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Review Article

From Germline Susceptibility to Somatic Evolution: The Genetic Trajectory of Pancreatic Ductal Adenocarcinoma and Implications for Screening and Early Detection

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is often diagnosed too late for curative resection, and durable responses to systemic therapy remain uncommon. However, research on inherited susceptibility, precursor lesions, and somatic evolution has often developed separately, obscuring a unified view of disease progression. Here, we integrate these areas within a germline-to-somatic framework, including limited Asian-population evidence, and examine implications for inherited-risk assessment, high-risk surveillance, early detection, and treatment selection. Pathogenic germline variants occur in a minority of patients, affecting pathways involved in homologous recombination repair, DNA damage responses, cell-cycle control, mismatch repair, and pancreatitis susceptibility. Common susceptibility alleles exert smaller individual effects and may refine multifactorial risk models. Biallelic inactivation of *BRCA1*, *BRCA2*, or *PALB2* can produce homologous recombination deficiency and extensive structural variation, potentially increasing platinum sensitivity. Randomized evidence supports maintenance olaparib for metastatic PDAC with pathogenic germline *BRCA1* or *BRCA2* variants after at least 16 weeks of platinum-based chemotherapy without disease progression. Tumor initiation proceeds through several precursor routes. Pancreatic intraepithelial neoplasia commonly acquires early *KRAS* mutations, while additional tumor-suppressor and chromosomal alterations accompany progression. Acinar-to-ductal metaplasia creates a plastic cell state that can support *KRAS*-driven neoplasia after injury. Intraductal papillary mucinous neoplasms may follow branching or multiclonal trajectories involving *KRAS*, *GNAS*, and *RNF43*. After invasion, gradual driver accumulation coexists with punctuated genome remodeling. Copy-number evolution, transcriptional plasticity, and subclonal selection continue during metastatic dissemination and treatment. Clinical translation includes germline testing for all patients with PDAC and imaging-based surveillance for individuals with defined genetic or familial risk. Tumor profiling informs treatment selection in actionable subgroups, whereas blood-based early detection and longitudinal molecular monitoring remain investigational. Overall, PDAC follows a branching genetic trajectory that informs risk stratification and molecular treatment selection. Further progress requires ancestry-diverse paired germline-tumor sequencing, multiregion and single-cell analyses, and prospective validation of clinically relevant biomarkers.

Keywords: Pancreatic ductal adenocarcinoma; Germline variants; Somatic evolution; Precursor lesions; High-risk surveillance; Early detection; Tumor profiling.
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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is among the solid malignancies with the poorest prognosis. According to Global Cancer Observatory 2020 estimates, pancreatic cancer ranked 12th in global cancer incidence but seventh in cancer mortality. Projections based on cancer incidence and mortality trends in the United States suggest that pancreatic cancer may become the country's second leading cause of cancer-related death by 2040.[1,2]

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Late diagnosis and limited therapeutic benefit contribute substantially to this poor outcome.[3] At diagnosis, approximately 30%–35% of patients have locally advanced disease and about 50% have metastatic disease, leaving most patients ineligible for curative resection.[4] PDAC is also characterized by a dense desmoplastic stroma, hypoxia, metabolic reprogramming, and an immunosuppressive microenvironment, all of which contribute to treatment resistance.[5]

PDAC risk reflects both inherited susceptibility and nongenetic factors. Modifiable risk factors include cigarette smoking, heavy alcohol intake, and obesity. Diabetes and chronic pancreatitis are also associated with increased PDAC risk.[3] The foundational understanding of PDAC genetics came largely from studies of its canonical driver genes. Activation of *KRAS* and inactivation of tumor suppressors such as *TP53*, *CDKN2A*, and *SMAD4* constitute the principal molecular features of the disease. Comprehensive genomic analyses subsequently showed that PDAC involves alterations across multiple core signaling pathways and diverse patterns of structural variation, rather than only a small set of recurrent mutations.[6,7]

Advances in multiregion and whole-genome sequencing have provided a clearer view of PDAC evolution. Phylogenetic analysis of matched primary tumors and metastases showed that metastatic clones arose from subclones already present in the primary tumor and had acquired additional progressor mutations, supporting gradual clonal evolution in the cases examined.[8] Whole-genome analysis subsequently showed that many copy-number alterations can arise in rapid bursts associated with chromothripsis, polyploidization, and related mitotic errors, consistent with punctuated genome remodeling.[9] Together, these findings indicate that gradual clonal evolution and punctuated genomic change can both contribute to PDAC progression.[10]

Germline genetic background provides an important context for this evolutionary process. Multigene germline testing has identified pathogenic variants in cancer-predisposition genes among patients with apparently sporadic PDAC, including many without a family history suggestive of inherited pancreatic cancer.[11-13] These susceptibility genes span homologous recombination repair, DNA damage responses, cell-cycle control, mismatch repair, and pancreatitis-related pathways, indicating that inherited predisposition can arise through biologically distinct mechanisms.[14,15] The extent to which specific germline backgrounds shape the subsequent selection of somatic clones remains incompletely defined and will require larger studies integrating paired germline and tumor genomes.

PubMed and the Web of Science Core Collection were searched from database inception to September 17, 2026. Search terms combined "pancreatic ductal adenocarcinoma" or "pancreatic cancer" with terms related to inherited susceptibility, precursor lesions, somatic and clonal evolution, metastasis, screening, surveillance, early detection, molecular profiling, and treatment. English-language original studies, systematic reviews, meta-analyses, consensus statements, and clinical guidelines were considered. Priority was given to studies that defined inherited risk, characterized precursor or clonal evolution, provided paired germline–tumor, multiregion, single-cell, or spatial data, or evaluated surveillance, biomarkers, and genomically informed treatment. Foundational studies were retained when they established widely used biological or clinical frameworks, while recent evidence was prioritized for clinical recommendations. Reference lists of relevant articles were also screened to identify additional studies. Study selection was based on relevance and evidentiary contribution to the review; no quantitative synthesis was undertaken.

PDAC evolution proceeds through precursor lesions, clonal expansion, structural variation, and genome remodeling, with inherited susceptibility providing an additional context in a subset of patients. It continues during metastatic dissemination and under treatment pressure. Here, we integrate evidence on germline susceptibility, precursor lesions, and somatic and metastatic evolution, including available data from Asian populations, and examine how this framework, illustrated in Figure 1, informs inherited-risk assessment, high-risk surveillance, early detection, and treatment selection in PDAC.

Germline genetic background in PDAC

The germline genetic architecture of PDAC includes rare pathogenic variants, common low-effect risk alleles, and genetic factors associated with pancreatitis. Rare pathogenic variants can substantially increase cancer risk and affect DNA repair, cell-cycle control, or tissue homeostasis. Common variants collectively contribute to polygenic risk, whereas pancreatitis-related variants are more closely associated with chronic inflammation and tissue injury. The clinical relevance of these inherited factors varies across genes and syndromes, and direct evidence linking individual germline backgrounds to subsequent somatic evolution remains uneven, as summarized in Table 1.[7,12,13,16-35]

Rare pathogenic variants and familial aggregation

Familial aggregation is well documented in PDAC. Pathogenic germline variants are also found in patients without a typical family history. In the Ontario Pancreas Cancer Study, weighted analysis of 290 participants from a population-based cohort of 708 patients estimated that 3.8% carried pathogenic variants in 13 cancer-predisposition genes.[11] Among 854 patients with surgically resected PDAC at Johns Hopkins, 33 patients (3.9%) carried deleterious germline variants, and only three reported a family history of pancreatic cancer.[12] In a Mayo Clinic case–control study of 3,030 patients with pancreatic cancer, 5.5% carried variants in six genes associated with pancreatic cancer risk; the prevalence was 5.2% among patients without a family history of pancreatic cancer.[13]

BRCA2 and *ATM* were among the most frequently identified susceptibility genes in large PDAC cohorts. In the Johns Hopkins cohort, 12 of the 33 carriers had *BRCA2* variants and 10 had *ATM* variants.[12] Across case–control studies, germline variants in *BRCA1*, *BRCA2*, and *ATM* were consistently associated with pancreatic cancer risk.[13,16,17] Additional associations with *CDKN2A*, *TP53*, and *MLH1* were identified in the Mayo Clinic cohort.[13] Germline truncating variants identified by exome sequencing in familial pancreatic cancer also established *PALB2* as a pancreatic cancer susceptibility gene.[18]

Additional inherited risk contexts include *CDKN2A*, *STK11*, mismatch-repair genes, and *TP53*. Germline *CDKN2A* loss-of-function variants occur in families with co-segregation of melanoma and pancreatic cancer.[19] Germline *STK11* variants

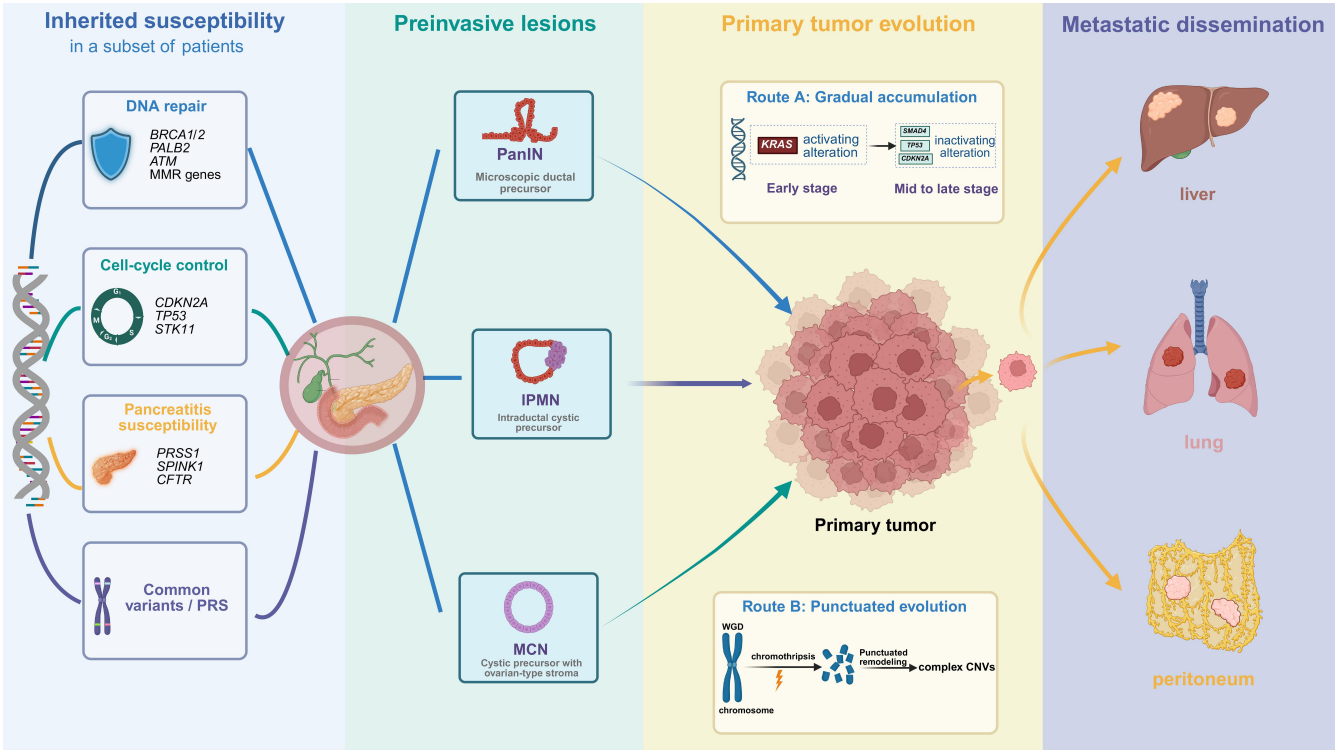


Fig. 1. Representative routes of PDAC evolution and inherited susceptibility. The schematic shows preinvasive lesions, primary tumor evolution, and metastatic dissemination in pancreatic ductal adenocarcinoma (PDAC), with germline susceptibility presented as a modifying context relevant to a subset of patients. Germline factors include rare variants affecting DNA repair, cell-cycle control, or pancreatitis susceptibility and common variants represented by polygenic risk scores (PRS). Pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) represent the principal preinvasive lesion categories. Progression involves somatic alterations that vary across routes. Primary tumors may evolve through gradual driver accumulation or punctuated genomic remodeling, including chromothripsis, whole-genome duplication (WGD), and complex copy-number variations (CNVs). Brown gene labels indicate activating alterations, green labels indicate inactivating alterations, and arrows indicate proposed progression. Line and arrow colors are used only for visual distinction. Germline–somatic effects are best established for *BRCA1*, *BRCA2*, and *PALB2*. Links involving other susceptibility genes are less well characterized. The routes shown are representative. This figure was created by the authors using BioRender. G1, gap 1 phase; G2, gap 2 phase; M, mitosis; MMR, mismatch repair; S, synthesis phase.

cause Peutz–Jeghers syndrome, which is associated with increased risks of gastrointestinal and extraintestinal cancers.[20] Carriers of mismatch-repair gene variants associated with Lynch syndrome also have an increased risk of pancreatic cancer.[21] Although uncommon, germline *TP53* variants have also been associated with pancreatic cancer risk.[13] These genes define distinct inherited risk contexts. Their effects on subsequent somatic evolution remain incompletely characterized.

Studies in Chinese populations provide additional evidence relevant to ancestry-specific risk assessment. In a study of 1,009 Chinese patients with PDAC, pathogenic germline variants were detected in 63 patients (6.2%); *BRCA2* and *PALB2* were significantly associated with pancreatic cancer risk, and variants in homologous-recombination DNA-damage-repair genes were detected in 3.4% of patients.[22] A 2025 study of 1,123 Chinese patients with pancreatic adenocarcinoma identified both shared and distinct germline variant patterns compared with Western cohorts. Established susceptibility genes, including *BRCA1*, *BRCA2*, *ATM*, *CDKN2A*, and *CHEK2*, were less frequent in the Chinese cohort than in Western cohorts, whereas variants in *CFTR*, *RAD51D*, *FANCA*, *ERCC2*, and *GNAS* were observed predominantly in Asian patients. Loss-of-heterozygosity analysis, multi-omics profiling, and functional experiments provided additional support for *CFTR* as a candidate susceptibility gene.[23] These findings support the use of ancestry-matched controls and functional evidence when interpreting population-specific variants.[22,23]

DNA repair defects and somatic genome evolution

BRCA1, *BRCA2*, and *PALB2* participate in homologous recombination repair of DNA double-strand breaks. A germline variant usually affects one allele first; subsequent loss or inactivation of the remaining allele in the tumor may allow the repair defect to manifest as genomic instability. In a paired germline and tumor analysis of 289 patients with resected PDAC, somatic second hits were identified in 12 of 27 evaluable carriers of pathogenic germline variants across several cancer-susceptibility genes.[24] In a larger genomic profiling study, 79.2% of pancreatic cancers with predicted germline *BRCA1* mutations and 79.7% of those with predicted germline *BRCA2* mutations were classified as biallelic.[36]

Whole-genome sequencing has further linked structural-variation patterns to DNA-repair deficiency. In 100 PDACs, unstable tumors showed extensive structural variation and were associated

Table 1. Germline susceptibility genes in PDAC: genetic and clinical features

Gene or genetic factor	Hereditary context	Principal function	Association with PDAC	Clinical relevance	Representative references
BRCA2, BRCA1, PALB2	Hereditary breast and ovarian cancer syndrome; familial pancreatic cancer	Homologous recombination repair	Strong, statistically significant PDAC risk associations for *BRCA1* and *BRCA2*; established PDAC susceptibility for *PALB2*; biallelic loss may produce HRD and structural instability	Germline testing and counseling; platinum sensitivity; olaparib maintenance for eligible metastatic germline *BRCA1/2* PDAC	[7,13,16-18,24,33]
ATM	Cancer susceptibility (heterozygous); ataxia-telangiectasia (biallelic)	DNA damage sensing and cell-cycle checkpoint control	Strong, statistically significant PDAC risk association in case–control studies	Germline testing and hereditary risk assessment	[12,13,17]
CDKN2A	Familial atypical multiple mole melanoma syndrome	G1/S cell-cycle control	Melanoma-pancreatic cancer kindreds; increased PDAC risk	Genetic counseling and high-risk surveillance	[13,19,32]
STK11	Peutz-Jeghers syndrome	Cell polarity, energy sensing, and growth control	Peutz-Jeghers syndrome with increased pancreatic cancer risk	Genetic counseling and high-risk surveillance	[20,32]
TP53	Li-Fraumeni syndrome	DNA damage response, cell-cycle arrest, and apoptosis	Uncommon PDAC susceptibility gene	Li-Fraumeni syndrome assessment and counseling	[13]
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	DNA mismatch repair	Lynch syndrome-associated pancreatic cancer risk; dMMR/MSI-H phenotype	Germline and tumor MMR/MSI assessment; PD-1 blockade for MSI-H/dMMR disease	[21,34,35]
PRSS1, CPA1	Hereditary or familial pancreatitis	Trypsin control; digestive-enzyme misfolding and endoplasmic-reticulum stress	Marked PDAC risk in hereditary pancreatitis; *CPA1*-driven inflammation and acinar plasticity cooperate with oncogenic *Kras*	*PRSS1*: established pancreatitis-associated risk; *CPA1*: mechanistic evidence	[29,30]
SPINK1, CFTR	Chronic or recurrent pancreatitis; cystic fibrosis-related disease	Trypsin inhibition; ductal ion and fluid transport	Pancreatitis susceptibility; PDAC-associated signals in Chinese cohorts, including functional support for selected *CFTR* variants	Interpretation integrates pancreatitis phenotype, ancestry, and family history	[22,23,31]
GWAS loci and PRS	Aggregate effects of common small-effect variants	Pancreatic development, telomere biology, digestive-enzyme, and signaling pathways	Risk loci include *NR5A2*, *CLPTM1L-TERT*, *PDX1*, *ZNRF3*, and *BCAR1/CTRB1/CTRB2*; PRS aggregates small-effect variants	Investigational for multifactorial risk stratification; prospective ancestry-specific validation required before routine screening	[25-28]

dMMR, deficient mismatch repair; GWAS, genome-wide association study; G1/S, gap 1/synthesis phase transition; HRD, homologous recombination deficiency; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PRS, polygenic risk score.

with inactivation of *BRCA1*, *BRCA2*, or *PALB2* and features of defective DNA repair.[7] When a germline variant is accompanied by a somatic second hit, the resulting repair defect may lead to widespread DNA breakage, chromosomal rearrangements, and copy-number alterations.[7,24] This phenotype is not present in all germline variant carriers.[24]

Gene-level alterations do not capture the full spectrum of homologous recombination deficiency (HRD). A systematic review and meta-analysis showed that analyses limited to germline or somatic mutations in core HRD genes identify only a proportion of affected patients. Incorporating genomic scars, mutational signatures, and whole-genome or whole-exome sequencing data identifies additional patients with HRD features.[37] Mutational-signature models such as HRDetect suggest that tumors with features of *BRCA1/2* deficiency may be identified even in the absence of a clear germline *BRCA1/2* variant. HRDetect has undergone initial application in a whole-genome pancreatic cancer cohort, although its tissue-specific parameters and predictive value for treatment response require further validation.[38]

Common variants, polygenic risk scores, and population risk stratification

In addition to rare pathogenic variants, PDAC risk is influenced by numerous common variants with small individual effects. Early genome-wide association studies identified pancreatic cancer susceptibility loci at 13q22.1, 1q32.1, and 5p15.33. Subsequent studies identified additional risk signals near *PDX1, ZNRF3,* and *BCAR1/CTRB1/CTRB2*, while a larger meta-analysis identified several further susceptibility regions.[25-27]

Because their individual effects are modest, common variants can be combined into a polygenic risk score (PRS). In the UK Biobank, the PRS alone achieved an area under the receiver operating characteristic curve (AUC) of 0.605, whereas a clinical model incorporating age, diabetes-related measures, waist circumference, and a first-degree family history of digestive cancer achieved an AUC of 0.791; adding the PRS increased the AUC to 0.83. Together, these data support further evaluation of PRS in multifactorial risk models, with prospective, ancestry-specific validation required before its use in routine pancreatic cancer screening.[28]

Population differences also affect the interpretation of genetic risk. Risk genes and loci identified in Western cohorts may not be fully applicable to Chinese patients. Findings involving *BRCA2*, *PALB2*, *SPINK1*, *CFTR*, and selected variants of uncertain significance in Chinese cohorts therefore require interpretation alongside local control populations, functional studies, and longitudinal data.[22,23]

Pancreatitis-related genetic background and tissue injury

Hereditary pancreatitis provides evidence linking long-standing pancreatic inflammation to pancreatic cancer risk. In a cohort of 246 patients with hereditary pancreatitis, eight developed pancreatic adenocarcinoma, corresponding to a standardized incidence ratio of 53. The cumulative risk approached 40% by age 70, and cancers generally arose decades after pancreatitis onset.[29] This setting combines early disease onset, recurrent inflammation and prolonged tissue injury.

Experimental models support this relationship. The adult mouse pancreas is relatively resistant to oncogenic *Kras* alone, whereas chronic pancreatitis promotes the formation of *Kras*-driven pancreatic intraepithelial neoplasia (PanIN) and PDAC, indicating that tissue injury can cooperate with an early oncogenic event during tumor initiation.[39] In a hereditary chronic pancreatitis model, chronic inflammation and acinar-cell plasticity associated with the *CPA1* p.N256K variant cooperated with *Kras* p.G12D to promote early pancreatic carcinogenesis.[30]

SPINK1 and *CFTR* represent pancreatitis-related susceptibility genes. *SPINK1* variants are associated with chronic pancreatitis.[31] In a germline analysis of 1,009 Chinese patients with PDAC, *BRCA2* and *PALB2* variants were associated with PDAC risk, and deleterious *SPINK1* and *CFTR* variants were more frequent among patients with PDAC than in the East Asian subset of the Exome Aggregation Consortium.[22] These findings should be interpreted in the context of the reference population and the distinct contributions of pancreatitis susceptibility and cancer risk.

In a subsequent two-center case–control study in China, 88 patients who developed PDAC at least 2 years after chronic pancreatitis were compared with 410 age- and sex-matched patients with chronic pancreatitis without PDAC. Deleterious variants in homologous recombination pathway genes were detected in 13.6% and 2.2% of the two groups, respectively, and variants in *ATM*, *PALB2,* and *FANCC* were more frequent among patients who developed PDAC.[40] These findings link variants in several cancer-predisposition genes to PDAC development in the setting of chronic pancreatitis.

Associations were not uniform across pancreatitis-related genes. Deleterious *CFTR* variants occurred in 5.7% of patients with PDAC and 0.2% of chronic pancreatitis controls, whereas *SPINK1* variants were not enriched and the association between *PRSS1* variants and PDAC did not reach statistical significance.[40] The contribution of these variants therefore depends on the specific gene and variant, the clinical course of pancreatitis and ancestry.

Precursor lesions and early somatic evolution

PDAC can arise through several precursor states. PanIN and intraductal papillary mucinous neoplasm (IPMN) are well-defined pathological precursor lesions, whereas acinar-to-ductal metaplasia (ADM) is a reprogramming process in which acinar cells acquire a duct-like state following inflammation or tissue injury. All three are associated with PDAC development, but they differ in cellular origin, tissue context, and selective pressure. Activation of the KRAS–mitogen-activated protein kinase pathway is common in early lesions, whereas subsequent progression is associated with tumor-suppressor inactivation, chromosomal instability, inflammatory injury, and changes in the local microenvironment. Table 2 compares the pathological, molecular, and evolutionary features of the principal precursor lesions,[39,41-51] while Figure 2 illustrates how representative precursor routes converge on invasive PDAC.

PanIN: A common lesion with a progression bottleneck

PanIN is a common microscopic precursor of PDAC. The current classification groups PanIN-1A, PanIN-1B, and PanIN-2 as low-grade lesions and PanIN-3 as high-grade PanIN.[41,52] PanINs are more prevalent in the adult pancreas than previously recognized. Analyses of donor pancreata and three-dimensional genomic

Table 2. Pathological, molecular, and evolutionary features of PDAC precursor lesions

Lesion or state	Pathology and cell of origin	Main molecular features	Pattern of clonal evolution	Clinical relevance	Representative references
ADM	Injury-induced acinar-to-ductal plasticity	Pancreatitis cooperates with oncogenic *Kras*; *Sox9*, *TERT*-high states, and inflammatory memory promote persistence	Usually reversible; sustained inflammation and oncogenic signaling can stabilize precursor states	Mechanistic link between pancreatitis, acinar cells, and PanIN initiation	[39,45-47]
PanIN	Common microscopic ductal precursor graded by atypia	*KRAS* hotspot mutations; heterogeneous drivers and clonal architecture	Independent lesions, polyclonal lesions, and ductal spread; strong selection before invasion	Frequent precursor with low progression probability	[41-44]
IPMN	Macroscopic cystic intraductal lesion classified by duct involvement, subtype, and dysplasia	Early *KRAS/GNAS* alterations; later *TP53/CDKN2A/SMAD4/TGFBR2* alterations	Multiclonal origins with linear, branching, or independent progression	Imaging-based surveillance and risk-adapted management	[48-51]
MCN	Cystic precursor with ovarian-type stroma	Shared precursor alterations with additional changes during invasion	Progression of existing clones during invasion	Imaging and pathological risk stratification	[49]

ADM, acinar-to-ductal metaplasia; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma.

mapping have shown that these lesions can be widespread and frequently harbor *KRAS* hotspot mutations.[42,43] Some spatially separated PanINs share ancestral clones, indicating that precursor cells can spread through the pancreatic ductal system, whereas others arise independently.[43,44]

KRAS activation is an early and common event, but it is insufficient for progression. In 169 PanINs, *KRAS* mutations were detected across lesion grades, and the proportion of mutant *KRAS* alleles increased with lesion grade. *CDKN2A*, *GNAS,* and *BRAF* alterations occurred in subsets.[53] Copy-number alterations were uncommon in low- and intermediate-grade lesions. Isolated high-grade PanINs showed additional alterations, particularly in *CDKN2A* and *RNF43*, whereas *TP53* alterations were infrequent and nonsynonymous *SMAD4* alterations were not detected in the lesions examined.[54,55] These findings support the concept of a progression bottleneck: only a minority of *KRAS*-mutant lesions acquire the additional genetic changes associated with invasive PDAC.

ADM and the acinar cell-of-origin pathway

ADM is a reversible response to pancreatic injury. During ADM, acinar cells acquire duct-like morphological and transcriptional features; as the injury resolves, acinar characteristics can be restored. This cellular plasticity affects how acinar cells respond to oncogenic *Kras*. In adult mice, oncogenic *Kras* p.G12V alone was insufficient to induce neoplasia, whereas chronic pancreatitis enabled the formation of PanIN and PDAC.[39] Acinar-cell lineage tracing further showed that oncogenic *Kras* maintains the injury-induced duct-like state and that *Sox9* is required for progression to PanIN.[45]

Some inherited pancreatitis-associated variants can sustain this permissive state. Mice carrying the chronic pancreatitis-associated *Cpa1* p.N256K variant develop endoplasmic reticulum stress, chronic inflammation, and diffuse ADM, but only limited PanIN formation. When combined with *Kras* p.G12D, the variant increased both ADM and PanIN formation; at 10 weeks, PDAC was present in 6 of 10 mice carrying both alterations compared with 1 of 10 mice expressing *Kras* p.G12D alone.[30]

The response of acinar cells also varies with inherited background and cellular state. The PDAC risk-increasing T allele of rs3790844 is associated with lower *NR5A2* expression, and *Nr5a2* haploinsufficiency produces a pro-inflammatory acinar state and delays regeneration after injury.[56] A *TERT*-high acinar population shows enhanced clonal expansion after injury and can generate PanIN following *Kras* p.G12D activation.[46] In addition, previous pancreatitis can leave persistent transcriptional and chromatin memory that increases tumor formation when *Kras* is activated after recovery.[47]

Lineage-tracing studies further indicate that acinar-derived PDAC depends on both genotype and tissue-injury context. In the proCPA1-positive acinar lineage, *Kras* p.G12D alone induced low-grade PanIN at low frequency, whereas its combination with *Trp53* loss produced invasive and metastatic PDAC. Pancreatic

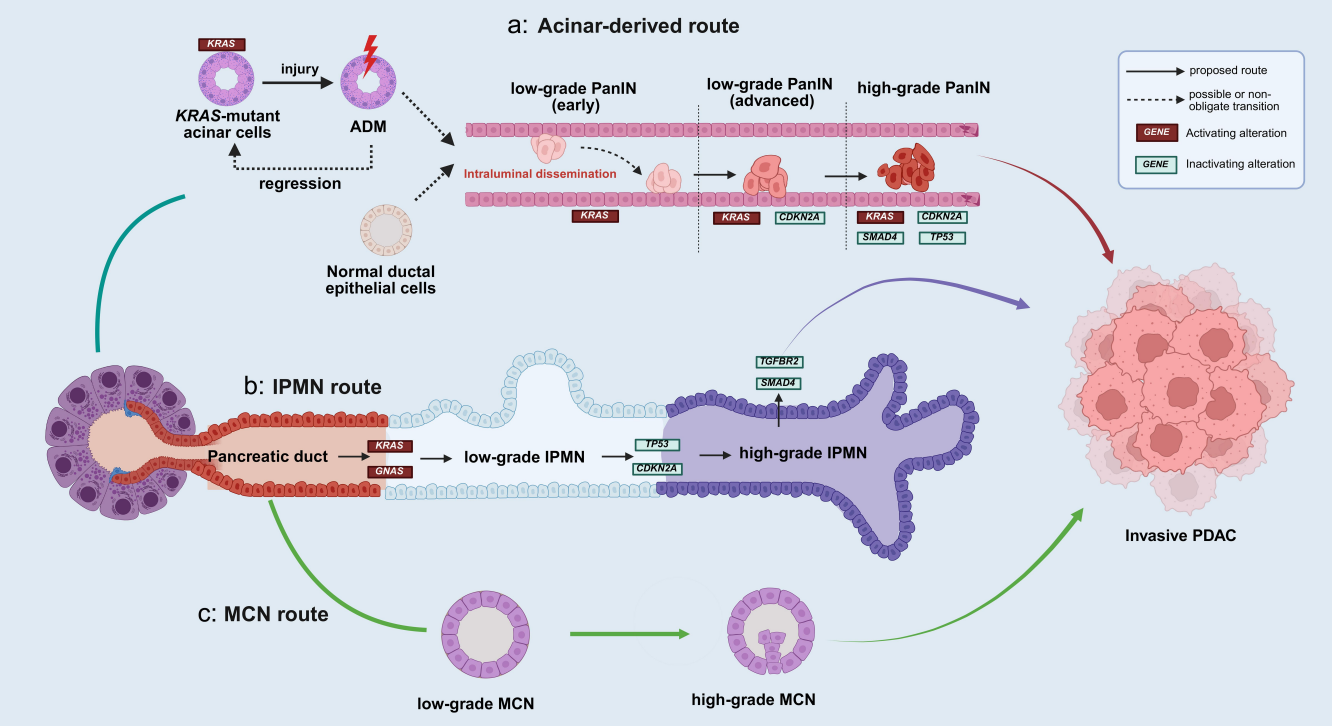


Fig. 2. Convergent precursor routes to invasive PDAC. The schematic summarizes representative evolutionary routes from acinar, ductal, and cystic precursor states to invasive pancreatic ductal adenocarcinoma (PDAC). Panels (a), (b), and (c) show the acinar-derived, intraductal papillary mucinous neoplasm, and mucinous cystic neoplasm routes, respectively. In the acinar-derived route, oncogenic *KRAS* activation and tissue injury may promote acinar-to-ductal metaplasia (ADM), followed by progression toward low-grade and high-grade pancreatic intraepithelial neoplasia (PanIN). ADM may also regress to a *KRAS*-mutant acinar cell state. The ductal-derived route is shown as a possible transition from normal ductal epithelial cells to PanIN. The cystic routes include progression from low-grade to high-grade intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN). Brown gene labels indicate activating alterations, whereas green labels indicate inactivating alterations. Solid arrows indicate proposed evolutionary routes; dashed arrows indicate possible or non-obligate transitions, including regression. Line and arrow colors are used only for visual distinction. Individual lesions may follow different evolutionary sequences. This figure was created by the authors using BioRender.

injury further increased tumorigenesis in some genetic contexts.[57] Together, these findings place ADM at the intersection of tissue injury, inherited pancreatitis susceptibility, and somatic *KRAS* activation, while showing that progression depends on the cellular and genetic context.

Branching evolution of IPMNs and cystic precursor lesions

IPMNs constitute a distinct cystic precursor route to PDAC. They arise in the main pancreatic duct or its branches, and activating *KRAS* and *GNAS* alterations are common early events. In a subset of IPMN-associated invasive carcinomas, these driver mutations are retained, supporting molecular continuity between the cystic lesion and the invasive tumor.[48]

Genomic studies indicate that progression involves both shared early alterations and later clonal divergence. *KRAS* and *GNAS* mutations can be shared between non-invasive and invasive components, whereas *SMAD4* and *TGFBR2* alterations are often restricted to invasive carcinoma. Multiregion sequencing has also shown that IPMNs may arise from multiple independent clones with distinct mutations, followed by clonal selection during progression. Mucinous cystic neoplasms represent another cystic precursor, although their evolutionary trajectories remain less well characterized.[49,50]

Spatial transcriptomic studies have begun to resolve biological heterogeneity within IPMNs. In low-grade gastric-type IPMNs, high *NKX6-2* expression is associated with a gastric pit–isthmus program and indolent biological potential, while other spatially resolved studies have identified markers and signaling programs linked to dysplasia grade and malignant transformation.[58,59] In a prospective cohort of 2,549 IPMNs without high-risk stigmata, 116 pancreatic carcinomas were diagnosed during a median follow-up of 7.1 years, including 56 IPMN-derived carcinomas and 60 concomitant PDACs. Baseline cyst size and growth during the first two years were associated with subsequent carcinoma risk.[51]

Somatic genomic evolution of primary PDAC

The genome of invasive PDAC is shaped by oncogenic driver events, tumor-suppressor inactivation, structural variation, copy-number alterations, and clonal selection, as summarized in Table 3.[6-9,24,60-70] The resulting genetic heterogeneity can also be accompanied by transitions in transcriptional state. The influence of germline variation on the somatic evolutionary trajectory of PDAC is likely to be gene-specific. Direct evidence remains

Table 3. Major genomic events in primary PDAC and their evolutionary significance

Genomic or transcriptional feature	Representative alterations	Main characteristics	Evolutionary significance	Potential clinical relevance	Representative references
Core driver genes	*KRAS, TP53, CDKN2A, SMAD4*	MAPK signaling, G1/S control, DNA damage response, and TGF-β signaling	Recurrent invasive-PDAC framework with pathway-level convergence	Defines the common genomic background	[6,61]
Low-frequency drivers	*ARID1A, ARID2, KDM6A, MLL3, TGFBR2, SF3B1, ATM, RNF43, GNAS, RREB1, PBRM1*	Low-frequency alterations converge on chromatin, Wnt/TGF-β, RNA-splicing, and DNA-repair pathways	Gene-level heterogeneity with pathway-level convergence	Molecular classification and selected targets in the context of *KRAS* status, histology, and co-alterations	[60,61]
Structural variation and HRD	Biallelic *BRCA1/2/PALB2* inactivation; rearrangements and copy-number change	WGS patterns: stable, locally rearranged, scattered, and unstable; unstable tumors often show HRD	Repair status shapes genome-wide structural evolution	Integrated assessment of germline variants, tumor second hits, genomic HRD, and platinum response	[7,24]
Punctuated genome remodeling	Chromothripsis, polyploidization, and complex copy-number rearrangements	Many CNVs and driver changes can arise within few cell divisions	Punctuated evolution in a subset of PDAC	Rapid clonal and gene-dosage shifts	[9]
Transcriptional continuum	Classical and basal-like states; *GATA6* and mutant *KRAS* copy-number changes	Classical and basal-like cells coexist along a transcriptional continuum	Basal-like states can emerge during progression; subtype is plastic	Tumor-purity-aware classification with potential prognostic and therapeutic value	[62-65]
KRAS allele and dosage	*KRAS* p.G12D, p.G12V, and p.G12R; mutant-allele gain	*KRAS* allele and dosage associate with stage, metastatic pattern, transcription, and survival	Allele- and dosage-dependent progression	Potential prognostic stratification	[66,67]
Alternative drivers in *KRAS*-wild-type PDAC	*BRAF* alterations; *FGFR2, ALK, RET, and NRG1* fusions; *NTRK* amplification	Minority of PDAC enriched for alternative MAPK drivers and actionable fusions	*KRAS*-independent oncogenic routes	Combined DNA/RNA profiling for fusion detection and therapy selection	[68]
Single-cell CNV architecture	Clonal driver SNVs; ongoing CNVs; variable second-hit routes in germline *BRCA2* tumors	Driver SNVs are mainly truncal; CNVs generate spatial heterogeneity	Copy-number evolution and subclonal selection continue after driver fixation	Higher truncal density was associated with shorter overall survival	[69,70]

CNV, copy-number variation; G1/S, gap 1/synthesis phase transition; HRD, homologous recombination deficiency; MAPK, mitogen-activated protein kinase; PDAC, pancreatic ductal adenocarcinoma; SNV, single-nucleotide variant; TGF-β, transforming growth factor beta; WGS, whole-genome sequencing.

largely confined to homologous recombination repair genes, whereas the downstream somatic consequences of most other susceptibility genes remain poorly defined.

Canonical driver genes and core pathways

Although the somatic landscape of PDAC varies among patients, alterations converge on a limited set of core genes and pathways. Early genomic studies implicated *KRAS* and transforming growth factor beta (TGF-β) signaling, WNT/NOTCH, cell-cycle control, DNA-damage responses, and chromatin regulation.[6] Subsequent analyses established *KRAS*, *TP53*, *CDKN2A* and *SMAD4* as central drivers and identified additional recurrent alterations in

these pathways.[60,61] This framework becomes progressively more complex during tumor development: *KRAS* activation is common in precursor lesions and remains a dominant feature of invasive PDAC.[7,53] Later tumor-suppressor inactivation, copy-number changes and structural variation further remodel the genome.[7,61]

Structural variation and punctuated evolution

Structural variation contributes to PDAC evolution through both gradual accumulation and punctuated chromosomal remodeling. Whole-genome studies identified a subset of tumors with extensive structural variation, often accompanied by inactivation of *BRCA1*, *BRCA2*, or *PALB2* and signatures of defective DNA repair.[7] Other tumors showed chromothripsis, polyploidization, and related rearrangements that could alter several driver genes during a concentrated episode of genome remodeling, supporting punctuated evolution.[9] These findings extend the conventional stepwise model and show that PDAC genomes can be reshaped either progressively or through episodic chromosomal events.

Molecular subtypes and transcriptional state transitions

Bulk transcriptomic studies initially proposed several expression classes in PDAC.[62] Across these systems, classical/progenitor and basal-like/squamous states have emerged as the most reproducible tumor-intrinsic phenotypes after accounting for stromal and normal-tissue signals.[61,63,64] Purified-tumor and single-cell analyses place these states along an expression continuum shaped by tumor-cell composition and plasticity. Alterations involving *GATA6* and mutant *KRAS* are associated with these states. Longitudinal sampling suggests that basal-like features can emerge during progression through expansion of minor clones.[65] Transcriptional subtype therefore reflects both the state sampled and ongoing clonal evolution.

KRAS status, dosage, and alternative drivers

KRAS mutations occur in most PDACs, but their effects depend on the mutant allele and its dosage. *KRAS* p.G12R is associated with earlier-stage disease, fewer distant recurrences and weaker *KRAS* and epithelial–mesenchymal transition programs than p.G12D, whereas increased mutant *KRAS* dosage is associated with advanced disease and poorer overall survival.[66,67] *KRAS*-wild-type PDAC can harbor *BRAF* alterations and fusions involving *FGFR2*, *ALK*, *RET*, or *NRG1*; *NTRK* amplification was also detected in a subset of cases.[68] These findings support molecular stratification beyond *KRAS* mutation status.

Intratumoral heterogeneity and pathway convergence in primary PDAC

Single-cell DNA sequencing has shown that most driver-gene single-nucleotide variants (SNVs) are clonal, whereas copy-number alterations account for much of spatial heterogeneity. It also revealed convergent loss of tumor-intrinsic TGF-β responsiveness through alterations affecting *SMAD4*, *TGFBR1*, or *TGFBR2*.[69] Truncal density quantifies SNVs acquired in the ancestral tumor lineage, normalized to the number of genomic positions with sufficient sequencing depth. Among 70 evaluable PDACs, higher truncal density was associated with shorter overall survival, although its prognostic value requires independent validation.[70] Driver SNVs generally arise early, whereas later copy-number remodeling and subclonal selection continue to shape intratumoral heterogeneity.

Metastatic dissemination, local ecology, and late-stage evolution

Metastatic dissemination generally preserves the major truncal driver alterations of the primary tumor, whereas structural variation, copy-number changes, and subclonal diversification may continue after dissemination.[71,72] Metastatic seeding may be monoclonal, polyclonal, or mixed, and the relative contribution of these patterns varies between patients.[70] Phylogenetic modeling also suggests that PDAC may evolve for a prolonged period before acquiring metastatic competence, although the estimated duration depends on the cohort and modeling assumptions.[8]

Single-cell DNA sequencing has shown that copy-number states and subclonal architecture can differ across primary and metastatic sites, even when major driver alterations are shared.[69] Spatial transcriptomic analyses of metastatic PDAC have identified site-associated lineage states and local tissue interactions.[73] Treatment pressure can further enrich residual malignant programs, transitional cell populations, and treatment-associated stromal states.[74,75]

These findings have implications for clinical sampling and longitudinal monitoring. Tissue sequencing preserves histopathological and spatial information but may underrepresent subclones present in other tumor regions or metastatic sites. Circulating tumor DNA (ctDNA) provides a complementary, minimally invasive approach for tracking tumor-derived alterations and recurrence after treatment.[76] Together, these approaches provide partially complementary views of tumor evolution across space and time.

Clinical translation: risk identification, therapeutic vulnerabilities, and dynamic monitoring

The clinical relevance of this framework lies in matching each evolutionary stage to an appropriate clinical task. Germline testing identifies inherited risk in patients and relatives. Surveillance is directed toward unaffected individuals with defined genetic or familial risk. Early detection seeks high-grade precursor lesions or early, resectable PDAC. Tumor profiling informs treatment selection, whereas longitudinal molecular assays support monitoring of residual disease, recurrence, and resistance. Population screening concerns asymptomatic average-risk individuals, whereas surveillance concerns selected high-risk populations. These complementary clinical applications are summarized in Table 4 and illustrated in Figure 3.[12,13,32-35,68,76-87]

Germline testing and high-risk surveillance

Germline testing is recommended for all patients with PDAC, irrespective of age or family history, because pathogenic variants may be identified even in patients without a suggestive family history.[77,78] Genetic counseling is recommended for individuals with a pathogenic germline variant and remains important when the personal or family history is strongly suggestive. It supports interpretation of test results, risk management, and cascade testing of relatives. Pancreatic surveillance is reserved for unaffected individuals who meet established genetic or familial risk criteria. Magnetic resonance imaging, magnetic resonance cholangiopan-

Table 4. Clinical translation of genetic evolution in PDAC

Clinical setting	Population or biomarker	Test or intervention	Main result	Current status	Representative references
Germline testing	All patients with PDAC	Germline multigene testing	Pathogenic variants may occur without a typical family history	Standard practice	[12,13,77,78]
High-risk surveillance	Eligible unaffected carriers and familial kindreds	MRI/MRCP and EUS	CAPS5: 1,461 participants; 7 of 9 surveillance-detected PDACs were stage I	Guideline-supported practice for selected high-risk individuals	[32,79]
PARP inhibitor maintenance	Metastatic germline *BRCA1/2* PDAC without progression after ≥ 16 weeks of first-line platinum	Maintenance olaparib	Median PFS, 7.4 *vs.* 3.8 months; OS, 19.0 *vs.* 19.2 months (not significant)	Clinically supported in a defined subgroup	[33,81]
Matched therapy	Profiled tumors, especially *KRAS*-wild-type PDAC	DNA/RNA profiling and matched therapy	Know Your Tumor: 46 matched patients had longer observed survival; actionable fusions occur in *KRAS*-wild-type tumors	Clinically supported in selected molecular subgroups (retrospective evidence)	[68,82]
KRAS p.G12C inhibition	Previously treated *KRAS* p.G12C metastatic PDAC	Sotorasib	38 patients; objective response rate, 21%; median PFS, 4.0 months	Clinically supported in a defined subgroup (single-arm evidence)	[83]
KRAS inhibitor resistance	*KRAS* p.G12C- or p.G12D-directed inhibitor exposure	Progression tissue or ctDNA; combination testing	Resistance includes *KRAS/PIK3CA* variants, *KRAS/MYC/MET/EGFR/CDK6* amplification, and transcriptional state shifts	Investigational (clinical and preclinical evidence)	[84,85]
MSI-H/dMMR immunotherapy	MSI-H/dMMR PDAC	Orthogonal MMR/MSI confirmation; PD-1 blockade	20 treated; 17 confirmed MSI-H; disease control, 80%	Standard biomarker-directed therapy; PDAC-specific evidence retrospective	[34,35]
Postoperative residual disease	Resected PDAC with trackable tumor alterations	Tumor-informed ctDNA or digital PCR	ctDNA predicted recurrence, preceding CT by 6.5 months on average	Investigational	[76]
Advanced-disease liquid biopsy	Advanced PDAC	cfDNA methylation and fragmentomics	33 patients; tumor-agnostic ctDNA estimates predicted PFS and OS	Investigational	[86]
Early blood-based detection	Case-control cohorts including early-stage PDAC	CA19-9, TIMP1, and pancreas-specific cfDNA methylation	Validation AUC, 0.86 *vs.* 0.82 for CA19-9 alone	Investigational	[80]
Organoid drug testing	Surgical or biopsy-derived PDOs	Drug-sensitivity testing	66 organoids; heterogeneous responses; selected concordance with patient outcomes	Preclinical/early translational	[87]

AUC, area under the receiver operating characteristic curve; CA19-9, carbohydrate antigen 19-9; CAPS5, fifth Cancer of the Pancreas Screening study;

cfDNA, cell-free DNA; CT, computed tomography; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; EUS, endoscopic ultrasonography; MMR, mismatch repair; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MSI, microsatellite instability; MSI-H, microsatellite instability-high; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PCR, polymerase chain reaction; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PDO, patient-derived organoid; PFS, progression-free survival; TIMP1, tissue inhibitor of metalloproteinases 1.

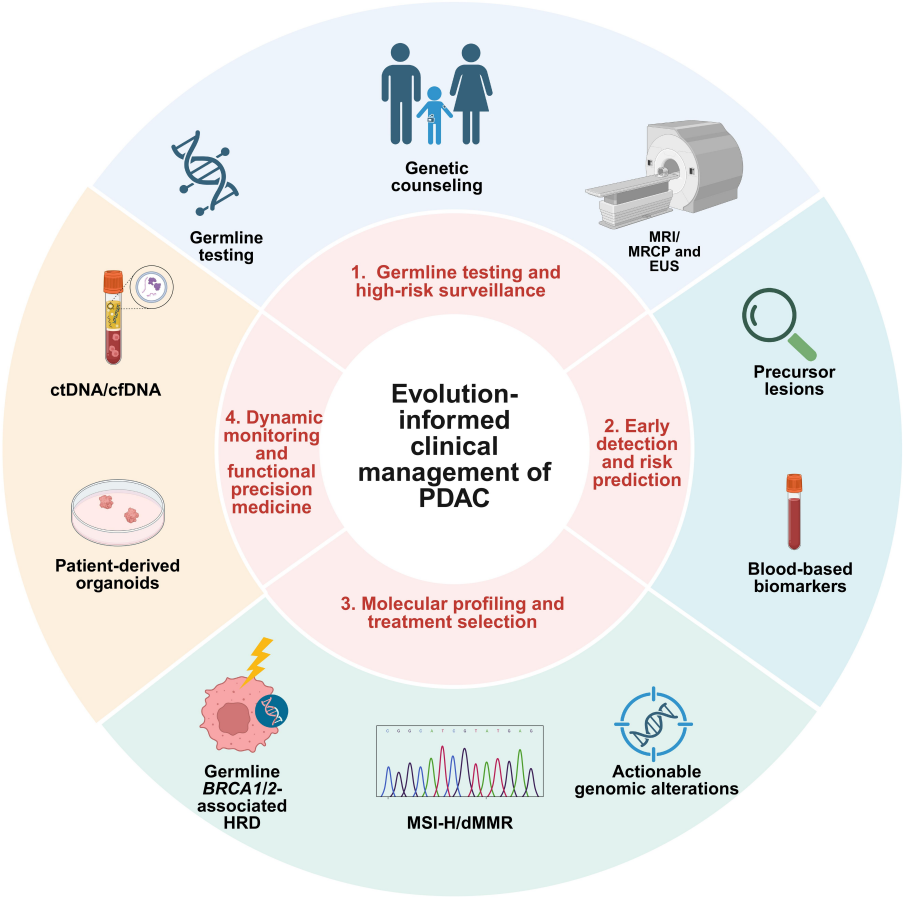


Fig. 3. Evolution-informed clinical management of PDAC. The schematic summarizes four clinical applications of pancreatic ductal adenocarcinoma evolution: germline testing and high-risk surveillance; early detection and risk prediction; molecular profiling and treatment selection; and dynamic monitoring and functional precision medicine. Representative approaches include genetic counseling, MRI/MRCP and EUS surveillance, assessment of precursor lesions and blood-based biomarkers, and genomic profiling for germline *BRCA1/2*-associated HRD, MSI-H/dMMR, and other actionable alterations. ctDNA and cfDNA may support longitudinal molecular monitoring, whereas patient-derived organoids provide a platform for functional drug-sensitivity testing. This figure was created by the authors using BioRender. cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; EUS, endoscopic ultrasonography; HRD, homologous recombination deficiency; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MSI-H, microsatellite instability-high; PDAC, pancreatic ductal adenocarcinoma.

creatography, and endoscopic ultrasonography are the principal surveillance modalities. They should be used in experienced multidisciplinary centers, with the age at initiation and surveillance interval tailored to the underlying pathogenic variant or syndrome and the family history.[32] The clinical goal is to identify high-grade precursor lesions or early, resectable PDAC.

Long-term surveillance studies provide clinical support for this strategy. Among 354 high-risk individuals, 24 developed neoplastic progression, including 14 PDACs and 10 high-grade precursor lesions. Nine of the 10 PDACs detected during routine surveillance were resectable.[88] The fifth Cancer of the Pancreas Screening study enrolled 1,461 high-risk individuals, and seven of the nine PDACs detected during surveillance were stage I. In the combined Cancer of the Pancreas Screening cohort, surveillance-detected PDAC was associated with better observed survival.[79] These findings support high-risk surveillance as a route to earlier-stage diagnosis. Stage and survival estimates should be interpreted in the context of cohort selection and the observational design of

surveillance studies.

Early detection and risk prediction

Surveillance and early detection are related but distinct clinical goals. Surveillance provides repeated assessment of individuals who are already known to be at high risk. Early-detection studies evaluate whether imaging or circulating biomarkers can identify precursor lesions or early PDAC before clinical progression.

Evidence for blood-based early detection remains largely at the case-control validation stage. A panel combining protein biomarkers with pancreas-specific cell-free DNA methylation improved the discrimination of early-stage PDAC in an independent validation set.[80] These findings support continued biomarker development, while prospective studies in asymptomatic or high-risk populations are needed to define clinical performance. Future risk-prediction models should integrate germline status, family history, imaging findings, protein biomarkers, and cell-free DNA signals.

Molecular profiling and treatment selection

Homologous recombination repair deficiency represents the most clearly established therapeutic vulnerability. The POLO trial enrolled patients with metastatic PDAC carrying germline *BRCA1* or *BRCA2* variants whose disease had not progressed after at least 16 weeks of first-line platinum-based chemotherapy. Maintenance poly(ADP-ribose) polymerase inhibition significantly prolonged progression-free survival.[33] In the subsequent analysis, median overall survival was 19.0 months with olaparib and 19.2 months with placebo, without a statistically significant difference. However, the estimated three-year survival and time to subsequent therapy suggested that some patients may derive sustained benefit.[81] The clinical interpretation of a germline *BRCA1* or *BRCA2* variant is further informed by tumor genomic features, evidence of biallelic inactivation, homologous recombination deficiency, and prior platinum response.[7,24]

Molecular profiling also provides therapeutic opportunities for a minority of patients with uncommon molecular profiles. In the retrospective Know Your Tumor registry study, patients who received molecularly matched therapy had longer survival than patients with actionable alterations who did not receive matched therapy.[82] *KRAS*-wild-type PDAC can harbor *BRAF* alterations and fusions involving *FGFR2*, *ALK*, *RET*, or *NRG1*; *NTRK* amplification has also been reported.[68] Among 38 previously treated patients with metastatic pancreatic cancer carrying *KRAS* p.G12C, sotorasib produced an objective response rate of 21%, demonstrating clinical activity in this uncommon subgroup.[83] In the phase 3 RASolute 302 trial, daraxonrasib, an oral RAS(ON) multiselective inhibitor, prolonged median overall survival (13.2 *vs.* 6.6 months; hazard ratio, 0.40) and progression-free survival (7.3 *vs.* 3.5 months; hazard ratio, 0.45) compared with investigator's-choice chemotherapy in previously treated metastatic PDAC with mutations at RAS codon 12.[89]

Immunotherapy has limited activity in unselected PDAC. Microsatellite instability-high (MSI-H) and deficient mismatch repair tumors represent a rare but clinically actionable subgroup.[5] Pan-cancer studies have shown that mismatch repair deficiency predicts response to programmed cell death protein 1 (PD-1) blockade across solid tumors.[34] In a selected cohort of 55 patients with pancreatic cancer carrying Lynch syndrome-associated germline pathogenic variants or somatic mismatch repair variants, orthogonal microsatellite instability testing reclassified several specimens with low tumor cellularity. Twenty patients received immune checkpoint blockade, 17 of whom had MSI-H tumors, and the disease control rate was 80%.[35] For PDAC, the available clinical evidence comes mainly from selected mismatch repair-altered cohorts.

Dynamic monitoring and functional precision medicine

Therapeutic pressure can further reshape clonal composition. Analyses of resistant patient samples and preclinical models have identified emergent *KRAS* and *PIK3CA* mutations, amplifications involving *KRAS*, *MYC*, *MET*, *EGFR*, and *CDK6*, and transcriptional changes after KRAS inhibition.[84] Studies using genetically engineered mouse models, transplantation models, and patient-derived xenografts have also shown rapid enrichment of a classical epithelial state after KRAS inhibition. This state may serve as a reservoir for disease relapse.[85] These findings provide a rationale for investigating serial molecular profiling during treatment and disease progression.

Dynamic monitoring provides a direct link between tumor evolution and longitudinal clinical management. In resectable PDAC, persistent postoperative ctDNA detection was associated with recurrence and poor outcomes, and molecular recurrence was detected earlier than recurrence on computed tomography.[76] In colorectal, gastroesophageal, and biliary cancers, post-progression cell-free DNA more frequently identified multiple resistance alterations than single-lesion tissue biopsy. This provides methodological support for multi-lesion molecular monitoring in PDAC.[90] In 33 patients with advanced pancreatic cancer, models based on DNA methylation and fragmentomic features demonstrated the feasibility of tumor-agnostic ctDNA detection and prognostic stratification.[86]

Patient-derived organoids are being developed as a functional complement to genomic profiling. Across 66 patient-derived PDAC organoid cultures, responses to chemotherapeutic agents were heterogeneous. The available concordance between organoid drug sensitivity and patient outcomes was based mainly on case-level analyses and small retrospective comparisons.[87] Prospective studies are needed to determine whether organoid drug testing improves clinical decision-making.

Future directions

An important goal is to distinguish precursor lesions that remain indolent from those likely to progress. Multiple, clonally independent PanINs can coexist in the pancreas before disease becomes clinically apparent, highlighting the difficulty of identifying which lesions will progress to invasive cancer.[42,43] Longitudinal imaging and molecular studies in high-risk individuals will be needed to define the changes that accompany progression.

A second priority is to determine how inherited susceptibility shapes tumor evolution. In tumors carrying germline *BRCA1*, *BRCA2*, or *PALB2* variants, somatic second hits can produce homologous recombination deficiency and structural instability. The extent and timing of biallelic inactivation vary among tumors.[7,24] Paired germline–tumor studies are needed to determine how germline variants in *ATM*, mismatch repair genes, *CDKN2A*, *STK11*, and pancreatitis-associated genes influence subsequent

evolution. Such studies should include diverse populations and consistent approaches to variant interpretation.[23]

Finally, the timing of major evolutionary events remains uncertain. Whole-genome and single-cell studies suggest that structural remodeling and copy-number diversification can occur at different stages of PDAC evolution.[9,69] Integrating multiregion sampling with longitudinal ctDNA analysis, spatial transcriptomics, and single-cell profiling could reveal when invasive, metastatic, and treatment-resistant clones emerge. This information may help align surveillance and molecular monitoring with the pace of tumor evolution.

Limitations

Several limitations constrain interpretation of the current evidence. First, direct links between germline susceptibility and later somatic evolution are supported most clearly for homologous recombination repair genes, whereas paired germline–tumor sequencing remains limited for many other susceptibility genes. Second, much of the available evidence comes from retrospective cohorts, selected surgical series, and preclinical models, with variation in ancestry, eligibility criteria, sequencing platforms, and variant-classification strategies. Third, the natural history of precursor lesions remains incompletely resolved: many PanINs and other precursor states remain indolent, and current data do not reliably identify which clones will progress to invasion or metastasis. Finally, biomarkers and monitoring approaches based on HRD features, liquid biopsy, single-cell profiling, and organoid drug testing require prospective validation before routine clinical use. These limitations should be considered when translating the reviewed findings into risk assessment, surveillance, and treatment decisions.

Conclusions

PDAC develops through a continuous but branching genetic trajectory rather than a single obligatory sequence. Germline susceptibility, tissue injury, precursor lesions, somatic driver acquisition, structural genome remodeling, and clonal selection contribute at different stages, while metastatic dissemination and treatment pressure further shape tumor evolution. The germline–somatic relationship is most firmly established for homologous recombination repair genes, whereas the clinical implications of many other susceptibility backgrounds remain less certain. Integrating inherited risk, precursor-lesion biology, tumor profiling, and longitudinal monitoring provides a framework for risk stratification and molecular treatment selection, while the representative routes summarized here may vary across patients.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization (WG, LY). Literature review and synthesis (CM, HZ, ZyL, YQ, XL, XZ). Writing—original draft (CM, HZ). Writing—review and editing (KJ, ZpL, WG, LY). Supervision (KJ, ZpL, WG, LY). All authors read and approved the final manuscript.

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