and nivolumab (41.3%).[353] Nevertheless, the PRINCE trial identified plasma ctKRAS G12D levels as a potential predictive biomarker for immunotherapy response.[354] A promising early phase combination trial evaluated GnP plus penpulimab (anti-PD1) and anlotinib

(antiangiogenesis), demonstrating a 50% response rate and 95% disease control rate.[292] However, despite isolated successes, most immunotherapy studies in PDAC have failed, with objective response rates below 20%.[355] Immunotherapy combinations in the second-line setting have been similarly ineffective. The CheckMate 032 trial (nivolumab, ipilimumab, and cobimetinib) demonstrated response rates ≤5%.[356] These findings highlight the challenges in overcoming PDAC's immune resistance and the need for predictive biomarkers and optimized treatment strategies. Nevertheless, in rare instances—particularly in PDAC with high microsatellite instability—exceptional responses can be observed, including, in some patients, complete responses without surgery.[357,358] Finally, emerging immunotherapeutic approaches are exploring chimeric antigen receptor T-cell therapy. The CT041 chimeric antigen receptor T-cell therapy, targeting claudin 18.2, has demonstrated efficacy and safety in a pooled analysis of two multicenter trials.[359] In addition, dendritic cell-based immunotherapy has shown promise in patients with resected PDAC, although its role in advanced disease remains uncertain.[360]

Anti-KRAS therapy, poly(adenosine diphosphate-ribose) polymerase inhibitors, and other targeted agents

Advances in the molecular characterization of PDAC have identified potential therapeutic targets.[361] One key development has been the identification of targetable molecular drivers that contribute to PDAC progression.

For patients with locally advanced or metastatic, KRAS wild-type PDAC, GnP has significantly improved overall and progression-free survival.[362] However, KRAS mutations are identified in 90% of PDAC cases,[90] with the p.G12C variant accounting for 1%–2% of cases.[363] The development of sotorasib, a small molecule inhibitor that specifically and irreversibly binds to KRAS G12C, has challenged the long-standing belief that KRAS mutations are undruggable.[364] Targeting a pocket beneath the switch II region locks KRAS in its inactive guanosine diphosphate-bound state, thereby inhibiting oncogenic signaling.[365] The CodeBreaK 100 trial (Table 5) evaluated sotorasib in 38 heavily pretreated patients with advanced PDAC, reporting an objective response rate of 21%, a median progression-free survival of 4 months, and a median overall survival of 6.9 months, underscoring the need for further investigation.[294]

Beyond KRAS, carriers of *BRCA1* and *BRCA2* germline pathogenic variants[366] have an increased susceptibility to DNA-damaging agents, such as platinum-based chemotherapy and poly(adenosine diphosphate-ribose) polymerase inhibitors.[87] A phase 2 trial found gemcitabine and cisplatin effective against PDAC in patients with germline *BRCA/PALB2* pathogenic variants.[309] More importantly, the POLO trial, conducted in 2019 and updated in 2023 (Table 5), demonstrated that maintenance olaparib after first-line platinum-based chemotherapy significantly improved quality-of-life measures and prolonged progression-free survival (HR, 0.53; $p = .004$).[296,308,367,368] However, the study did not demonstrate a statistically significant overall survival, leading to discussions regarding the clinical utility and cost effectiveness of maintenance olaparib.[369–371] Also, the POLO trial's design has been the subject of debate[237,372] because of the randomization of patients who were responding to chemotherapy to either olaparib or placebo, as well as the control arm design, which was given a placebo despite demonstrating a response to first-line treatment.[237,372] In addition, the use of progression-free survival as the primary end point (which was met), rather than overall survival (which was similar between groups), has been questioned, particularly given the high fatality rate of metastatic PDAC, in which overall survival is often reached within the study period.[373,374] Although these discussions highlight essential considerations in trial design and clinical applicability, the POLO trial still led to the approval of olaparib.[296,308,367,368]

Unlike the addition of erlotinib to gemcitabine,[289] the addition of other targeted therapies have not demonstrated similar success. For instance, the ViP study demonstrated that adding vandetanib, a tyrosine kinase inhibitor of VEGFR2, RET, and EGFR, to gemcitabine did not improve overall survival.[301] Several novel therapeutic targets are under investigation. GnP plus CEND-1 (a first-in-class agent targeting alphaV integrin and neuropilin-1) demonstrated promising results in a phase 1 study (objective response rates of 59% and a median overall survival of 13.2 months).[299] GnP plus elraglusib (a first-in-class inhibitor of GSK-3B) improved overall survival (HR, 0.63; $p = .016$) compared with GnP alone, but not progression-free survival.[375] Another key challenge in PDAC treatment is its desmoplastic stroma, which is characterized by the accumulation of hyaluronan, leading to impaired drug delivery. To address this, PEGPH20, a hyaluronan-degrading enzyme, was investigated with GnP. The phase 2 HALO 202 study demonstrated a modest improvement in progression-free survival (HR, 0.73; $p = .49$), with the most pronounced benefit observed in patients with high hyaluronan levels (HR, 0.51; $p = .048$).[376] However, the subsequent phase 3 HALO 109-301 trial, which focused on patients with high hyaluronan levels, did not demonstrate significant improvements in progression-free or overall survival despite an increase in the overall response rate (47% vs. 36%).[377] Inflammation-driven pathways, particularly PI3K activation, have been implicated in PDAC drug resistance but have not led to large-scale clinical trials to date.[378] Multiple attempts at targeting novel targets, including drugs against autophagy (hydroxychloroquine),[379] mitochondrial respiration and oxidative phosphorylation (demivistat),[300,312,380,381] and innovative oncolytic viruses (LOAd703),[297] have all proven ineffective to date. Although these studies underscore the challenges associated with developing effective targeted therapies for PDAC, they also highlight key areas for future investigation. The identification of predictive biomarkers, the refinement of patient-selection strategies, and explorations of novel combination regimens will be crucial to enhancing the efficacy of targeted approaches in PDAC.

CONCLUSIONS

PDAC remains a challenging disease characterized by its aggressive nature and poor prognosis. Despite significant advancements in recent years, early detection and effective treatment strategies remain the most promising, yet elusive, avenues for scientific exploration. Surgical resection offers the best chance of cure; however, unfortunately, the majority of patients present with advanced disease, limiting curative options. Systemic therapies have emerged as crucial components of treatment, with GnP, NALIRIFOX, and FOLFIRINOX establishing themselves as standard-of-care regimens for advanced disease. However, the need for more effective and tolerable therapies persists, particularly for patients with poor prognostic factors. Emerging therapeutic strategies, including targeted therapies and immunotherapies, hold promise but have thus far yielded limited success. The complex tumor microenvironment, characterized by a dense desmoplastic stroma, presents significant challenges to drug delivery and immune cell infiltration. Targeting specific components of the tumor microenvironment, such as hyaluronan, may offer novel therapeutic avenues. Understanding the underlying genetic and molecular alterations driving PDAC is crucial for developing personalized treatment approaches. Although significant progress has been made in identifying key oncogenic drivers and potential therapeutic targets, further research is needed to translate these insights into effective clinical therapies.

In conclusion, whereas substantial progress has been made in managing pancreatic cancer, significant challenges remain. Continued research efforts are essential to detangling the complexities of this disease and developing innovative therapeutic strategies that can improve patient outcomes.

ACKNOWLEDGMENTS

This work was supported by the National Cancer Institute and the National Institute of Health (Grants CA202797, CA214254, and CA271243). The funders had no role in study design, data collection and analysis, the decision to publish, or the preparation of the article.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

ORCID

Alessandro Mannucci https://orcid.org/0000-0002-1655-6762
Ajay Goel https://orcid.org/0000-0003-1396-6341

REFERENCES

1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45. doi:10.3322/caac.21871
2. Maina JG, Pascat V, Zudina L, et al. Abdominal obesity is a more important causal risk factor for pancreatic cancer than overall obesity. *Eur J Hum Genet*. 2023;31(8):962-966. doi:10.1038/s41431-023-01301-3
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578. doi:10.1016/s0140-6736(08)60269-x
4. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. doi:10.3322/caac.21834
5. Aslanian HR, Lee JH, Canto MI. AGA clinical practice update on pancreas cancer screening in high-risk individuals: expert review. *Gastroenterology*. 2020;159(1):358-362. doi:10.1053/j.gastro.2020.03.088
6. Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology*. 2020;159(1):335-349.e15. doi:10.1053/j.gastro.2020.02.068
7. Wang S, Zheng R, Li J, et al. Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: a population-based systematic analysis of GLOBOCAN. *Lancet Gastroenterol Hepatol*. 2024;9(3):229-237. doi:10.1016/s2468-1253(23)00366-7
8. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
9. Cronin KA, Scott S, Firth AU, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. *Cancer*. 2022;128(24):4251-4284. doi:10.1002/cncr.34479
10. Rosenberg PS, Miranda-Filho A. Cancer incidence trends in successive social generations in the US. *JAMA Netw Open*. 2024;7(6):e2415731. doi:10.1001/jamanetworkopen.2024.15731
11. Lillemoe KD, Yeo CJ, Cameron JL. Pancreatic cancer: state-of-the-art care. *CA Cancer J Clin*. 2000;50(4):241-268. doi:10.3322/canjclin.50.4.241
12. US Preventive Services Task Force; Owens DK, Davidson KW, et al. Screening for pancreatic cancer: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2019;322(5):438-444. doi:10.1001/jama.2019.10232
13. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. *Gastroenterology*. 2003;124(5):1292-1299. doi:10.1016/s0016-5085(03)00272-5
14. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes, and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer*. 2005;93(11):1310-1315. doi:10.1038/sj.bjc.6602868
15. Mocci E, Kundu P, Wheeler W, et al. Smoking modifies pancreatic cancer risk loci on 2q21.3. *Cancer Res*. 2021;81(11):3134-3143. doi:10.1158/0008-5472.can-20-3267
16. Park JH, Hong JY, Shen JJ, Han K, Park YS, Park JO. Smoking cessation and pancreatic cancer risk in individuals with prediabetes and diabetes: a nationwide cohort study. *J Natl Compr Canc Netw*. 2023;21(11):1149-1155.e3. doi:10.6004/jnccn.2023.7060
17. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res*. 2004;64(7):2634-2638. doi:10.1158/0008-5472.can-03-3823
18. Yeo TP, Hruban RH, Brody J, Brune K, Fitzgerald S, Yeo CJ. Assessment of "gene-environment" interaction in cases of familial and sporadic pancreatic cancer. *J Gastrointest Surg*. 2009;13(8):1487-1494. doi:10.1007/s11605-009-0923-6
19. Yuan C, Morales-Oyarvide V, Babic A, et al. Cigarette smoking and pancreatic cancer survival. *J Clin Oncol*. 2017;35(16):1822-1828. doi:10.1200/jco.2016.71.2026
20. Gallicchio L, Kouzis A, Genkinger JM, et al. Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med*. 2006;42(3):200-205. doi:10.1016/j.ypmed.2005.12.014

21. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology*. 2008;134(4):981-987. doi:10.1053/j.gastro.2008.01.039
22. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas*. 2013;42(2):198-201. doi:10.1097/mpa.0b013e3182592c96
23. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology*. 2005;129(2):504-511. doi:10.1016/j.gastro.2005.05.007
24. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes*. 2017;66(5):1103-1110. doi:10.2337/db16-1477
25. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. *Gastroenterology*. 2018;155(2):490-500.e2. doi:10.1053/j.gastro.2018.04.025
26. Shen B, Li Y, Sheng CS, et al. Association between age at diabetes onset or diabetes duration and subsequent risk of pancreatic cancer: results from a longitudinal cohort and Mendelian randomization study. *Lancet Reg Health West Pac*. 2023;30:100596. doi:10.1016/j.lanwpc.2022.100596
27. Tang H, Dong X, Hassan M, Abbruzzese JL, Li D. Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):779-792. doi:10.1158/1055-9965.epi-10-0845
28. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2014;106(1):19-26. doi:10.1016/j.diabres.2014.04.007
29. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology*. 2011;141(1):150-156. doi:10.1053/j.gastro.2011.02.018
30. Vrang N, Jelsing J, Simonsen L, et al. The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis. *Am J Physiol Endocrinol Metab*. 2012;303(2):E253-E264. doi:10.1152/ajpendo.00182.2012
31. Storgaard H, Cold F, Gluud LL, Vilsboll T, Knop FK. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19(6):906-908. doi:10.1111/dom.12885
32. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(2):105-113. doi:10.1016/s2213-8587(17)30412-6
33. Azoulay L, Filion KB, Platt RW, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. *BMJ*. 2016;352:i581. doi:10.1136/bmj.i581
34. Knapen LM, van Dalem J, Keulemans YC, et al. Use of incretin agents and risk of pancreatic cancer: a population-based cohort study. *Diabetes Obes Metab*. 2016;18(3):258-265. doi:10.1111/dom.12605
35. Dankner R, Murad H, Agay N, Olmer L, Freedman LS. Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk in patients with type 2 diabetes. *JAMA Netw Open*. 2024;7(1):e2350408. doi:10.1001/jamanetworkopen.2023.50408
36. Drucker DJ. Efficacy and safety of GLP-1 medicines for type 2 diabetes and obesity. *Diabetes Care*. 2024;47(11):1873-1888. doi:10.2337/dci24-0003
37. Miyashita Y, Hitsumoto T, Fukuda H, et al. Metabolic syndrome is linked to the incidence of pancreatic cancer. *eClinicalMedicine*. 2024;67:102353. doi:10.1016/j.eclinm.2023.102353
38. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776-785. doi:10.1016/s2213-8587(19)30249-9
39. Ikramuddin S, Billington CJ, Lee WJ, et al. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. *Lancet Diabetes Endocrinol*. 2015;3(6):413-422. doi:10.1016/s2213-8587(15)00089-3
40. Huang J, Lok V, Ngai CH, et al. Worldwide burden of, risk factors for, and trends in pancreatic cancer. *Gastroenterology*. 2021;160(3):744-754. doi:10.1053/j.gastro.2020.10.007
41. Park JH, Han K, Hong JY, et al. Changes in metabolic syndrome status are associated with altered risk of pancreatic cancer: a nationwide cohort study. *Gastroenterology*. 2022;162(2):509-520.e7. doi:10.1053/j.gastro.2021.09.070
42. Pinto LC, Falcetta MR, Rados DV, Leitao CB, Gross JL. Glucagon-like peptide-1 receptor agonists and pancreatic cancer: a meta-analysis with trial sequential analysis. *Sci Rep*. 2019;9(1):2375. doi:10.1038/s41598-019-38956-2
43. Yang Z, Lv Y, Yu M, et al. GLP-1 receptor agonist-associated tumor adverse events: a real-world study from 2004 to 2021 based on FAERS. *Front Pharmacol*. 2022;13:925377. doi:10.3389/fphar.2022.925377
44. Bulsei J, Chierici A, Alifano M, et al. Bariatric surgery reduces the risk of pancreatic cancer in individuals with obesity before the age of 50 years: a nationwide administrative data study in France. *Eur J Surg Oncol*. 2023;49(4):788-793. doi:10.1016/j.ejso.2022.11.013
45. Wang L, Wang Q, Li L, Kaelber DC, Xu R. GLP-1 receptor agonists and pancreatic cancer risk: target trial emulation using real-world data. *J Natl Cancer Inst*. 2024;117(3):476-485. doi:10.1093/jnci/djae260
46. Nam SY, Jo J, Cho CM. A population-based cohort study of longitudinal change of high-density lipoprotein cholesterol impact on gastrointestinal cancer risk. *Nat Commun*. 2024;15(1):2923. doi:10.1038/s41467-024-47193-9
47. Patel VR, Adamson AS, Liu JB, Welch HG. Increasing incidence and stable mortality of pancreatic cancer in young Americans. *Ann Intern Med*. 2025;178(1):142-144. doi:10.7326/annals-24-00635
48. Abboud Y, Samaan JS, Oh J, et al. Increasing pancreatic cancer incidence in young women in the United States: a population-based time-trend analysis, 2001–2018. *Gastroenterology*. 2023;164(6):978-989.e6. doi:10.1053/j.gastro.2023.01.022
49. Gaddam S, Abboud Y, Oh J, et al. Incidence of pancreatic cancer by age and sex in the US, 2000–2018. *JAMA*. 2021;326(20):2075-2077. doi:10.1001/jama.2021.18859
50. Yuan C, Kim J, Wang QL, et al. The age-dependent association of risk factors with pancreatic cancer. *Ann Oncol*. 2022;33(7):693-701. doi:10.1016/j.annonc.2022.03.276
51. Schneider R, Slater EP, Sina M, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years' experience. *Fam Cancer*. 2011;10(2):323-330. doi:10.1007/s10689-010-9414-x
52. Petersen GM. Familial pancreatic cancer. *Semin Oncol*. 2016;43(5):548-553. doi:10.1053/j.seminoncol.2016.09.002
53. Lal G, Liu G, Schmocker B, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. *Cancer Res*. 2000;60(2):409-416.
54. Sharma S, Tapper WJ, Collins A, Hamady ZZR. Predicting pancreatic cancer in the UK Biobank cohort using polygenic risk scores and diabetes mellitus. *Gastroenterology*. 2022;162(6):1665-1674.e2. doi:10.1053/j.gastro.2022.01.016
55. Lynch HT, Fitzsimmons ML, Smyrk TC, et al. Familial pancreatic cancer: clinicopathologic study of 18 nuclear families. *Am J Gastroenterol*. 1990;85(1):54-60.
56. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. *Semin Oncol*. 1996;23(2):251-275.

57. Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. *Curr Treat Options Oncol*. 2005;6(5):437-445. doi:10.1007/s11864-005-0046-6
58. Jacobs EJ, Chanock SJ, Fuchs CS, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Int J Cancer*. 2010;127(6):1421-1428. doi:10.1002/ijc.25148
59. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78-85. doi:10.1056/nejm200007133430201
60. Vege SS, Chari ST. Chronic pancreatitis. *N Engl J Med*. 2022;386(9):869-878. doi:10.1056/nejmcp1809396
61. Greenhalf W, Levy P, Gress T, et al. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatology*. 2020;20(5):910-918. doi:10.1016/j.pan.2020.05.011
62. Yadav D, Park WG, Fogel EL, et al. PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies: rationale and study design for PROCEED from the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas*. 2018;47(10):1229-1238. doi:10.1097/mpa.0000000000001170
63. Muller N, Sarantitis I, Rouanet M, et al. Natural history of SPINK1 germline mutation related-pancreatitis. *eBioMedicine*. 2019;48:581-591. doi:10.1016/j.ebiom.2019.09.032
64. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. *Gastroenterology*. 2015;148(3):556-564. doi:10.1053/j.gastro.2014.11.042
65. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst*. 2003;95(3):214-221. doi:10.1093/jnci/95.3.214
66. Rosso C, Marciano ND, Nathan D, et al. Hereditary cancer clinics improve adherence to NCCN germline testing guidelines for pancreatic cancer. *J Natl Compr Canc Netw*. 2024;22(5):299-305. doi:10.6004/jnccn.2023.7333
67. Seeber A, Zimmer K, Kocher F, et al. Molecular characteristics of BRCA1/2 and PALB2 mutations in pancreatic ductal adenocarcinoma. *ESMO Open*. 2020;5(6):e000942. doi:10.1136/esmoopen-2020-000942
68. Slater EP, Langer P, Niemczyk E, et al. PALB2 mutations in European familial pancreatic cancer families. *Clin Genet*. 2010;78(5):490-494. doi:10.1111/j.1399-0004.2010.01425.x
69. Earl J, Galindo-Pumarino C, Encinas J, et al. A comprehensive analysis of candidate genes in familial pancreatic cancer families reveals a high frequency of potentially pathogenic germline variants. *eBioMedicine*. 2020;53:102675. doi:10.1016/j.ebiom.2020.102675
70. Mizukami K, Iwasaki Y, Kawakami E, et al. Genetic characterization of pancreatic cancer patients and prediction of carrier status of germline pathogenic variants in cancer-predisposing genes. *eBioMedicine*. 2020;60:103033. doi:10.1016/j.ebiom.2020.103033
71. Klatte DCF, Boekestijn B, Onnekink AM, et al. Surveillance for pancreatic cancer in high-risk individuals leads to improved outcomes: a propensity score-matched analysis. *Gastroenterology*. 2023;164(7):1223-1231.e4. doi:10.1053/j.gastro.2023.02.032
72. Klatte DCF, Boekestijn B, Wasser M, et al. Pancreatic cancer surveillance in carriers of a germline CDKN2A pathogenic variant: yield and outcomes of a 20-year prospective follow-up. *J Clin Oncol*. 2022;40(28):3267-3277. doi:10.1200/jco.22.00194
73. Zaffaroni G, Mannucci A, Koskenvuo L, et al. Updated European guidelines for clinical management of familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), gastric adenocarcinoma, proximal polyposis of the stomach (GAPPS) and other rare adenomatous polyposis syndromes: a joint EHTG-ESCP revision. *Br J Surg*. 2024;111(5):znae070. doi:10.1093/bjs/znae070
74. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. *Gastroenterology*. 2018;155(3):740-751.e2. doi:10.1053/j.gastro.2018.05.035
75. Paiella S, Capurso G, Carrara S, et al. Outcomes of a 3-year prospective surveillance in individuals at high risk of pancreatic cancer. *Am J Gastroenterol*. 2024;119(4):739-747. doi:10.14309/ajg.0000000000002546
76. Paiella S, Capurso G, Cavestro GM, et al. Results of first-round of surveillance in individuals at high-risk of pancreatic cancer from the AISP (Italian Association for the Study of the Pancreas) Registry. *Am J Gastroenterol*. 2019;114(4):665-670. doi:10.1038/s41395-018-0414-z
77. Vasen H, Ibrahim I, Ponce CG, et al. Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. *J Clin Oncol*. 2016;34(17):2010-2019. doi:10.1200/jco.2015.64.0730
78. Crippa S, Marchegiani G, Belfiori G, et al. Impact of age, comorbidities and relevant changes on surveillance strategy of intraductal papillary mucinous neoplasms: a competing risk analysis. *Gut*. 2024;73(8):1336-1342. doi:10.1136/gutjnl-2023-329961
79. Hamada T, Oyama H, Tange S, et al. The revised Kyoto criteria and risk of malignancy among patients with intraductal papillary mucinous neoplasms. *Clin Gastroenterol Hepatol*. 2024;22(12):2413-2423.e18. doi:10.1016/j.cgh.2024.05.043
80. Hamada T, Yuan C, Yurgelun MB, et al. Family history of cancer, Ashkenazi Jewish ancestry, and pancreatic cancer risk. *Br J Cancer*. 2019;120(8):848-854. doi:10.1038/s41416-019-0426-5
81. Hart PA, Chari ST. Is screening for pancreatic cancer in high-risk individuals one step closer or a fool's errand? *Clin Gastroenterol Hepatol*. 2019;17(1):36-38. doi:10.1016/j.cgh.2018.09.024
82. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA*. 2018;319(23):2401-2409. doi:10.1001/jama.2018.6228
83. Jensson BO, Arnadottir GA, Katrinardottir H, et al. Actionable genotypes and their association with life span in Iceland. *N Engl J Med*. 2023;389(19):1741-1752. doi:10.1056/nejmoa2300792
84. Braxton AM, Kiemen AL, Grahn MP, et al. 3D genomic mapping reveals multifocality of human pancreatic precancers. *Nature*. 2024;629(8012):679-687. doi:10.1038/s41586-024-07359-3
85. Chen K, Wang Q, Li M, et al. Single-cell RNA-seq reveals dynamic change in tumor microenvironment during pancreatic ductal adenocarcinoma malignant progression. *eBioMedicine*. 2021;66:103315. doi:10.1016/j.ebiom.2021.103315
86. Kanda M, Matthaei H, Wu J, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology*. 2012;142(4):730-733e9. doi:10.1053/j.gastro.2011.12.042
87. Tong X, Qu N, Kong X, et al. Deep representation learning of chemical-induced transcriptional profile for phenotype-based drug discovery. *Nat Commun*. 2024;15(1):5378. doi:10.1038/s41467-024-49620-3
88. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature*. 2015;518(7540):495-501. doi:10.1038/nature14169
89. Baba T, Finetti P, Pancreatic Cancer Group, et al. A lesson in transcriptional plasticity: classical identity is silenced, but not lost,

in pancreatic ductal adenocarcinoma cell lines. *Gastroenterology*. 2022;163(5):1450-1453.e3. doi:10.1053/j.gastro.2022.07.005
90. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016;531(7592):47-52. doi:10.1038/nature16965
91. Lupo F, Pezzini F, Pasini D, et al. Axon guidance cue SEMA3A promotes the aggressive phenotype of basal-like PDAC. *Gut*. 2024;73(8):1321-1335. doi:10.1136/gutjnl-2023-329807
92. Hayashi A, Fan J, Chen R, et al. A unifying paradigm for transcriptional heterogeneity and squamous features in pancreatic ductal adenocarcinoma. *Nat Cancer*. 2020;1(1):59-74. doi:10.1038/s43018-019-0010-1
93. Suurmeijer JA, Soer EC, Dings MPG, et al. Impact of classical and basal-like molecular subtypes on overall survival in resected pancreatic cancer in the SPACIOUS-2 multicentre study. *Br J Surg*. 2022;109(11):1150-1155. doi:10.1093/bjs/znac272
94. Aung KL, Fischer SE, Denroche RE, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. *Clin Cancer Res*. 2018;24(6):1344-1354. doi:10.1158/1078-0432.ccr-17-2994
95. Pishvaian MJ, Blais EM, Brody JR, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor Registry trial. *Lancet Oncol*. 2020;21(4):508-518. doi:10.1016/s1470-2045(20)30074-7
96. Mahadevan KK, Dyevoich AM, Chen Y, et al. Type I conventional dendritic cells facilitate immunotherapy in pancreatic cancer. *Science*. 2024;384(6703):eadh4567. doi:10.1126/science.adh4567
97. Yang J, Zhang Q, Wang J, et al. Dynamic profiling of immune microenvironment during pancreatic cancer development suggests early intervention and combination strategy of immunotherapy. *eBioMedicine*. 2022;78:103958. doi:10.1016/j.ebiom.2022.103958
98. Caronni N, La Terza F, Vittoria FM, et al. IL-1beta(+) macrophages fuel pathogenic inflammation in pancreatic cancer. *Nature*. 2023;623(7986):415-422. doi:10.1038/s41586-023-06685-2
99. Gonda TA, Everett JN, Wallace M, et al. Recommendations for a more organized and effective approach to the early detection of pancreatic cancer from the PRECEDE (Pancreatic Cancer Early Detection) Consortium. *Gastroenterology*. 2021;161(6):1751-1757. doi:10.1053/j.gastro.2021.08.036
100. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17. doi:10.1136/gutjnl-2019-319352
101. Fulton AJ, Lamarca A, Nuttall C, et al. Identification of patients with pancreatic adenocarcinoma due to inheritable mutation: challenges of daily clinical practice. *World J Gastrointest Oncol*. 2019;11(2):102-116. doi:10.4251/wjgo.v11.i2.102
102. Saftoiu A, Hassan C, Areia M, et al. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European Society of Gastrointestinal Endoscopy (ESGE) position statement. *Endoscopy*. 2020;52(4):293-304. doi:10.1055/a-1104-5245
103. Sawhney MS, Calderwood AH, Thosani NC, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. *Gastrointest Endosc*. 2022;95(5):817-826. doi:10.1016/j.gie.2021.12.001
104. Daly MB, Pal T, Maxwell KN, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024. *J Natl Compr Canc Netw*. 2023;21(10):1000-1010. doi:10.6004/jnccn.2023.0051
105. Oldfield L, Stott M, Hanson R, et al. United Kingdom Early Detection Initiative (UK-EDI): protocol for establishing a national multicentre cohort of individuals with new-onset diabetes for early detection of pancreatic cancer. *BMJ Open*. 2022;12(10):e068010.
106. Pereira S, Hippisley-Cox J, Timms J, et al. ADEPTS (Accelerated Diagnosis of neuroEndocrine and Pancreatic TumourS) and EDRA (Early Diagnosis Research Alliance). *Pancreatology*. 2020;20:e14.
107. Hart PA, Andersen DK, Mather KJ, et al. Evaluation of a mixed meal test for diagnosis and characterization of pancrEaTogEniC diabetes secondary to pancreatic cancer and chronic pancreatitis: rationale and methodology for the DETECT study from the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. *Pancreas*. 2018;47(10):1239-1243.
108. Mahajan UM, Oehrle B, Goni E, et al. Validation of two plasma multimetabolite signatures for patients at risk of or with suspected pancreatic ductal adenocarcinoma (METAPAC): a prospective, multicentre, investigator-masked, enrichment design, phase 4 diagnostic study. *Lancet Gastroenterol Hepatol*. 2025;10(7):634-647. doi:10.1016/s2468-1253(25)00056-1
109. Cao K, Xia Y, Yao J, et al. Large-scale pancreatic cancer detection via non-contrast CT and deep learning. *Nat Med*. 2023;29(12):3033-3043.
110. Nakamura K, Zhu Z, Roy S, et al. An exosome-based transcriptomic signature for noninvasive, early detection of patients with pancreatic ductal adenocarcinoma: a multicenter cohort study. *Gastroenterology*. 2022;163(5):1252-1266.e2. doi:10.1053/j.gastro.2022.06.090
111. Yin L, Cao C, Lin J, et al. Development and validation of a cell-free DNA fragmentomics-based model for early detection of pancreatic cancer. *J Clin Oncol*. 2025. doi:10.1200/jco.24.00287
112. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018;359(6378):926-930. doi:10.1126/science.aar3247
113. Xu C, Jun E, Okugawa Y, et al. A circulating panel of circRNA biomarkers for the noninvasive and early detection of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2024;166(1):178-190.e16. doi:10.1053/j.gastro.2023.09.050
114. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32(9):1167-1177. doi:10.1016/j.annonc.2021.05.806
115. Fahrmann JF, Schmidt CM, Mao X, et al. Lead-time trajectory of CA19-9 as an anchor marker for pancreatic cancer early detection. *Gastroenterology*. 2021;160(4):1373-1383e6. doi:10.1053/j.gastro.2020.11.052
116. Luan Y, Zhong G, Li S, et al. A panel of seven protein tumour markers for effective and affordable multi-cancer early detection by artificial intelligence: a large-scale and multicentre case-control study. *eClinicalMedicine*. 2023;61:102041. doi:10.1016/j.eclinm.2023.102041
117. Boyd LNC, Ali M, Leeflang MMG, et al. Diagnostic accuracy and added value of blood-based protein biomarkers for pancreatic cancer: a meta-analysis of aggregate and individual participant data. *eClinicalMedicine*. 2023;55:101747. doi:10.1016/j.eclinm.2022.101747
118. Oldfield L, Evans A, Rao RG, et al. Blood levels of adiponectin and IL-1Ra distinguish type 3c from type 2 diabetes: implications for earlier pancreatic cancer detection in new-onset diabetes. *eBioMedicine*. 2022;75:103802. doi:10.1016/j.ebiom.2021.103802
119. Zvereva M, Roberti G, Durand G, et al. Circulating tumour-derived KRAS mutations in pancreatic cancer cases are predominantly carried by very short fragments of cell-free DNA. *eBioMedicine*. 2020;55:102462. doi:10.1016/j.ebiom.2019.09.042

120. Jahan R, Ganguly K, Smith LM, et al. Trefoil factor(s) and CA19.9: a promising panel for early detection of pancreatic cancer. *eBioMedicine*. 2019;42:375-385. doi:10.1016/j.ebiom.2019.03.056
121. Haan D, Bergamaschi A, Friedl V, et al. Epigenomic blood-based early detection of pancreatic cancer employing cell-free DNA. *Clin Gastroenterol Hepatol*. 2023;21(7):1802-1809.e6. doi:10.1016/j.cgh.2023.03.016
122. Kartal E, Schmidt TSB, Molina-Montes E, et al. A faecal microbiota signature with high specificity for pancreatic cancer. *Gut*. 2022;71(7):1359-1372. doi:10.1136/gutjnl-2021-324755
123. Gaiser RA, Halimi A, Alkharaan H, et al. Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer. *Gut*. 2019;68(12):2186-2194. doi:10.1136/gutjnl-2018-317458
124. Wei L, Yao K, Gan S, Suo Z. Clinical utilization of serum- or plasma-based miRNAs as early detection biomarkers for pancreatic cancer: a meta-analysis up to now. *Medicine (Baltimore)*. 2018;97(35):e12132. doi:10.1097/md.0000000000012132
125. Chen YL, Hu CM, Hsu JT, et al. Cellular 5-hydroxylmethylcytosine content determines tumorigenic potential and prognosis of pancreatic ductal adenocarcinoma. *Am J Cancer Res*. 2018;8(12):2548-2563.
126. Guler GD, Ning Y, Ku CJ, et al. Detection of early stage pancreatic cancer using 5-hydroxymethylcytosine signatures in circulating cell free DNA. *Nat Commun*. 2020;11(1):5270. doi:10.1038/s41467-020-18965-w
127. Schrag D, Beer TM, McDonnell CH 3rd, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *Lancet*. 2023;402(10409):1251-1260. doi:10.1016/s0140-6736(23)01700-2
128. Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *Lancet Oncol*. 2023;24(7):733-743. doi:10.1016/s1470-2045(23)00277-2
129. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology*. 2019;156(7):2024-2040. doi:10.1053/j.gastro.2019.01.259
130. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. American College of G: ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110(2):223-262; quiz 263. doi:10.1038/ajg.2014.435
131. Dbouk M, Katona BW, Brand RE, et al. The Multicenter Cancer of Pancreas Screening Study: impact on stage and survival. *J Clin Oncol*. 2022;40(28):3257-3266. doi:10.1200/jco.22.00298
132. Canto MI, Kerdsirichairat T, Yeo CJ, et al. Surgical outcomes after pancreatic resection of screening-detected lesions in individuals at high risk for developing pancreatic cancer. *J Gastrointest Surg*. 2020;24(5):1101-1110. doi:10.1007/s11605-019-04230-z
133. Paiella S, Salvia R, De Pastena M, et al. Screening/surveillance programs for pancreatic cancer in familial high-risk individuals: a systematic review and proportion meta-analysis of screening results. *Pancreatology*. 2018;18(4):420-428. doi:10.1016/j.pan.2018.04.002
134. Overbeek KA, Levink IJM, Koopmann BDM, et al. Long-term yield of pancreatic cancer surveillance in high-risk individuals. *Gut*. 2022;71(6):1152-1160. doi:10.1136/gutjnl-2020-323611
135. Corral JE, Mareth KF, Riegert-Johnson DL, Das A, Wallace MB. Diagnostic yield from screening asymptomatic individuals at high risk for pancreatic cancer: a meta-analysis of cohort studies. *Clin Gastroenterol Hepatol*. 2019;17(1):41-53. doi:10.1016/j.cgh.2018.04.065
136. de Pretis N, Mukewar S, Aryal-Khanal A, Bi Y, Takahashi N, Chari S. Pancreatic cysts: diagnostic accuracy and risk of inappropriate resections. *Pancreatology*. 2017;17(2):267-272. doi:10.1016/j.pan.2017.01.002
137. Romutis S, Brand R. Burden of new pancreatic cyst diagnosis. *Gastrointest Endosc Clin N Am*. 2023;33(3):487-495. doi:10.1016/j.giec.2023.03.001
138. de Jong K, Nio CY, Hermans JJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol*. 2010;8(9):806-811. doi:10.1016/j.cgh.2010.05.017
139. Pozzi-Mucelli RM, Rinta-Kiikka I, Wunsche K, et al. Pancreatic MRI for the surveillance of cystic neoplasms: comparison of a short with a comprehensive imaging protocol. *Eur Radiol*. 2017;27(1):41-50. doi:10.1007/s00330-016-4377-4
140. Kromrey ML, Bulow R, Hubner J, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut*. 2018;67(1):138-145. doi:10.1136/gutjnl-2016-313127
141. Schweber AB, Agarunov E, Brooks C, Hur C, Gonda TA. Prevalence, incidence, and risk of progression of asymptomatic pancreatic cysts in large sample real-world data. *Pancreas*. 2021;50(9):1287-1292. doi:10.1097/mpa.0000000000001918
142. Sheel ARG, Harrison S, Sarantitis I, et al. Identification of cystic lesions by secondary screening of familial pancreatic cancer (FPC) kindreds is not associated with the stratified risk of cancer. *Am J Gastroenterol*. 2019;114(1):155-164. doi:10.1038/s41395-018-0395-y
143. Aziz H, Acher AW, Krishna SG, Cloyd JM, Pawlik TM. Comparison of society guidelines for the management and surveillance of pancreatic cysts: a review. *JAMA Surg*. 2022;157(8):723-730. doi:10.1001/jamasurg.2022.2232
144. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148(4):824-848e2. doi:10.1053/j.gastro.2015.01.014
145. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol*. 2018;113(4):464-479. doi:10.1038/ajg.2018.14
146. Megibow AJ, Baker ME, Morgan DE, et al. Management of incidental pancreatic cysts: a white paper of the ACR Incidental Findings Committee. *J Am Coll Radiol*. 2017;14(7):911-923. doi:10.1016/j.jacr.2017.03.010
147. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut*. 2018;67(5):789-804. doi:10.1136/gutjnl-2018-316027
148. Ohtsuka T, Fernandez-Del Castillo C, Furukawa T, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology*. 2024;24(2):255-270. doi:10.1016/j.pan.2023.12.009
149. Ohno E, Hirooka Y, Kawashima H, et al. Natural history of pancreatic cystic lesions: a multicenter prospective observational study for evaluating the risk of pancreatic cancer. *J Gastroenterol Hepatol*. 2018;33(1):320-328. doi:10.1111/jgh.13967
150. Yoon JG, Smith D, Ojili V, Paspulati RM, Ramaiya NH, Tirumani SH. Pancreatic cystic neoplasms: a review of current recommendations for surveillance and management. *Abdom Radiol (NY)*. 2021;46(8):3946-3962. doi:10.1007/s00261-021-03030-x
151. Nilsson LN, Keane MG, Shamali A, et al. Nature and management of pancreatic mucinous cystic neoplasm (MCN): a systematic review of the literature. *Pancreatology*. 2016;16(6):1028-1036. doi:10.1016/j.pan.2016.09.011
152. Zamboni G, Scarpa A, Bogina G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and

relationship to other mucinous cystic tumors. *Am J Surg Pathol*. 1999;23(4):410-422. doi:10.1097/00000478-199904000-00005
153. Taya M, Hecht EM, Huang C, Lo GC. Pancreatic cystic lesions: imaging techniques and diagnostic features. *Gastrointest Endosc Clin N Am*. 2023;33(3):497-518. doi:10.1016/j.giec.2023.03.007
154. Fasanella KE, McGrath K. Cystic lesions and intraductal neoplasms of the pancreas. *Best Pract Res Clin Gastroenterol*. 2009;23(1):35-48. doi:10.1016/j.bpg.2008.11.011
155. Klibansky DA, Reid-Lombardo KM, Gordon SR, Gardner TB. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. *Clin Gastroenterol Hepatol*. 2012;10(5):555-558. doi:10.1016/j.cgh.2011.12.029
156. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. *Gastroenterology*. 2013;144(6):1303-1315. doi:10.1053/j.gastro.2013.01.073
157. Rosenblatt R, Dorfman V, Epelboym I, et al. Demographic features and natural history of intermediate-risk multifocal versus unifocal intraductal papillary mucinous neoplasms. *Pancreas*. 2015;44(3):478-483. doi:10.1097/mpa.0000000000000264
158. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148(4):819-822; quiz e12-e13. doi:10.1053/j.gastro.2015.01.015
159. Tamburrino D, de Pretis N, Perez-Cuadrado-Robles E, et al. Identification of patients with branch-duct intraductal papillary mucinous neoplasm and very low risk of cancer: multicentre study. *Br J Surg*. 2022;109(7):617-622. doi:10.1093/bjs/znac103
160. de la Fuente J, Chatterjee A, Lui J, et al. Long-term outcomes and risk of pancreatic cancer in intraductal papillary mucinous neoplasms. *JAMA Netw Open*. 2023;6(10):e2337799. doi:10.1001/jamanetworkopen.2023.37799
161. Gonda TA, Cahen DL, Farrell JJ. Pancreatic cysts. *N Engl J Med*. 2024;391(9):832-843. doi:10.1056/nejmra2309041
162. Huang C, Chopra S, Bolan CW, et al. Pancreatic cystic lesions: next generation of radiologic assessment. *Gastrointest Endosc Clin N Am*. 2023;33(3):533-546. doi:10.1016/j.giec.2023.03.004
163. Hernandez LV, Mishra G, Forsmark C, et al. Role of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration in the diagnosis and treatment of cystic lesions of the pancreas. *Pancreas*. 2002;25(3):222-228. doi:10.1097/00006676-200210000-00002
164. Kim YC, Choi JY, Chung YE, et al. Comparison of MRI and endoscopic ultrasound in the characterization of pancreatic cystic lesions. *AJR Am J Roentgenol*. 2010;195(4):947-952. doi:10.2214/ajr.09.3985
165. Lisotti A, Napoleon B, Facciorusso A, et al. Contrast-enhanced EUS for the characterization of mural nodules within pancreatic cystic neoplasms: systematic review and meta-analysis. *Gastrointest Endosc*. 2021;94(5):881-889e5. doi:10.1016/j.gie.2021.06.028
166. Thosani N, Thosani S, Qiao W, Fleming JB, Bhutani MS, Guha S. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Dis Sci*. 2010;55(10):2756-2766. doi:10.1007/s10620-010-1361-8
167. Westerveld DR, Ponniah SA, Draganov PV, Yang D. Diagnostic yield of EUS-guided through-the-needle microforceps biopsy versus EUS-FNA of pancreatic cystic lesions: a systematic review and meta-analysis. *Endosc Int Open*. 2020;8(5):E656-E667. doi:10.1055/a-1119-6543
168. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738-753. doi:10.1016/j.pan.2017.07.007
169. van Huijgevoort NCM, Hoogenboom SAM, Lekkerkerker SJ, et al. Diagnostic accuracy of the AGA, IAP, and European guidelines for detecting advanced neoplasia in intraductal papillary mucinous neoplasm/neoplasia. *Pancreatology*. 2023;23(3):251-257. doi:10.1016/j.pan.2023.01.011
170. Marchegiani G, Pollini T, Burelli A, et al. Surveillance for presumed BD-IPMN of the pancreas: stability, size, and age identify targets for discontinuation. *Gastroenterology*. 2023;165(4):1016-1024e5. doi:10.1053/j.gastro.2023.06.022
171. Chhoda A, Singh S, Sheth AH, et al. Benefit of extended surveillance of low-risk pancreatic cysts after 5-year stability: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2023;21(6):1430-1446. doi:10.1016/j.cgh.2022.04.025
172. Park JW, Jang JY, Kang MJ, Kwon W, Chang YR, Kim SW. Mucinous cystic neoplasm of the pancreas: is surgical resection recommended for all surgically fit patients? *Pancreatology*. 2014;14(2):131-136. doi:10.1016/j.pan.2013.12.006
173. Paniccia A, Polanco PM, Boone BA, et al. Prospective, multi-institutional, real-time next-generation sequencing of pancreatic cyst fluid reveals diverse genomic alterations that improve the clinical management of pancreatic cysts. *Gastroenterology*. 2023;164(1):117-133e7. doi:10.1053/j.gastro.2022.09.028
174. Nikiforova MN, Wald AI, Spagnolo DM, et al. A combined DNA/RNA-based next-generation sequencing platform to improve the classification of pancreatic cysts and early detection of pancreatic cancer arising from pancreatic cysts. *Ann Surg*. 2023;278(4):e789-e797. doi:10.1097/sla.0000000000005904
175. Tan JY, Yeo YH, Ng WL, et al. Pancreatic cancer mortality trends in the United States: how much have we moved the needle? *J Gastrointest Oncol*. 2024;15(4):1789-1795. doi:10.21037/jgo-24-213
176. Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. *Lancet Public Health*. 2019;4(3):e137-e147. doi:10.1016/s2468-2667(18)30267-6
177. Cabasag CJ, Ferlay J, Laversanne M, et al. Pancreatic cancer: an increasing global public health concern. *Gut*. 2022;71(8):1686-1687. doi:10.1136/gutjnl-2021-326311
178. Ponz de Leon Pisani R, Altieri G, Stasio RC, et al. Gastrointestinal symptoms in the journey of pancreatic cancer patients. *Expert Rev Anticancer Ther*. 2025;25(8):883-900. doi:10.1080/14737140.2025.2517888
179. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395(10242):2008-2020. doi:10.1016/s0140-6736(20)30974-0
180. Walter FM, Mills K, Mendonca SC, et al. Symptoms and patient factors associated with diagnostic intervals for pancreatic cancer (SYMPTOM pancreatic study): a prospective cohort study. *Lancet Gastroenterol Hepatol*. 2016;1(4):298-306. doi:10.1016/s2468-1253(16)30079-6
181. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *JAMA*. 2021;326(9):851-862. doi:10.1001/jama.2021.13027
182. Okuno K, Tokunaga M, Von Hoff D, et al. Intratumoral Malassezia globosa levels predict survival and therapeutic response to adjuvant chemotherapy in patients with pancreatic ductal adenocarcinoma. *Gastroenterology*. 2023;165(2):502-504e2. doi:10.1053/j.gastro.2023.04.017
183. Wang XY, Yang F, Jin C, Fu DL. Utility of PET/CT in diagnosis, staging, assessment of resectability and metabolic response of pancreatic cancer. *World J Gastroenterol*. 2014;20(42):15580-15589. doi:10.3748/wjg.v20.i42.15580
184. Lee JS, Park SS, Lee YK, Norton JA, Jeffrey SS. Liquid biopsy in pancreatic ductal adenocarcinoma: current status of circulating tumor cells and circulating tumor DNA. *Mol Oncol*. 2019;13(8):1623-1650. doi:10.1002/1878-0261.12537
185. Bhayana R, Nanda B, Dehkharghanian T, et al. Large language models for automated synoptic reports and resectability

categorization in pancreatic cancer. *Radiology*. 2024;311(3):e233117. doi:10.1148/radiol.233117
186. Strobel O, Neoptolemos J, Jager D, Buchler MW. Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol*. 2019;16(1):11-26. doi:10.1038/s41571-018-0112-1
187. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. 2018;18(1):2-11. doi:10.1016/j.pan.2017.11.011
188. Springfeld C, Ferrone CR, Katz MHG, et al. Neoadjuvant therapy for pancreatic cancer. *Nat Rev Clin Oncol*. 2023;20(5):318-337. doi:10.1038/s41571-023-00746-1
189. Groot VP, Rezaee N, Wu W, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. *Ann Surg*. 2018;267(5):936-945. doi:10.1097/sla.0000000000002234
190. Seelen LWF, Floortje van Oosten A, Brada LJH, et al. Early recurrence after resection of locally advanced pancreatic cancer following induction therapy: an international multicenter study. *Ann Surg*. 2023;278(1):118-126. doi:10.1097/sla.0000000000005666
191. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379(25):2395-2406. doi:10.1056/nejmoa1809775
192. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011-1024. doi:10.1016/s0140-6736(16)32409-6
193. Brown ZJ, Cloyd JM. Trends in the utilization of neoadjuvant therapy for pancreatic ductal adenocarcinoma. *J Surg Oncol*. 2021;123(6):1432-1440. doi:10.1002/jso.26384
194. Stoop TF, Theijse RT, Seelen LWF, et al. Preoperative chemotherapy, radiotherapy and surgical decision-making in patients with borderline resectable and locally advanced pancreatic cancer. *Nat Rev Gastroenterol Hepatol*. 2024;21(2):101-124. doi:10.1038/s41575-023-00856-2
195. Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst*. 2014;106(3):dju011. doi:10.1093/jnci/dju011
196. Brown ZJ, Heh V, Labiner HE, et al. Surgical resection rates after neoadjuvant therapy for localized pancreatic ductal adenocarcinoma: meta-analysis. *Br J Surg*. 2022;110(1):34-42. doi:10.1093/bjs/znac354
197. Khachfe HH, Habib JR, Nassour I, Al Harthi S, Jamali FR. Borderline resectable and locally advanced pancreatic cancers: a review of definitions, diagnostics, strategies for treatment, and future directions. *Pancreas*. 2021;50(9):1243-1249. doi:10.1097/mpa.0000000000001924
198. Habib JR, Wolfgang CL. Commentary: Anatomic versus biologic resectability: the role of predictive biomarkers in guiding surgical management. *Surgery*. 2020;168(6):1017-1018. doi:10.1016/j.surg.2020.07.032
199. Khorana AA, McKernin SE, Berlin J, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37(23):2082-2088. doi:10.1200/jco.19.00946
200. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34(22):2654-2668. doi:10.1200/jco.2016.67.5561
201. Anger F, Doring A, van Dam J, et al. Impact of borderline resectability in pancreatic head cancer on patient survival: biology matters according to the new international consensus criteria. *Ann Surg Oncol*. 2021;28(4):2325-2336. doi:10.1245/s10434-020-09100-6
202. Tzeng CW, Katz MH, Fleming JB, et al. Morbidity and mortality after pancreaticoduodenectomy in patients with borderline resectable type C clinical classification. *J Gastrointest Surg*. 2014;18(1):146-155; discussion 155-146. doi:10.1007/s11605-013-2371-6
203. Tsai S, Christians KK, Ritch PS, et al. Multimodality therapy in patients with borderline resectable or locally advanced pancreatic cancer: importance of locoregional therapies for a systemic disease. *J Oncol Pract*. 2016;12(10):915-923. doi:10.1200/jop.2016.016162
204. Chatzizacharias NA, Tsai S, Griffin M, et al. Locally advanced pancreas cancer: staging and goals of therapy. *Surgery*. 2018;163(5):1053-1062. doi:10.1016/j.surg.2017.09.012
205. Fromer MW, Hawthorne J, Philips P, et al. An improved staging system for locally advanced pancreatic cancer: a critical need in the multidisciplinary era. *Ann Surg Oncol*. 2021;28(11):6201-6210. doi:10.1245/s10434-021-10174-z
206. Inoue Y, Oba A, Ono Y, Sato T, Ito H, Takahashi Y. Radical resection for locally advanced pancreatic cancers in the era of new neoadjuvant therapy-arterial resection, arterial divestment and total pancreatectomy. *Cancers (Basel)*. 2021;13(8):1818. doi:10.3390/cancers13081818
207. Gemenetzis G, Blair AB, Nagai M, et al. Anatomic criteria determine resectability in locally advanced pancreatic cancer. *Ann Surg Oncol*. 2022;29(1):401-414. doi:10.1245/s10434-021-10663-1
208. Suker M, Koerkamp BG, Coene PP, et al. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. *Eur J Surg Oncol*. 2019;45(10):1906-1911. doi:10.1016/j.ejso.2019.06.004
209. Takadate T, Morikawa T, Ishida M, et al. Staging laparoscopy is mandatory for the treatment of pancreatic cancer to avoid missing radiologically negative metastases. *Surg Today*. 2021;51(5):686-694. doi:10.1007/s00595-020-02121-4
210. Neuzillet C, Gaujoux S, Williet N, et al. Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC). *Dig Liver Dis*. 2018;50(12):1257-1271. doi:10.1016/j.dld.2018.08.008
211. Paracha M, Van Orden K, Patts G, Tseng J, McAneny D, Sachs T. Opportunity lost? Diagnostic laparoscopy in patients with pancreatic cancer in the National Surgical Quality Improvement Program database. *World J Surg*. 2019;43(3):937-943. doi:10.1007/s00268-018-4855-8
212. Fong ZV, Alvino DML, Fernandez-Del Castillo C, et al. Reappraisal of staging laparoscopy for patients with pancreatic adenocarcinoma: a contemporary analysis of 1001 patients. *Ann Surg Oncol*. 2017;24(11):3203-3211. doi:10.1245/s10434-017-5973-5
213. Sell NM, Fong ZV, Del Castillo CF, et al. Staging laparoscopy not only saves patients an incision, but may also help them live longer. *Ann Surg Oncol*. 2018;25(4):1009-1016. doi:10.1245/s10434-017-6317-1
214. Raptis DA, Sanchez-Velazquez P, Machairas N, et al. Defining benchmark outcomes for pancreatoduodenectomy with portomesenteric venous resection. *Ann Surg*. 2020;272(5):731-737. doi:10.1097/sla.0000000000004267
215. Groen JV, Michiels N, van Roessel S, et al. Venous wedge and segment resection during pancreatoduodenectomy for pancreatic cancer: impact on short- and long-term outcomes in a nationwide

cohort analysis. *Br J Surg*. 2021;109(1):96-104. doi:10.1093/bjs/znab345
216. Hackert T, Klaiber U, Hinz U, et al. Portal vein resection in pancreatic cancer surgery: risk of thrombosis and radicality determine survival. *Ann Surg*. 2023;277(6):e1291-e1298. doi:10.1097/sla.0000000000005444
217. Schneider M, Hackert T, Strobel O, Buchler MW. Technical advances in surgery for pancreatic cancer. *Br J Surg*. 2021;108(7):777-785. doi:10.1093/bjs/znab133
218. Loos M, Kester T, Klaiber U, et al. Arterial resection in pancreatic cancer surgery: effective after a learning curve. *Ann Surg*. 2022;275(4):759-768. doi:10.1097/sla.0000000000004054
219. Del Chiaro M, Schulick RD. Commentary on: Divestment or skeletonization of the SMA or the hepatic artery for locally advanced pancreatic ductal cancer after neoadjuvant therapy. *Surgery*. 2021;169(5):1039-1040. doi:10.1016/j.surg.2020.10.042
220. Kamarajah SK, Naffouje SA, Salti GI, Dahdaleh FS. Neoadjuvant chemotherapy for pancreatic ductal adenocarcinoma is associated with lower post-pancreatectomy readmission rates: a population-based cohort study. *Ann Surg Oncol*. 2021;28(4):1896-1905. doi:10.1245/s10434-020-09470-x
221. Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami international evidence-based guidelines on minimally invasive pancreas resection. *Ann Surg*. 2020;271(1):1-14. doi:10.1097/sla.0000000000003590
222. de Rooij T, van Hilst J, van Santvoort H, et al. Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg*. 2019;269(1):2-9. doi:10.1097/sla.0000000000002979
223. Bjornsson B, Larsson AL, Hjalmarsson C, Gasslander T, Sandstrom P. Comparison of the duration of hospital stay after laparoscopic or open distal pancreatectomy: randomized controlled trial. *Br J Surg*. 2020;107(10):1281-1288. doi:10.1002/bjs.11554
224. Korrel M, Jones LR, van Hilst J, et al. Minimally invasive versus open distal pancreatectomy for resectable pancreatic cancer (DIPLOMA): an international randomised non-inferiority trial. *Lancet Reg Health Eur*. 2023;31:100673. doi:10.1016/j.lanepe.2023.100673
225. Adam MA, Thomas S, Youngwirth L, Pappas T, Roman SA, Sosa JA. Defining a hospital volume threshold for minimally invasive pancreaticoduodenectomy in the United States. *JAMA Surg*. 2017;152(4):336-342. doi:10.1001/jamasurg.2016.4753
226. van Hilst J, de Graaf N, Festen S, Hilal MA, Besselink M; European Consortium on Minimally Invasive Pancreatic Surgery (E-MIS). Laparoscopic versus open pancreatoduodenectomy for pancreatic or peri-ampullary tumours. *Lancet Gastroenterol Hepatol*. 2021;6(9):688-689. doi:10.1016/s2468-1253(21)00227-2
227. Adam MA, Choudhury K, Dinan MA, et al. Minimally invasive versus open pancreaticoduodenectomy for cancer: practice patterns and short-term outcomes among 7061 patients. *Ann Surg*. 2015;262(2):372-377. doi:10.1097/sla.0000000000001055
228. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Ann Surg*. 2014;260(4):633-638; discussion 638-640. doi:10.1097/sla.0000000000000937
229. Poves I, Burdio F, Morato O, et al. Comparison of perioperative outcomes between laparoscopic and open approach for pancreatoduodenectomy: the PADULAP randomized controlled trial. *Ann Surg*. 2018;268(5):731-739. doi:10.1097/sla.0000000000002893
230. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. *Br J Surg*. 2017;104(11):1443-1450. doi:10.1002/bjs.10662
231. Abu HM, van Ramshorst TME, Boggi U, et al. The Brescia Internationally Validated European Guidelines on Minimally Invasive Pancreatic Surgery (EGUMIPS). *Ann Surg*. 2024;279(1):45-57. doi:10.1097/SLA.0000000000006006
232. Sattari SA, Sattari AR, Makary MA, Hu C, He J. Laparoscopic versus open pancreatoduodenectomy in patients with periampullary tumors: a systematic review and meta-analysis. *Ann Surg*. 2023;277(5):742-755. doi:10.1097/sla.0000000000005785
233. Klotz R, Mihaljevic AL, Kulu Y, et al. Robotic versus open partial pancreatoduodenectomy (EUROPA): a randomised controlled stage 2b trial. *Lancet Reg Health Eur*. 2024;39:100864. doi:10.1016/j.lanepe.2024.100864
234. Liu Q, Li M, Gao Y, et al. Effect of robotic versus open pancreaticoduodenectomy on postoperative length of hospital stay and complications for pancreatic head or periampullary tumours: a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024;9(5):428-437. doi:10.1016/s2468-1253(24)00005-0
235. Boggi U, Napoli N, Kauffmann EF. Disentangling seemingly contradictory results of the first two randomised controlled trials comparing open and robotic pancreatoduodenectomy. *Lancet Reg Health Eur*. 2024;40:100900. doi:10.1016/j.lanepe.2024.100900
236. Neshan M, Padmanaban V, Chick RC, Pawlik TM. Open vs robotic-assisted pancreaticoduodenectomy, cost-effectiveness and long-term oncologic outcomes: a systematic review and meta-analysis. *J Gastrointest Surg*. 2024;28(11):1933-1942. doi:10.1016/j.gassur.2024.08.013
237. Gyawali B, Booth CM. Treatment of metastatic pancreatic cancer: 25 years of innovation with little progress for patients. *Lancet Oncol*. 2024;25(2):167-170. doi:10.1016/s1470-2045(23)00516-8
238. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342. doi:10.1001/jamaoncol.2017.0589
239. Leonhardt CS, Gustorff C, Klaiber U, et al. Prognostic factors for early recurrence after resection of pancreatic cancer: a systematic review and meta-analysis. *Gastroenterology*. 2024;167(5):977-992. doi:10.1053/j.gastro.2024.05.028
240. Nishiwada S, Cui Y, Sho M, et al. Transcriptomic profiling identifies an exosomal microRNA signature for predicting recurrence following surgery in patients with pancreatic ductal adenocarcinoma. *Ann Surg*. 2022;276(6):e876-e885. doi:10.1097/sla.0000000000004993
241. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350(12):1200-1210. doi:10.1056/nejmoa032295
242. Knaebel HP, Marten A, Schmidt J, et al. Phase III trial of postoperative cisplatin, interferon alpha-2b, and 5-FU combined with external radiation treatment versus 5-FU alone for patients with resected pancreatic adenocarcinoma—CapRI: study protocol [ISRCTN62866759]. *BMC Cancer*. 2005;5(1):37. doi:10.1186/1471-2407-5-37
243. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013;310(14):1473-1481. doi:10.1001/jama.2013.279201
244. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297(3):267-277. doi:10.1001/jama.297.3.267
245. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for

Pancreatic Cancer. *Br J Cancer*. 2009;101(6):908-915. doi:10.1038/sj.bjc.6605256

246. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304(10):1073-1081. doi:10.1001/jama.2010.1275
247. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388(10041):248-257. doi:10.1016/s0140-6736(16)30583-9
248. Sinn M, Bahra M, Liersch T, et al. CONKO-005: adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial. *J Clin Oncol*. 2017;35(29):3330-3337. doi:10.1200/jco.2017.72.6463
249. Abrams RA, Winter KA, Safran H, et al. Results of the NRG Oncology/RTOG 0848 adjuvant chemotherapy question—erlotinib+gemcitabine for resected cancer of the pancreatic head: a phase II randomized clinical trial. *Am J Clin Oncol*. 2020;43(3):173-179. doi:10.1097/coc.0000000000000633
250. Sinn M, Liersch T, Riess H, et al. CONKO-006: a randomised double-blinded phase IIb-study of additive therapy with gemcitabine + sorafenib/placebo in patients with R1 resection of pancreatic cancer—final results. *Eur J Cancer*. 2020;138:172-181. doi:10.1016/j.ejca.2020.06.032
251. Conroy T, Castan F, Lopez A, et al. Five-year outcomes of FOLFIRINOX vs gemcitabine as adjuvant therapy for pancreatic cancer: a randomized clinical trial. *JAMA Oncol*. 2022;8(11):1571-1578. doi:10.1001/jamaoncol.2022.3829
252. Tempero MA, Pelzer U, O'Reilly EM, et al. Adjuvant nab-paclitaxel + gemcitabine in resected pancreatic ductal adenocarcinoma: results from a randomized, open-label, phase III trial. *J Clin Oncol*. 2023;41(11):2007-2019. doi:10.1200/JCO.22.01134
253. Palmer DH, Jackson R, Springfeld C, et al. Pancreatic adenocarcinoma: long-term outcomes of adjuvant therapy in the ESPAC4 phase III trial. *J Clin Oncol*. 2024;43(10):1240-1253. doi:10.1200/jco.24.01118
254. Zhu X, Liu W, Cao Y, et al. Effect of stereotactic body radiotherapy dose escalation plus pembrolizumab and trametinib versus stereotactic body radiotherapy dose escalation plus gemcitabine for locally recurrent pancreatic cancer after surgical resection on survival outcomes: a secondary analysis of an open-label, randomised, controlled, phase 2 trial. *eClinicalMedicine*. 2023;55:101764. doi:10.1016/j.eclinm.2022.101764
255. Zhu X, Cao Y, Liu W, et al. Stereotactic body radiotherapy plus pembrolizumab and trametinib versus stereotactic body radiotherapy plus gemcitabine for locally recurrent pancreatic cancer after surgical resection: an open-label, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2022;23(3):e105-e115. doi:10.1016/s1470-2045(22)00066-3
256. Hoyer K, Hablesreiter R, Inoue Y, et al. A genetically defined signature of responsiveness to erlotinib in early-stage pancreatic cancer patients: results from the CONKO-005 trial. *eBioMedicine*. 2021;66:103327. doi:10.1016/j.ebiom.2021.103327
257. Springfeld C, Buchler MW, Neoptolemos JP. Interpreting primary end points in randomized trials of pancreatic cancer. *J Clin Oncol*. 2023;41(25):4182-4183. doi:10.1200/jco.23.00779
258. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol*. 2014;32(6):504-512. doi:10.1200/jco.2013.50.7657
259. Nicolle R, Bachet JB, Harle A, et al. Prediction of adjuvant gemcitabine sensitivity in resectable pancreatic adenocarcinoma using the GemPred RNA signature: an ancillary study of the PRODIGE-24/CCTG PA6 clinical trial. *J Clin Oncol*. 2024;42(9):1067-1076. doi:10.1200/jco.22.02668
260. Poultsides GA, Reddy S, Cameron JL, et al. Histopathologic basis for the favorable survival after resection of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma of the pancreas. *Ann Surg*. 2010;251(3):470-476. doi:10.1097/sla.0b013e3181cf8a19
261. Tan MC, Basturk O, Brannon AR, et al. GNAS and KRAS mutations define separate progression pathways in intraductal papillary mucinous neoplasm-associated carcinoma. *J Am Coll Surg*. 2015;220(5):845-854e1. doi:10.1016/j.jamcollsurg.2014.11.029
262. Koh YX, Chok AY, Zheng HL, Tan CS, Goh BK. Systematic review and meta-analysis comparing the surgical outcomes of invasive intraductal papillary mucinous neoplasms and conventional pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2014;21(8):2782-2800. doi:10.1245/s10434-014-3639-0
263. Aronsson L, Marinko S, Ansari D, Andersson R. Adjuvant therapy in invasive intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a systematic review. *Ann Transl Med*. 2019;7(22):689. doi:10.21037/atm.2019.10.37
264. Habib JR, Kinny-Koster B, Javed AA, et al. Impact of adjuvant chemotherapy on resected intraductal papillary mucinous neoplasm-derived pancreatic cancer: results from an international multicenter study. *J Clin Oncol*. 2024;42(36):4317-4326. doi:10.1200/JCO.23.02313
265. Neoptolemos JP, Cox TF. Bayesian analysis unravels pancreas-cancer adjuvant therapy. *Lancet Oncol*. 2013;14(11):1034-1035. doi:10.1016/s1470-2045(13)70403-0
266. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358(9293):1576-1585. doi:10.1016/s0140-6736(01)06651-x
267. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. *HPB (Oxford)*. 2017;19(2):83-92. doi:10.1016/j.hpb.2016.11.001
268. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol*. 2015;191(1):7-16. doi:10.1007/s00066-014-0737-7
269. Reni M, Balzano G, Zanon S, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. *Lancet Gastroenterol Hepatol*. 2018;3(6):413-423. doi:10.1016/s2468-1253(18)30081-5
270. Motoi F, Kosuge T, Ueno H, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol*. 2019;49(2):190-194. doi:10.1093/jjco/hyy190
271. Sohal DPS, Duong M, Ahmad SA, et al. Efficacy of perioperative chemotherapy for resectable pancreatic adenocarcinoma: a phase 2 randomized clinical trial. *JAMA Oncol*. 2021;7(3):421-427. doi:10.1001/jamaoncol.2020.7328
272. Ahmad SA, Duong M, Sohal DPS, et al. Surgical outcome results from SWOG S1505: a randomized clinical trial of mFOLFIRINOX versus gemcitabine/nab-paclitaxel for perioperative treatment of resectable pancreatic ductal adenocarcinoma. *Ann Surg*. 2020;272(3):481-486. doi:10.1097/sla.0000000000004155
273. Versteijne E, van Dam JL, Suker M, et al. Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the Dutch randomized PREOPANC trial. *J Clin Oncol*. 2022;40(11):1220-1230. doi:10.1200/jco.21.02233

274. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. *J Clin Oncol*. 2020;38(16):1763-1773. doi:10.1200/jco.19.02274
275. Katz MHG, Shi Q, Meyers J, et al. Efficacy of preoperative mFOLFIRINOX vs mFOLFIRINOX plus hypofractionated radiotherapy for borderline resectable adenocarcinoma of the pancreas: the A021501 phase 2 randomized clinical trial. *JAMA Oncol*. 2022;8(9):1263-1270. doi:10.1001/jamaoncol.2022.2319
276. Ghaneh P, Palmer D, Cicconi S, et al. Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(2):157-168. doi:10.1016/s2468-1253(22)00348-x
277. Seufferlein T, Uhl W, Kornmann M, et al. Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (NEONAX)—a randomized phase II trial of the AIO Pancreatic Cancer Group. *Ann Oncol*. 2023;34(1):91-100. doi:10.1016/j.annonc.2022.09.161
278. Labori KJ, Bratlie SO, Andersson B, et al. Neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer (NORPACT-1): a multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2024;9(3):205-217. doi:10.1016/s2468-1253(23)00405-3
279. Yamada D, Kobayashi S, Takahashi H, et al. Results of a randomized clinical study of gemcitabine plus nab-paclitaxel versus gemcitabine plus S-1 as neoadjuvant chemotherapy for resectable and borderline resectable pancreatic ductal adenocarcinoma (RCT, CSGO-HBP-015). *Ann Surg Oncol*. 2024;31(7):4621-4633. doi:10.1245/s10434-024-15199-8
280. Reni M, Macchini M, Orsi G, et al. Results of a randomized phase III trial of pre-operative chemotherapy with mFOLFIRINOX or PAXG regimen for stage I-III pancreatic ductal adenocarcinoma [abstract]. *J Clin Oncol*. 2025;43(17 suppl):LBA0004. doi:10.1200/jco.2025.43.17_suppl.lba4004
281. Fietkau R, Ghadimi M, Grutzmann R, et al. Benefit of chemoradiotherapy versus chemotherapy after induction therapy for conversion of unresectable into resectable pancreatic cancer: the randomized CONKO-007 trial. *J Clin Oncol*. 2025. doi:10.1200/JCO-24-01502
282. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg*. 2018;268(2):215-222. doi:10.1097/sla.0000000000002705
283. Motoi F, Satoi S, Honda G, et al.; Study Group of Preoperative Therapy for Pancreatic Cancer. A single-arm, phase II trial of neoadjuvant gemcitabine and S1 in patients with resectable and borderline resectable pancreatic adenocarcinoma: PREP-01 study. *J Gastroenterol*. 2019;54(2):194-203. doi:10.1007/s00535-018-1506-7
284. Casadei R, Di Marco M, Ricci C, et al. Neoadjuvant chemoradiotherapy and surgery versus surgery alone in resectable pancreatic cancer: a single-center prospective, randomized, controlled trial which failed to achieve accrual targets. *J Gastrointest Surg*. 2015;19(10):1802-1812. doi:10.1007/s11605-015-2890-4
285. van Dam JL, Janssen QP, Besselink MG, et al. Neoadjuvant therapy or upfront surgery for resectable and borderline resectable pancreatic cancer: a meta-analysis of randomised controlled trials. *Eur J Cancer*. 2022;160:140-149. doi:10.1016/j.ejca.2021.10.023
286. Cecchini M, Salem RR, Robert M, et al. Perioperative modified FOLFIRINOX for resectable pancreatic cancer: a nonrandomized controlled trial. *JAMA Oncol*. 2024;10(8):1027. doi:10.1001/jamaoncol.2024.1575
287. Stoop TF, Oba A, Wu YHA, et al. Pathological complete response in patients with resected pancreatic adenocarcinoma after preoperative chemotherapy. *JAMA Netw Open*. 2024;7(6):e2417625. doi:10.1001/jamanetworkopen.2024.17625
288. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413. doi:10.1200/jco.1997.15.6.2403
289. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(15):1960-1966. doi:10.1200/jco.2006.07.9525
290. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27(33):5513-5518. doi:10.1200/jco.2009.24.2446
291. Haldar SD, Azad NS. Unlocking the promise of RAS inhibition in pancreatic cancer. *Nat Rev Gastroenterol Hepatol*. 2024;21(8):535-536. doi:10.1038/s41575-024-00951-y
292. Sha H, Tong F, Ni J, et al. First-line penpulimab (an anti-PD1 antibody) and anlotinib (an angiogenesis inhibitor) with nab-paclitaxel/gemcitabine (PAAG) in metastatic pancreatic cancer: a prospective, multicentre, biomolecular exploratory, phase II trial. *Signal Transduct Target Ther*. 2024;9(1):143. doi:10.1038/s41392-024-01857-6
293. Van Laethem JL, Borbath I, Prenen H, et al. Combining CD40 agonist mitazalimab with mFOLFIRINOX in previously untreated metastatic pancreatic ductal adenocarcinoma (OPTIMIZE-1): a single-arm, multicentre phase 1b/2 study. *Lancet Oncol*. 2024;25(7):853-864. doi:10.1016/s1470-2045(24)00263-8
294. Strickler JH, Satake H, George TJ, et al. Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. *N Engl J Med*. 2023;388(1):33-43. doi:10.1056/nejmoa2208470
295. Leidner R, Sanjuan Silva N, Huang H, et al. Neoantigen T-cell receptor gene therapy in pancreatic cancer. *N Engl J Med*. 2022;386(22):2112-2119. doi:10.1056/nejmoa2119662
296. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317-327. doi:10.1056/nejmoa1903387
297. Musher BL, Rowinsky EK, Smaglo BG, et al. LOAd703, an oncolytic virus-based immunostimulatory gene therapy, combined with chemotherapy for unresectable or metastatic pancreatic cancer (LOKON001): results from arm 1 of a non-randomised, single-centre, phase 1/2 study. *Lancet Oncol*. 2024;25(4):488-500. doi:10.1016/s1470-2045(24)00079-2
298. Bekaii-Saab T, Okusaka T, Goldstein D, et al. Napabucasin plus nab-paclitaxel with gemcitabine versus nab-paclitaxel with gemcitabine in previously untreated metastatic pancreatic adenocarcinoma: an adaptive multicentre, randomised, open-label, phase 3, superiority trial. *eClinicalMedicine*. 2023;58:101897. doi:10.1016/j.eclinm.2023.101897
299. Dean A, Gill S, McGregor M, Broadbridge V, Jarvelainen HA, Price T. Dual alphaV-integrin and neuropilin-1 targeting peptide CEND-1 plus nab-paclitaxel and gemcitabine for the treatment of metastatic pancreatic ductal adenocarcinoma: a first-in-human, open-label, multicentre, phase 1 study. *Lancet Gastroenterol Hepatol*. 2022;7(10):943-951. doi:10.1016/s2468-1253(22)00167-4
300. Alistar A, Morris BB, Desnoyer R, et al. Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial. *Lancet Oncol*. 2017;18(6):770-778. doi:10.1016/s1470-2045(17)30314-5

301. Middleton G, Palmer DH, Greenhalf W, et al. Vandetanib plus gemcitabine versus placebo plus gemcitabine in locally advanced or metastatic pancreatic carcinoma (ViP): a prospective, randomised, double-blind, multicentre phase 2 trial. *Lancet Oncol*. 2017;18(4):486-499. doi:10.1016/s1470-2045(17)30084-0
302. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10018):545-557. doi:10.1016/s0140-6736(15)00986-1
303. Karim S, Zhang-Salomans J, Biagi JJ, Asmis T, Booth CM. Uptake and effectiveness of FOLFIRINOX for advanced pancreatic cancer: a population-based study. *Clin Oncol*. 2018;30(1):e16-e21. doi:10.1016/j.clon.2017.10.017
304. Luyendijk M, Visser O, Blommestein HM, et al. Changes in survival in de novo metastatic cancer in an era of new medicines. *J Natl Cancer Inst*. 2023;115(6):628-635. doi:10.1093/jnci/djad020
305. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. *World J Oncol*. 2019;10(1):10-27. doi:10.14740/wjon1166
306. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825. doi:10.1056/nejmoa1011923
307. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703. doi:10.1056/nejmoa1304369
308. Kindler HL, Hammel P, Reni M, et al. Overall survival results from the POLO trial: a phase III study of active maintenance olaparib versus placebo for germline BRCA-mutated metastatic pancreatic cancer. *J Clin Oncol*. 2022;40(34):3929-3939. doi:10.1200/jco.21.01604
309. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol*. 2020;38(13):1378-1388. doi:10.1200/jco.19.02931
310. Ludmir EB, Sherry AD, Fellman BM, et al. Addition of metastasis-directed therapy to systemic therapy for oligometastatic pancreatic ductal adenocarcinoma (EXTEND): a multicenter, randomized phase II trial. *J Clin Oncol*. 2024;42(32):3795-3805. doi:10.1200/jco.24.00081
311. Rinaldi Y, Pointet AL, Khemissa Akouz F, et al. Gemcitabine plus nab-paclitaxel until progression or alternating with FOLFIRI.3, as first-line treatment for patients with metastatic pancreatic adenocarcinoma: the Federation Francophone de Cancerologie Digestive-PRODIGE 37 randomised phase II study (FIRGEMAX). *Eur J Cancer*. 2020;136:25-34. doi:10.1016/j.ejca.2020.05.018
312. Philip PA, Sahai V, Bahary N, et al. Devimistat (CPI-613) with modified fluorouracil, oxaliplatin, irinotecan, and leucovorin (FFX) versus FFX for patients with metastatic adenocarcinoma of the pancreas: the phase III AVENGER 500 study. *J Clin Oncol*. 2024;42(31):3692-3701. doi:10.1200/jco.23.02659
313. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *Lancet*. 2023;402(10409):1272-1281. doi:10.1016/s0140-6736(23)01366-1
314. Ohba A, Ozaka M, Ogawa G, et al. Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): a multicentred, randomized, open-label, three-arm, phase II/III trial. *Ann Oncol*. 2023;34:S894. doi:10.1016/j.annonc.2023.09.2565
315. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P; ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii33-vii40. doi:10.1093/annonc/mds224
316. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic pancreatic cancer: ASCO guideline update. *J Clin Oncol*. 2020;38(27):3217-3230. doi:10.1200/jco.20.01364
317. Sohal DPS, Kennedy EB, Khorana A, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36(24):2545-2556. doi:10.1200/jco.2018.78.9636
318. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*. 2011;29(34):4548-4554. doi:10.1200/jco.2011.36.5742
319. Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107(2):dju413. doi:10.1093/jnci/dju413
320. Macarulla T, Pazo-Cid R, Guillen-Ponce C, et al. Phase I/II trial to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with pancreatic cancer and an ECOG performance status of 2. *J Clin Oncol*. 2019;37(3):230-238. doi:10.1200/jco.18.00089
321. Ramanathan RK, Goldstein D, Korn RL, et al. Positron emission tomography response evaluation from a randomized phase III trial of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas. *Ann Oncol*. 2016;27(4):648-653. doi:10.1093/annonc/mdw020
322. Bachet JB, Hammel P, Desrame J, et al. Nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil as first-line therapy for metastatic pancreatic adenocarcinoma (AFUGEM GERCOR): a non-comparative, multicentre, open-label, randomised phase 2 trial. *Lancet Gastroenterol Hepatol*. 2017;2(5):337-346. doi:10.1016/s2468-1253(17)30046-8
323. Dorman K, Boeck S, Caca K, et al. Alternating gemcitabine plus nab-paclitaxel and gemcitabine alone versus continuous gemcitabine plus nab-paclitaxel after induction treatment of metastatic pancreatic cancer (ALPACA): a multicentre, randomised, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2024;9(10):935-943. doi:10.1016/s2468-1253(24)00197-3
324. Taieb J, Prager GW, Melisi D, et al. First-line and second-line treatment of patients with metastatic pancreatic adenocarcinoma in routine clinical practice across Europe: a retrospective, observational chart review study. *ESMO Open*. 2020;5(1):e000587. doi:10.1136/esmoopen-2019-000587
325. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol*. 2014;32(23):2423-2429. doi:10.1200/jco.2013.53.6995
326. Gill S, Ko YJ, Cripps C, et al. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. *J Clin Oncol*. 2016;34(32):3914-3920. doi:10.1200/jco.2016.68.5776
327. Hurwitz H, Van Cutsem E, Bendell J, et al. Ruxolitinib + capecitabine in advanced/metastatic pancreatic cancer after disease progression/intolerance to first-line therapy: JANUS 1 and 2 randomized phase III studies. *Invest New Drugs*. 2018;36(4):683-695. doi:10.1007/s10637-018-0580-2
328. Ioka T, Ueno M, Ueno H, et al. TAS-118 (S-1 plus leucovorin) versus S-1 in patients with gemcitabine-refractory advanced pancreatic cancer: a randomised, open-label, phase 3 study (GRAPE trial). *Eur J Cancer*. 2019;106:78-88. doi:10.1016/j.ejca.2018.10.004
329. Le DT, Picozzi VJ, Ko AH, et al. Results from a phase IIb, randomized, multicenter study of GVAX pancreas and CRS-207 compared with chemotherapy in adults with previously treated

metastatic pancreatic adenocarcinoma (ECLIPSE study). *Clin Cancer Res*. 2019;25(18):5493-5502. doi:10.1158/1078-0432.ccr-18-2992

330. Go SI, Lee SC, Bae WK, et al. Modified FOLFIRINOX versus S-1 as second-line chemotherapy in gemcitabine-failed metastatic pancreatic cancer patients: a randomised controlled trial (MPACA-3). *Eur J Cancer*. 2021;157:21-30. doi:10.1016/j.ejca.2021.08.002
331. Hecht JR, Lonardi S, Bendell J, et al. Randomized phase III study of FOLFOX alone or with pegilodecakin as second-line therapy in patients with metastatic pancreatic cancer that progressed after gemcitabine (SEQUOIA). *J Clin Oncol*. 2021;39(10):1108-1118. doi:10.1200/jco.20.02232
332. De La Fouchardiere C, Malka D, Cropet C, et al. Gemcitabine and paclitaxel versus gemcitabine alone after 5-fluorouracil, oxaliplatin, and irinotecan in metastatic pancreatic adenocarcinoma: a randomized phase III PRODIGE 65-UCGI 36-GEMPAX UNICANCER study. *J Clin Oncol*. 2024;42(9):1055-1066. doi:10.1200/jco.23.00795
333. Timmer FEF, Geboers B, Nieuwenhuizen S, et al. Locoregional treatment of metastatic pancreatic cancer utilizing resection, ablation and embolization: a systematic review. *Cancers (Basel)*. 2021;13(7):1608. doi:10.3390/cancers13071608
334. Wang X, Wang W, Zou S, et al. Combination therapy of KRAS G12V mRNA vaccine and pembrolizumab: clinical benefit in patients with advanced solid tumors. *Cell Res*. 2024;34(9):661-664. doi:10.1038/s41422-024-00990-9
335. Nishiwada S, Sho M, Banwait JK, et al. A microRNA signature identifies pancreatic ductal adenocarcinoma patients at risk for lymph node metastases. *Gastroenterology*. 2020;159(2):562-574. doi:10.1053/j.gastro.2020.04.057
336. Timmer FEF, Geboers B, Ruarus AH, et al. MRI-guided stereotactic ablative body radiotherapy versus CT-guided percutaneous irreversible electroporation for locally advanced pancreatic cancer (CROSSFIRE): a single-centre, open-label, randomised phase 2 trial. *Lancet Gastroenterol Hepatol*. 2024;9(5):448-459. doi:10.1016/s2468-1253(24)00017-7
337. Taniguchi CM, Frakes JM, Aguilera TA, et al. Stereotactic body radiotherapy with or without selective dismutase mimetic in pancreatic adenocarcinoma: an adaptive, randomised, double-blind, placebo-controlled, phase 1b/2 trial. *Lancet Oncol*. 2023;24(12):1387-1398. doi:10.1016/s1470-2045(23)00478-3
338. Fujisawa T, Tsuchiya T, Kato M, et al. STNM01, the RNA oligonucleotide targeting carbohydrate sulfotransferase 15, as second-line therapy for chemotherapy-refractory patients with unresectable pancreatic cancer: an open label, phase I/IIa trial. *eClinicalMedicine*. 2023;55:101731. doi:10.1016/j.eclinm.2022.101731
339. Reiss KA, Mick R, Teitelbaum U, et al. Niraparib plus nivolumab or niraparib plus ipilimumab in patients with platinum-sensitive advanced pancreatic cancer: a randomised, phase 1b/2 trial. *Lancet Oncol*. 2022;23(8):1009-1020. doi:10.1016/s1470-2045(22)00369-2
340. Kunzmann V, Siveke JT, Algul H, et al. Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2021;6(2):128-138. doi:10.1016/s2468-1253(20)30330-7
341. Philip PA, Lacy J, Portales F, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol*. 2020;5(3):285-294. doi:10.1016/s2468-1253(19)30327-9
342. Suker M, Nuyttens JJ, Eskens F, et al. Efficacy and feasibility of stereotactic radiotherapy after FOLFIRINOX in patients with locally advanced pancreatic cancer (LAPC-1 trial). *eClinicalMedicine*. 2019;17:100200. doi:10.1016/j.eclinm.2019.10.013
343. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol*. 2016;17(6):801-810. doi:10.1016/s1470-2045(16)00172-8
344. Nywening TM, Wang-Gillam A, Sanford DE, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. *Lancet Oncol*. 2016;17(5):651-662. doi:10.1016/s1470-2045(16)00078-4
345. Uemura K, Kondo N, Sudo T, et al. Long-term outcomes of neoadjuvant gemcitabine, nab-paclitaxel, and S1 (GAS) in borderline resectable pancreatic cancer with arterial contact: results from a phase II trial. *J Hepatobiliary Pancreat Sci*. 2024;31(5):351-362. doi:10.1002/jhbp.1412
346. Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Kung M. Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: results of the PANOVA phase 2 study. *Pancreatology*. 2019;19(1):64-72. doi:10.1016/j.pan.2018.10.004
347. Babiker HM, Picozzi V, Chandana SR, et al. Tumor treating fields with gemcitabine and nab-paclitaxel for locally advanced pancreatic adenocarcinoma: randomized, open-label, pivotal phase III PANOVA-3 study. *J Clin Oncol*. 2025;43(21):2350-2360. doi:10.1200/JCO-25-00746
348. Mastrantoni L, Chiaravalli M, Spring A, et al. Comparison of first-line chemotherapy regimens in unresectable locally advanced or metastatic pancreatic cancer: a systematic review and Bayesian network meta-analysis. *Lancet Oncol*. 2024;25(12):1655-1665. doi:10.1016/s1470-2045(24)00511-4
349. Reni M, Zanon S, Peretti U, et al. Nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in metastatic pancreatic adenocarcinoma (PACT-19): a randomised phase 2 trial. *Lancet Gastroenterol Hepatol*. 2018;3(10):691-697. doi:10.1016/s2468-1253(18)30196-1
350. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10. doi:10.1200/jco.19.02105
351. Kim IK, Diamond MS, Yuan S, et al. Plasticity-induced repression of Irf6 underlies acquired resistance to cancer immunotherapy in pancreatic ductal adenocarcinoma. *Nat Commun*. 2024;15(1):1532. doi:10.1038/s41467-024-46048-7
352. O'Hara MH, O'Reilly EM, Varadhachary G, et al. CD40 agonistic monoclonal antibody APX005M (sotigalimab) and chemotherapy, with or without nivolumab, for the treatment of metastatic pancreatic adenocarcinoma: an open-label, multicentre, phase 1b study. *Lancet Oncol*. 2021;22(1):118-131. doi:10.1016/S1470-2045(20)30532-5
353. Padron LJ, Maurer DM, O'Hara MH, et al. Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial. *Nat Med*. 2022;28(6):1167-1177. doi:10.1038/s41591-022-01829-9
354. Till JE, McDaniel L, Chang C, et al. Circulating KRAS G12D but not G12V is associated with survival in metastatic pancreatic ductal adenocarcinoma. *Nat Commun*. 2024;15(1):5763. doi:10.1038/s41467-024-49915-5
355. Wainberg ZA, Hochster HS, Kim EJ, et al. Open-label, phase I study of nivolumab combined with nab-paclitaxel plus gemcitabine in advanced pancreatic cancer. *Clin Cancer Res*. 2020;26(18):4814-4822. doi:10.1158/1078-0432.ccr-20-0099
356. Callahan M, Amin A, Kaye FJ, et al. Nivolumab monotherapy or combination with ipilimumab with or without cobimetinib in

previously treated patients with pancreatic adenocarcinoma (CheckMate 032). *J Immunother Cancer*. 2024;12(2):e007883. doi:10.1136/jitc-2023-007883
357. Sugumar K, Alabd A, Alabd A, et al. Exceptional responders to immunotherapy in pancreatic cancer: a multi-institutional case series of a rare occurrence. *Oncotarget*. 2025;16(1):427-442. doi:10.18632/oncotarget.28739
358. Taieb J, Sayah L, Heinrich K, et al. Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: an AGEO European cohort. *Eur J Cancer*. 2023;188:90-97. doi:10.1016/j.ejca.2023.04.012
359. Qi C, Zhang P, Liu C, et al. Safety and efficacy of CT041 in patients with refractory metastatic pancreatic cancer: a pooled analysis of two early-phase trials. *J Clin Oncol*. 2024;42(21):2565-2577. doi:10.1200/jco.23.02314
360. van't Land FR, Willemsen M, Bezemer K, et al. Dendritic cell-based immunotherapy in patients with resected pancreatic cancer. *J Clin Oncol*. 2024;42(26):3083-3093. doi:10.1200/jco.23.02585
361. Johannet P, Abdelfattah S, Wilde C, et al. Molecular and clinicopathologic impact of GNAS variants across solid tumors. *J Clin Oncol*. 2024;42(32):3847-3857. doi:10.1200/jco.24.00186
362. Qin S, Li J, Bai Y, et al. Nimotuzumab plus gemcitabine for K-ras wild-type locally advanced or metastatic pancreatic cancer. *J Clin Oncol*. 2023;41(33):5163-5173. doi:10.1200/jco.22.02630
363. Luo J. KRAS mutation in pancreatic cancer. *Semin Oncol*. 2021;48(1):10-18. doi:10.1053/j.seminoncol.2021.02.003
364. Spoerner M, Herrmann C, Vetter IR, Kalbitzer HR, Wittinghofer A. Dynamic properties of the Ras switch I region and its importance for binding to effectors. *Proc Natl Acad Sci U S A*. 2001;98(9):4944-4949. doi:10.1073/pnas.081441398
365. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548-551. doi:10.1038/nature12796
366. Lai E, Ziranu P, Spanu D, et al. BRCA-mutant pancreatic ductal adenocarcinoma. *Br J Cancer*. 2021;125(10):1321-1332. doi:10.1038/s41416-021-01469-9
367. Kindler HL, Yoo HK, Hettle R, et al. Patient-centered outcomes in the POLO study of active maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *Cancer*. 2023;129(9):1411-1418. doi:10.1002/cncr.34610
368. Wong W, Raufi AG, Safyan RA, Bates SE, Manji GA. BRCA mutations in pancreas cancer: spectrum, current management, challenges and future prospects. *Cancer Manag Res*. 2020;12:2731-2742. doi:10.2147/cmar.s211151
369. Li N, Zheng H, Huang Y, Zheng B, Cai H, Liu M. Cost-effectiveness analysis of olaparib maintenance treatment for germline BRCA-mutated metastatic pancreatic cancer. *Front Pharmacol*. 2021;12:632818. doi:10.3389/fphar.2021.632818
370. Mirzayeh FF, Levine M, Xie F, Blackhouse G, Tarride JE. Olaparib versus placebo in maintenance treatment of germline BRCA-mutated metastatic pancreatic cancer: a cost-utility analysis from the Canadian public payer's perspective. *Curr Oncol*. 2023;30(5):4688-4699. doi:10.3390/curroncol30050354
371. Wu B, Shi L. Cost-effectiveness of maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *J Natl Compr Canc Netw*. 2020;18(11):1528-1536. doi:10.6004/jnccn.2020.7587
372. Nishikawa G, Booth C, Prasad V. Olaparib for BRCA mutant pancreas cancer: should the POLO trial change clinical practice? *Cancer*. 2020;126(18):4087-4088. doi:10.1002/cncr.32979
373. Chen EY, Joshi SK, Tran A, Prasad V. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. *JAMA Intern Med*. 2019;179(5):642-647. doi:10.1001/jamainternmed.2018.8351
374. Makris EA, MacBarb R, Harvey DJ, Poultsides GA. Surrogate end points for overall survival in metastatic, locally advanced, or unresectable pancreatic cancer: a systematic review and meta-analysis of 24 randomized controlled trials. *Ann Surg Oncol*. 2017;24(8):2371-2378. doi:10.1245/s10434-017-5826-2
375. Devalingam M, Shroff RT, Carneiro BA, et al. Preliminary results from the randomized phase 2 study (1801 part 3B) of elraglusib in combination with gemcitabine/nab-paclitaxel (GnP) versus GnP alone in patients (pts) with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC) [abstract]. *J Clin Oncol*. 2025;43(16 suppl):4006. doi:10.1200/jco.2025.43.16_suppl.4006
376. Hingorani SR, Zheng L, Bullock AJ, et al. HALO 202: randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. *J Clin Oncol*. 2018;36(4):359-366. doi:10.1200/jco.2017.74.9564
377. Van Cutsem E, Tempero MA, Sigal D, et al. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. *J Clin Oncol*. 2020;38(27):3185-3194. doi:10.1200/jco.20.00590
378. Xie CK, Liao CY, Lin HY, et al. Sulindac (K-80003) with nab-paclitaxel and gemcitabine overcomes drug-resistant pancreatic cancer. *Mol Cancer*. 2024;23(1):215. doi:10.1186/s12943-024-02128-2
379. Karasic TB, O'Hara MH, Loaiza-Bonilla A, et al. Effect of gemcitabine and nab-paclitaxel with or without hydroxychloroquine on patients with advanced pancreatic cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5(7):993-998. doi:10.1001/jamaoncol.2019.0684
380. Karasinska JM, Topham JT, Kalloger SE, et al. Altered gene expression along the glycolysis-cholesterol synthesis axis is associated with outcome in pancreatic cancer. *Clin Cancer Res*. 2020;26(1):135-146. doi:10.1158/1078-0432.ccr-19-1543
381. Stuart SD, Schauble A, Gupta S, et al. A strategically designed small molecule attacks alpha-ketoglutarate dehydrogenase in tumor cells through a redox process. *Cancer Metab*. 2014;2(1):4. doi:10.1186/2049-3002-2-4

How to cite this article: Mannucci A, Goel A. Advances in pancreatic cancer early diagnosis, prevention, and treatment: The past, the present, and the future. *CA Cancer J Clin*. 2026; e70035. doi:10.3322/caac.70035