Review Article

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Genomic alterations in pancreatic cystic neoplasms: from molecular characterization to precision clinical management

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Abstract

Pancreatic cystic neoplasms (PCNs) are a heterogeneous group of pancreatic lesions with the potential for malignant transformation. Next-generation sequencing has revealed subtype-specific driver mutations and pathways that govern the initiation and progression of PCN. Evidence suggests that subtype-specific genetic trajectories and temporal sequences of genetic and molecular events are pivotal in determining disease progression and malignant transformation. Novel methodologies in genetic testing, particularly through minimally invasive cyst fluid analysis and advanced tissue-based sequencing, have profoundly enhanced diagnostic accuracy and the molecular classification of PCNs. Furthermore, these genetic insights guide risk stratification, clinical decision-making, and personalized therapeutic interventions. This review systematically summarizes current genomic insights into the molecular landscape of PCNs, critically evaluates the comparative diagnostic performance of cyst fluid versus tissue-based genetic testing, and integrates these findings into a practical framework for clinical management.

Keywords: cyst fluid analysis, genomic sequencing, molecular diagnostics, pancreatic cystic neoplasms, risk stratification

Current understanding and characteristics of pancreatic cystic neoplasms

Pancreatic cystic neoplasms (PCNs) represent a diagnostically and therapeutically challenging group of lesions due to their histological heterogeneity and diverse malignant potential. Epidemiological data report PCN prevalence ranging from 2.2% to 44.7%, reflecting variations in imaging modalities and study populations[1-3]. Although the majority of PCNs are benign, such as serous cystic neoplasms (SCNs), a subset carries a risk of malignant transformation into pancreatic cancer. Notably, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are the principal pre-malignant mucinous subtypes, typically identified by mucin-rich cyst fluid. Less common entities such as solid pseudopapillary neoplasms (SPNs) and cystic pancreatic neuroendocrine tumors (NETs) further broaden the neoplastic spectrum. Moreover, solid tumors, including pancreatic ductal adenocarcinomas (PDACs), SPNs, and pancreatic neuroendocrine tumors, may develop cystic degeneration, further complicating diagnostic differentiation[4,5]. Age is a pivotal factor in PCN development and progression, with prevalence increasing notably after age 45. The estimated 7-year transformation risk is approximately

HIGHLIGHTS

- Elucidates core molecular mechanisms and oncogenic pathways driving the initiation, progression, and malignant transformation of PCNs.
- Critically evaluates the comparative value of cyst fluid and tissue-based genomic profiling in enhancing diagnostic accuracy and pathological classification.
- Integrates molecular insights into clinically relevant risk stratification frameworks to support individualized management and surgical decision-making.
- Explores the role of minimally invasive molecular platforms and advanced sequencing technologies in improving early detection and dynamic disease monitoring.
- Highlights future directions emphasizing the value of integration in advancing precision strategies for PCN care.

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3.0%, corresponding to an annual progression rate of 0.47%[6]. The overall malignancy risk in pancreatic cysts ranges from 0.5% to 1.5%, with a yearly progression rate of approximately 0.5%[6,7]. Conversely, mucinous cysts are estimated to account for 15% of pancreatic cancers and represent the only identifiable precursors of malignancy visible on cross-sectional imaging[8,9]. Imaging remains the cornerstone of PCN diagnosis, particularly as many lesions are incidentally detected in asymptomatic individuals[10]. It also plays a central role in risk stratification, as small asymptomatic cysts are typically indolent, whereas those located in the pancreatic head or presenting high-risk imaging features may require closer surveillance or surgical intervention[11–13].

Surgical resection remains the only curative treatment for PCNs, but it carries significant perioperative risks such as infection, bleeding, and pancreatic fistula formation. The difficulty distinguishing high-risk lesions complicates clinical decision-making, frequently leading to overtreatment of benign cysts or delayed intervention in malignant cases[14]. Beyond clinical consequences, such uncertainty imposes a substantial psychological burden, contributing to patient anxiety over cancer progression and surgical outcomes[5,9]. Despite technological advances, differentiating benign from malignant PCNs remains difficult due to nonspecific symptoms and overlapping imaging characteristics. Molecular profiling has emerged as a valuable tool for enhancing diagnostic precision. Key genetic alterations, most notably in *KRAS, GNAS*, and tumor protein 53 *(TP53)*, are now recognized as important markers for differentiating indolent from high-grade or malignant cystic lesions[15,16]. When integrated with advanced imaging modalities such as endoscopic ultrasound (EUS) and cyst fluid analysis, these genomic insights can potentially optimize clinical management strategies for PCNs[17]. Integrating molecular and imaging data may facilitate early detection, more accurate risk stratification, and personalized treatment planning.

This review provides a comprehensive synthesis of the molecular alterations underlying IPMNs, MCNs, and SCNs, focusing on key genetic drivers of neoplastic initiation and progression. We emphasize how advances in cyst fluid-based next-generation sequencing (NGS) have enabled minimally invasive, lineage-specific molecular profiling, offering improved diagnostic accuracy over traditional cytology and imaging in selected cases. By integrating genomic, radiologic, and clinical data, we outline a more refined approach to risk stratification and surgical decision-making. In contrast to previous literature that often addressed individual markers or subtypes in isolation, this review presents an integrated framework linking genotype to clinical behavior across the spectrum of PCNs. Through highlighting the translational relevance of molecular diagnostics, we aim to inform both current management strategies and future prospective research. This review also complies with the TITAN guideline for transparent reporting of artificial intelligence in biomedical research[18].

PanIN and cystic precursors in pancreatic cancer

PDAC arises through a stepwise progression from precursor lesions, including pancreatic intraepithelial neoplasia (PanIN), IPMNs, and MCNs[19,20]. Pancreatic intraepithelial neoplasias are the most prevalent among these, although IPMNs and MCNs account for a smaller subset of pancreatic cancer cases[9]. Pancreatic cancer from PanIN differs in the development and prognosis with PCN origins. Pancreatic intraepithelial neoplasias are asymptomatic microscopic lesions originating from interlobular pancreatic ducts[21]. Autopsy studies underscore the prevalence of PanIN lesions, with low-grade PanINs detected in over 75% of individuals without pancreatic cancer and high-grade lesions observed in 5%[22]. While early PanINs are common, progression to PDAC requires the accumulation of multiple genetic and chromosomal aberrations. Genomic analyses confirm high-grade PanINs as precursors to synchronous PDAC, sharing driver mutations and evolutionary trajectories[23]. Essential driver genes such as *KRAS,* cyclin-dependent kinase inhibitor 2A *(CDKN2A), TP53*, and mothers against decapentaplegic homolog 4 *(SMAD4)* play crucial roles in both the initiation and progression of these lesions[24,25]. Early pancreatic tumorigenesis features, notably oncogenic hotspot mutations in *KRAS* and telomere shortening, are prevalent in more than 90% of low-grade PanINs[26]. *KRAS* mutations are present in over 90% of PDAC cases, most commonly involving codon 12 substitutions such as G12D or G12V. Oncogenic *KRAS* activates the RAS-mitogen-activated protein kinase (MAPK) and PI3K-AKT pathways, promoting acinar-to-ductal metaplasia (ADM), an early morphological change that precedes PanIN formation[27–29]. Pancreatic intraepithelial neoplasia-1 lesions, characterized by low-grade dysplasia, harbor *KRAS* mutations, and telomere shortening, with minimal genetic instability as the initial step in the neoplastic cascade[23,26]. Progressive dysplasia in PanINs is associated with increasing mutation burdens in tumor suppressor genes such as *CDKN2A* and *TP53*. *CDKN2A*, affecting the $p16^{INK4A}$ pathway, is observed in ~ 60% of PDAC and represents a key event in intermediate-grade lesions[30–32]. Mutations disrupting the G1/S checkpoint drive uncontrolled proliferation, while epigenetic changes silencing tumor suppressor genes and dysregulated Notch and Wnt pathways further promote PanIN progression[24]. Progression to PanIN-2 involves increased cytological atypia, *CDKN2A* inactivation, and epigenetic changes such as DNA hypermethylation and histone modifications, which silence tumor suppressor genes and enhance proliferation and genomic instability[30,31]. Pancreatic intraepithelial neoplasia-3, the highest grade, exhibits high-grade dysplasia with mutations in *TP53* and *SMAD4*, impairing DNA damage repair and disrupting transforming growth factor beta signaling, critical for the transition to invasive carcinoma by conferring greater invasive and metastatic potential[20,33,34]. These genetic events are accompanied by chromosomal alterations such as chromothripsis and polyploidization, observed in 50% and 45% of PDAC cases[20]. Such structural rearrangements exacerbate genomic heterogeneity and promote clonal evolution (Fig. 1).

In contrast, PCNs represent macroscopic precancerous lesions with distinct, individualized processes that diverge from the pathogenesis of PanINs. Partial PCNs with malignant potential, in addition to their own risk of transformation, are associated with an increased likelihood of pancreatic cancer developing in regions distant from the preexisting cystic lesion[35]. Intraductal papillary mucinous neoplasm and MCNs can be identified earlier than PanIN due to macroscopic lesions, and surgical resection can achieve a better prognosis[5]. Representing a substantial portion of radiographically detected pancreatic cystic tumors, IPMNs carry an increased risk of

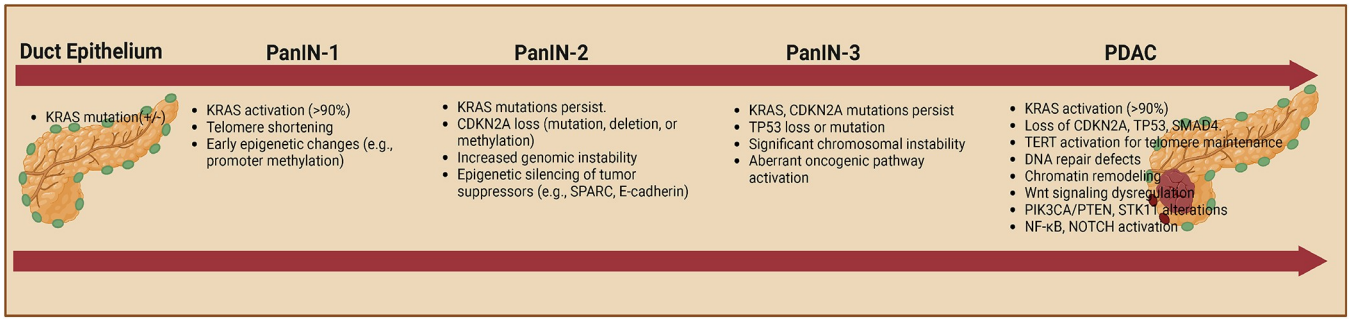


Figure 1. Genetic alterations in PanIN progression to PDAC.

PDAC progression, with a 5-year incidence rate of approximately 7% under active surveillance[36–38]. Nevertheless, IPMN-associated pancreatic cancer has better survival outcomes and older average age at diagnosis than non-IPMN pancreatic cancer[39], suggesting differences in the pathogenesis and driver genes between IPMNs and PanINs.

Additionally, they share some key driver genes in the disease progression and some similarities during disease evolution. Pathologically, PanINs are widely distributed throughout the pancreatic ductal system, often forming discontinuous lesions with a leapfrogging distribution[40]. In contrast, IPMNs follow the pancreatic ductal system more consistently and typically coexist with PanINs[41]. Collectively, both PanINs and PCNs contribute to pancreatic tumorigenesis through a cumulative acquisition of genetic alterations, although their origins and progression patterns differ. Taken together, exploring genomic alterations from precancerous lesions to pancreatic cancer is imperative and favorable for understanding the development of pancreatic cancer.

Developmental insights of genetic alterations in PCNs

IPMNs

Intraductal papillary mucinous neoplasms can arise throughout the pancreatic ductal system and are classified as main-duct, branch-duct, or mixed types. Histologically, they include gastric-type, intestinal-type, pancreaticobiliary-type, and mixed-type subtypes, each associated with distinct molecular features and varying degrees of malignant potential[42]. As established precursors to pancreatic cancer, approximately 5–10% of IPMNs progress to invasive carcinoma through a multistep sequence involving low-grade dysplasia, high-grade dysplasia, and eventually invasive cancer[9,19]. Early-stage IPMNs often contain multiple genetically distinct clones, suggesting a polyclonal origin[43]. *KRAS* and *GNAS* mutations are frequently detected in low-grade lesions, indicating a model in which these mutations drive early genetic heterogeneity, followed by clonal selection that may lead to malignant transformation.

KRAS and *GNAS* are recognized as key driver genes in IPMNs, being more frequently detected in IPMNs than in MCNs or SCNs[44]. Recurrent and multiple IPMNs exhibit a higher frequency of malignancy and a greater detection of *KRAS* and *GNAS* mutations[41]. Mutations in *GNAS* (codon 201) and *KRAS* are reported at the 40–70% and 40–65% detection rate in IPMN cases, which are central driver genes in the early stage of IPMN, influencing the pathophysiology[45]. *KRAS* mutations primarily drive adenocarcinoma progression, whereas *GNAS* mutations promote mucin production and the formation of large cystic lesions[46]. In mouse models, ADM-like changes can only be induced by $KRAS^{G12D}$ rather than $GNAS^{R201C}$[47]. However, *KRAS* mutation mainly occurred in PanIN-derived PDAC due to the higher expression in acinar regions compared to the ductal areas[47]. Moreover, *GNAS*-mutant human pluripotent stem cell-derived pancreatic duct-like organoids form IPMN-like lesions, whereas *KRAS*-mutant organoids exhibit dysplastic features[48]. These observations underscore the distinct molecular mechanisms through which *KRAS* and *GNAS* drive the initiation and progression of IPMN[49].

The cooperative role of *KRAS* and *GNAS* mutations has been primarily explored in preclinical models. In genetically engineered mice, co-expression of $KRAS^{G12D}$ and $GNAS^{R201C}$ synergistically induces IPMN-like lesions[50]. $KRAS^{G12D}$ and $GNAS^{R201C}$ co-expression induces gastric pyloric metaplasia and increased glycolytic dependency, while $GNAS^{R201C}$ further accelerates IPMN progression to invasive PDAC in the presence of TP53 loss[51,52]. $GNAS^{R201C}$ promotes ductal differentiation sequesters phosphorylated yes-associated protein 1 in the cytoplasm, thereby modulating tumor progression[53]. Interestingly, *GNAS* can antagonize *KRAS*-driven oncogenic signaling, limiting its full tumorigenic capacity[54]. *KRAS* and *GNAS* mutations define two distinct but converging molecular trajectories in IPMN tumorigenesis. This molecular heterogeneity underscores the need for mutation-specific approaches to guide risk stratification and targeted therapy.

Although *KRAS* and *GNAS* mutations initiate early tumorigenesis, the progression to malignancy in IPMNs is predominantly mediated by additional mutations in tumor suppressors such as ring finger protein 43 *(RNF43), CDKN2A, TP53*, and *SMAD4*, which disrupt cell cycle regulation, genomic integrity, and cellular differentiation[55–57]. Despite their role in tumor initiation, *KRAS* and *GNAS* mutations do not independently predict malignant transformation or clinical outcome. Instead, the progression to malignancy and patient outcomes are primarily influenced by the presence of key PDAC risk genes[58]. *GNAS* mutations occur less frequently than *KRAS* in malignant IPMNs and are preferentially associated with the colloid carcinoma subtype, noted for its mucin-rich histology and relatively favorable prognosis[59,60]. Additionally, *GNAS*-mutant IPMNs

exhibit reduced perivascular and perineural invasion rates and lymph node metastasis and are linked to significantly improved overall survival[61]. *KRAS* mutations and increased phospho-ERK signaling are more common in gastric-type IPMNs, while intestinal-type lesions are frequently associated with SMAD1/5/8 pathway activation[62].

The oncogenic potential of *KRAS* is markedly amplified by the concomitant inactivation of tumor suppressor genes, collectively accelerating the initiation and progression of IPMNs. For instance, co-expression of $KRAS^{G12D}$ and *PTEN* loss promotes the development of intraductal papillary and glandular neoplasms, with β-catenin critically mediating their differentiation into mucinous cell-rich IPMNs[63,64]. Additionally, ACVR1B loss enhances *KRAS*-driven tumorigenesis through NOTCH4 activation and p16 suppression, whereas Jagged1 deletion leads to a phenotypic transition from malignant carcinoma to benign cystic lesions, underscoring the complexity of IPMN regulatory pathways[65–67]. Cyclooxygenase-2 (COX-2), functioning as both an inflammatory mediator and a co-activator of $KRAS^{G12D}$, facilitates the progression of IPMNs. The combined activity of COX-2 and *KRAS* promotes the development of pancreatic intraepithelial lesions with cystic papillary architecture resembling human IPMNs. Notch1 signaling, modulated by COX-2, is particularly linked to gastric-type IPMNs[68]. Loss of brahma-related gene 1, a critical component of the switch/sucrose non-fermentable chromatin remodeling complex, synergizes with $KRAS^{G12D}$ to induce cystic neoplastic lesions resembling human IPMNs similar to human IPMNs, which may subsequently progress to pancreatic ductal adenocarcinoma[69]. Human epidermal growth factor receptor 2 overexpression, seen in 40% of PDACs and 29% of invasive IPMNs, is associated with developing cystic neoplastic lesions resembling human IPMNs in mouse models[70]. Accordingly, *KRAS*-driven IPMN evolution is contingent upon multiple genetic alterations and cumulative and synergistic activation, which promote neoplastic progression and malignant transformation.

Mutations in *GNAS* and *RNF43* are hallmark alterations in IPMNs, frequently co-occurring with other key driver mutations such as *KRAS, TP53*, and *CDKN2A*, which are also prevalent in pancreatic ductal adenocarcinoma[71]. *GNAS* encodes the Gsα subunit, which activates the protein kinase A pathway through cyclic AMP signaling, thereby regulating cell differentiation and cell cycle stability[72–74]. *GNAS* mutations occur more frequently in main-duct IPMNs than branch-duct types, potentially due to enhanced mucin secretion driven by *GNAS* activation[75–77]. *GNAS* mutations are common in most intestinal-type IPMNs and present in roughly half of gastric-type cases, suggesting their involvement in the phenotypic transition from gastric to intestinal types via upregulation of *CDX2* and *MUC2* expression[44,78]. This mutation pattern suggests a nuanced role of *GNAS* in tumorigenesis, potentially moderating malignancy and influencing the prognosis of IPMN through its interaction with KRAS signaling[52,54,79]. *RNF43*, a tumor suppressor gene, frequently acquires loss-of-function mutations alongside *GNAS* mutations during IPMN progression. It negatively regulates Wnt signaling by suppressing Frizzled receptor expression, thereby rendering PDAC cells Wnt-dependent[80,81]. In IPMNs of the pancreas, *RNF43* mutations are relatively common, ranging from 14% to 75%, with a higher prevalence in mucinous lesions[44,82]. *RNF43* mutations synergize with *GNAS* alterations, promoting malignant transformation in IPMNs[80]. Similarly, *RNF43* mutation commonly occurs in intestinal-type IPMNs and is accompanied by *GNAS* mutations[78]. The combined effect of *RNF43* mutations, β-catenin pathway activation, and CDX2 expression facilitates the progression from gastric-type to intestinal-type IPMNs, characterized by enhanced intestinal differentiation, architectural complexity, and malignant potential[78]. Notably, *RNF43* mutations tend to occur earlier than alterations in SMAD4 and TGFBR2, which are more commonly found in non-invasive lesions[83]. IPMNs driven by *GNAS* and *RNF43* mutations tend to follow a distinct tumorigenic pathway associated with a comparatively favorable prognosis.

In the advanced stages of tumor progression, the accumulation of mutations in key pancreatic cancer driver genes, *CDKN2A, TP53*, and *SMAD4*, facilitates the transformation of IPMN into invasive carcinoma[84]. By comparison, *TP53* mutations, occurring later than *CDKN2A* and *SMAD4* mutations, are specifically associated with the progression to invasive carcinoma[85]. The loss of *CDKN2A* correlated with the transition from low-grade to high-grade dysplasia and the progression toward invasive carcinoma[65,86]. *CDKN2A* deletion may contribute to the adenomatous transformation of IPMNs in murine models[87]. *KRAS* mutation with *CDKN2A* loss develops dedifferentiated PDACs based on IPMN[48]. Similarly, loss of *SMAD4* expression in IPMN is a strong marker for invasive carcinoma, playing a key role in tumor transformation and invasive growth[88,89]. *TP53* alterations occur later than *CDKN2A* and *SMAD4* loss and are observed independently in PDAC and invasive carcinoma[89]. *TP53* mutations are more frequently associated with progression to high-grade PanIN and PDAC but are less commonly seen in invasive IPMN-associated carcinoma[90,91]. Additionally, phosphatidylinositol 3-kinase catalytic alpha polypeptide *(PIK3CA)* mutations activate the PI3K/AKT/mTOR signaling pathway, enhancing cell proliferation, suppressing apoptosis, and promoting tumor progression, thereby contributing to the malignant transformation of IPMNs[92]. Notably, while the PI3K pathway is implicated in the progression of mucin-producing neoplasms, it does not play a significant role in PanIN[93]. Recent advances, particularly spatial transcriptomics, have uncovered additional driver genes in IPMNs, such as NK6 homeobox 2, which regulates gastric cell identity in low-grade lesions, and Kruppel-like factor 4, whose mutations are enriched in early-stage IPMNs[94,95]. Germline mutations, including those in ataxia telangiectasia mutated *(ATM), PTH1*, and suppressor of fused homolog, have been shown to correlate with increased cancer susceptibility and a higher incidence of IPMN, directly linking these genetic alterations to pancreatic cancer risk[96]. These mutations accumulate, driving tumor progression toward malignancy (Fig. 2).

Based on this stepwise mutational framework, recent evidence suggests that distinct histological subtypes of IPMN follow unique molecular trajectories, defined by specific gene alterations and differing risks of malignant progression (Fig. 3). Gastric-type IPMNs, most located in branch ducts, typically harbor *KRAS* mutations and infrequent *GNAS* alterations and usually remain indolent at the low-grade dysplasia stage[44,62]. Occasional transitions to intestinal-type phenotypes suggest

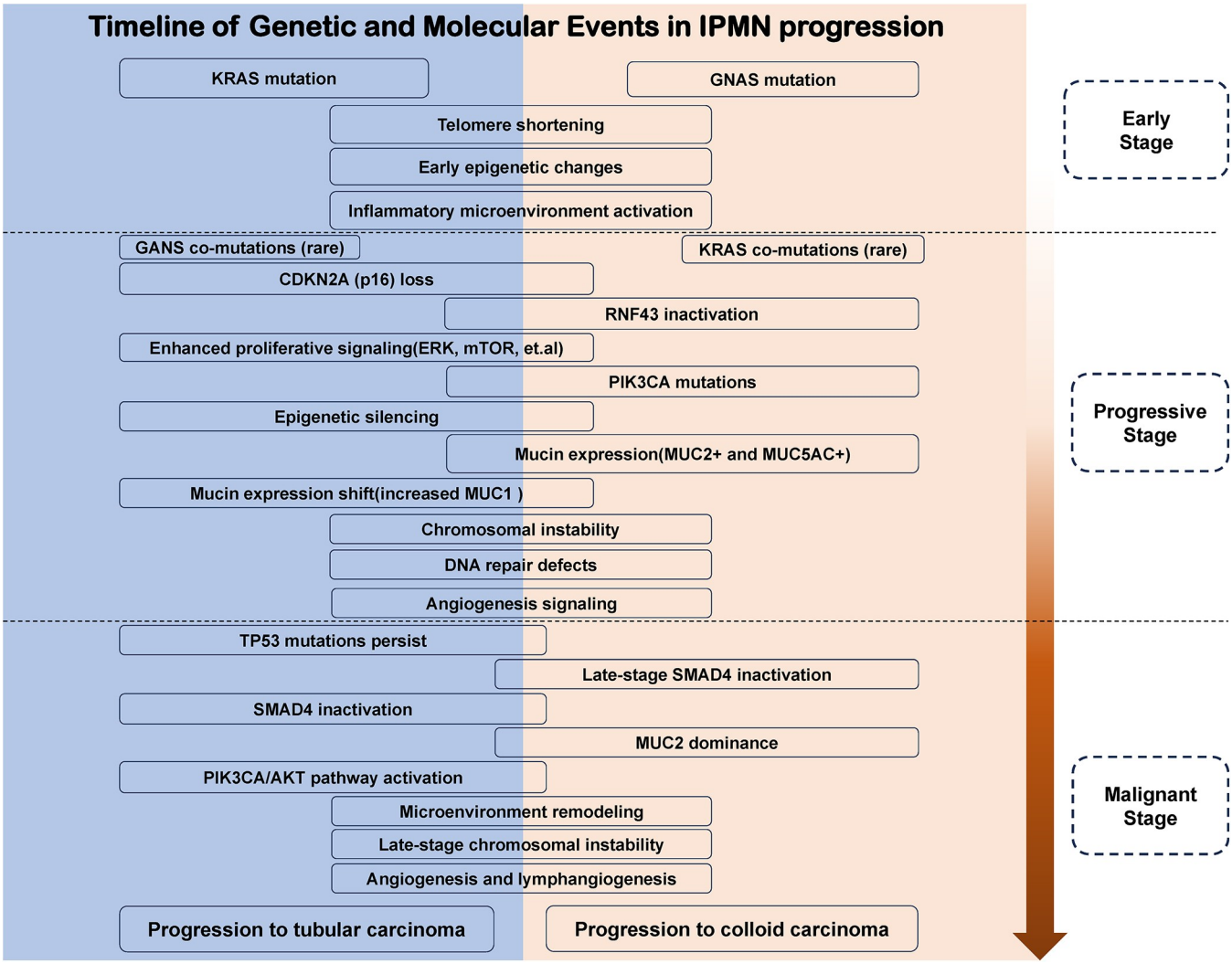


Figure 2. Genetic and molecular timeline delineating IPMN progression pathways.

a degree of lineage plasticity driven by transcriptional regulators such as *CDX2* and mucin expression programs[44,78]. Intestinal-type IPMNs often harbor early co-mutations in *KRAS* and *GNAS* and subsequently acquire additional alterations in *RNF43, PIK3CA*, and various chromatin-modifying genes during progression[44,57,58,78,80,83]. Despite histological progression, these lesions frequently maintain a MUC2$^+$/CDX2$^+$ immunophenotype and may evolve into colloid carcinomas associated with relatively favorable clinical outcomes[60,62]. In contrast, pancreaticobiliary-type IPMNs are genetically more aggressive, initiated by *KRAS* activation, and characterized by sequential inactivation of *TP53, SMAD4*, and *CDKN2A*, leading to loss of glandular architecture and high-grade transformation[62,88,89]. These molecular changes are associated with a phenotypic switch, potentially indicating a transition toward an invasive pancreaticobiliary phenotype. Lastly, mixed-type IPMNs, exhibiting hybrid histopathological features of gastric, intestinal, and pancreaticobiliary differentiation, display significant molecular heterogeneity reflective of their composite origin. The malignant potential of these mixed lesions is generally dictated by the genomic profile of the dominant histological component, highlighting the complexity of their risk stratification and clinical management[44,58].

Additionally, oncocytic-type IPMNs are recognized as distinct entities and have been reclassified as intraductal oncocytic papillary neoplasms (IOPNs) since their unique molecular and histopathological features. Intraductal oncocytic papillary neoplasms are characterized by *DNAJB1–PRKACA* or *PRKACB* gene fusions, frequent ERBB2, ARHGAP26, and PIK3CA mutations, and lacking *KRAS* and *GNAS* mutations. They generally exhibit indolent behavior, with limited malignant progression primarily associated with late-stage TP53 inactivation[17,46,62]. In summary, the molecular alterations that define each IPMN subtype are critical determinants of both malignant potential and clinical behavior, underscoring the importance of subtype-specific genetic analysis for accurate risk stratification and individualized management[44,78,97].

MCNs

MCNs represent a distinct subtype of PCNs, defined by mucin-producing epithelial lining and a characteristic ovarian-type

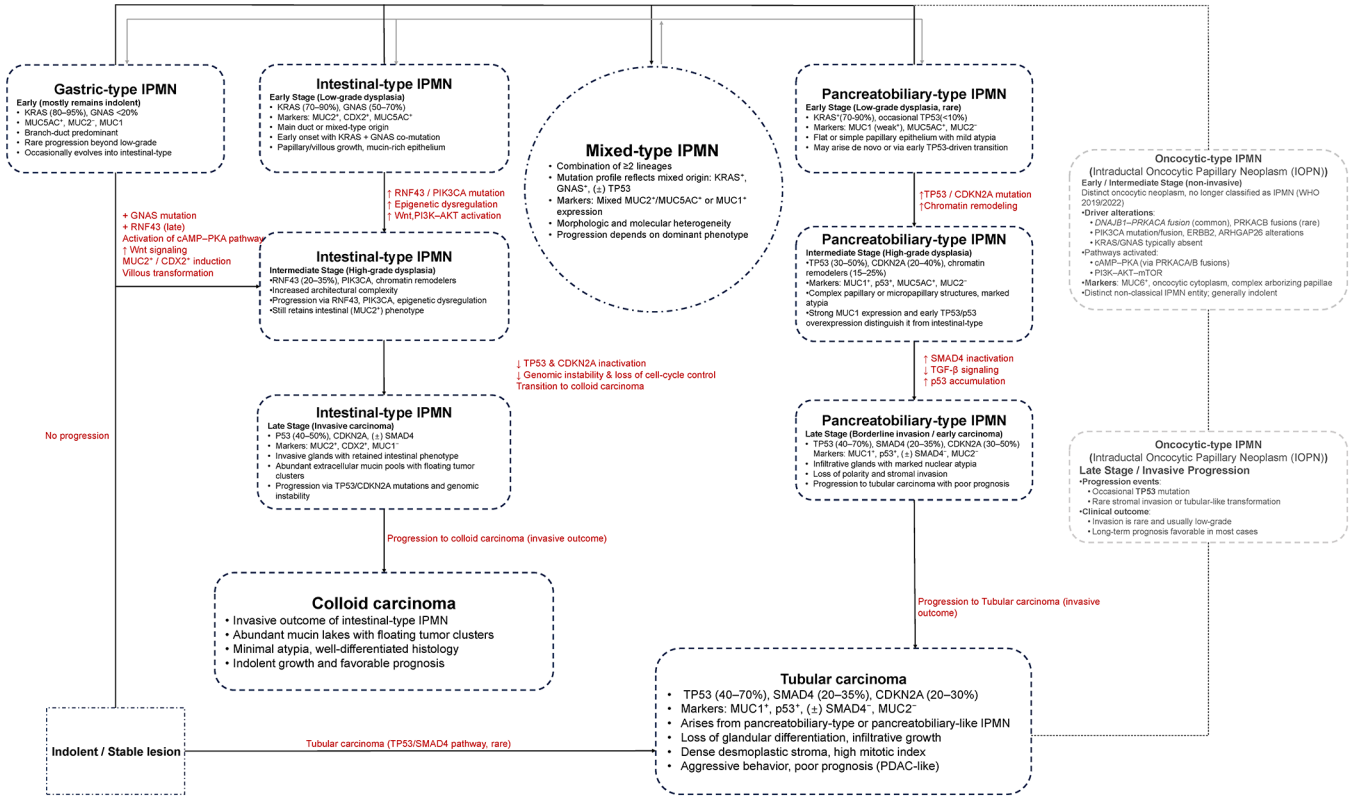


Figure 3. Progression map of IPMN subtypes illustrating distinct histologic features and associated molecular trajectories.

stroma. These histological features differentiate MCNs from other MCNs, particularly IPMNs[98]. In contrast to IPMNs, MCNs are typically encapsulated; solitary neoplasms predominantly located in the body or tail of the pancreas and exhibit a strong predilection for perimenopausal women[98,99]. The ovarian-type stroma may reflect an origin in aberrant embryologic development of the pancreatic ducts; however, the exact pathogenesis remains elusive. Advances in diagnostic imaging and pathological criteria have led to the reclassification of many lesions initially diagnosed as MCNs to IPMNs, resulting in a relative decline in the reported incidence of MCNs. Their shared embryological origin with mucinous ovarian tumors from primordial germ cells underscores their distinct biological characteristics[99]. MCNs primarily affect female patients and are histologically defined by the presence of ovarian-type stroma[100]. This stromal component has raised hypotheses regarding a non-pancreatic origin, potentially explaining the female predominance and localization to the pancreatic tail. Despite the low malignancy rate of MCNs, the prognosis for MCN-associated PDAC remains poor compared to non-MCN-associated PDAC, highlighting the critical need for early detection and personalized management strategies[101].

MCNs exhibit a distinct genetic profile dominated by mutations in *KRAS, TP53*, and *RNF43*[102]. *GNAS* mutations are uncommon in MCNs compared to IPMNs, and the co-detection of *KRAS* and *GNAS* mutations offers limited specificity in distinguishing MCNs from IPMNs[103]. Cyst fluid carcinoembryonic antigen (CEA) demonstrates higher diagnostic value among markers than *KRAS or GNAS* mutations[102]. High-grade or invasive MCNs frequently harbor mutations associated with PDAC, including *TP53* and *SMAD4*, which are strongly linked to malignant transformation[103]. *KRAS* mutations are considered a hallmark of MCNs and have been identified in up to 83% of recurrent cases[104]. *KRAS* mutations can be extensively detected in both mucinous and non-mucinous lining epithelium[105]. Moreover, identical *KRAS* mutations have been observed in both low- and high-grade regions of individual tumors, indicating their early role in tumorigenesis and potential contribution to tumor progression[106]. An analysis of 36 MCN cases found that while *SMAD4* expression was preserved in low- and high-grade dysplastic lesions, it was lost in 86% of invasive carcinoma cases, with this loss as a late-stage disease marker[107]. Approximately, half of invasive MCNs exhibit *SMAD4* loss, whereas benign MCNs do not[108,109]. Notably, ovarian-type stromal cells within MCNs do not exhibit *SMAD4* loss, suggesting their non-neoplastic property[110]. Co-expression of $KRAS^{G12D}$ and *SMAD4* haploinsufficiency promotes the progression of MCNs to invasive ductal adenocarcinoma, marked by *SMAD4 l*oss of heterozygosity and mutations in *TP53* or *CDKN2A*, highlighting their cooperative role in malignancy[111]. *TP53* mutations and *CDKN2A* loss are common in high-grade MCNs but absent in low-grade lesions, correlating with advanced disease stages and increased malignant potential[112]. Overexpression of *TP53*, often accompanied by *KRAS* mutations, is a late event restricted to carcinomas[113]. Murine models with adenomatous polyposis coli haploinsufficiency and *TP53* deletion develop MCNs with pathology identical to human disease, including stromal secretion of cyst fluid

and metastatic potential, further validating these findings[114]. *RNF43* mutations are predominantly observed in non-invasive MCNs, suggesting their involvement in the early stages of tumorigenesis[83]. Chromosomal instability induced by von Hippel-Lindau *(VHL)* mutation can be observed in around 17% of MCNs, suggesting a role in tumor progression[115]. Wnt/β-catenin signaling, predominantly active in the ovarian-type stroma but absent in the epithelial lining, plays a critical role in MCN development, underscoring the importance of stromal–epithelial interactions in tumorigenesis[116]. The genomic landscape of MCNs is dominated mainly by early *KRAS* mutations, with malignant progression driven by subsequent alterations in *TP53, CDKN2A*, and *SMAD4*. The ovarian-type stroma plays a pivotal role in this process, mediated partly by Wnt/β-catenin signaling, underscoring the importance of epithelial-stromal interactions in MCN pathogenesis (Fig. 4).

SCNs or SCAs

Serous cystic neoplasms, also known as serous cystadenomas, are benign epithelial neoplasms comprising approximately 11–16% of pancreatic cystic lesions and 1–2% of all pancreatic tumors[117]. They predominantly occur in older women, with a female-to-male ratio of 2:1, and are typically diagnosed in the sixth to seventh decade of life. Histologically, SCNs consist of glycogen-rich, cuboidal, or flattened non-mucinous epithelial cells exhibiting a clear cytoplasm. The glycogen-rich epithelium, PAS-positive and diastase-sensitive, is typically associated with a dense capillary network, contributing to the distinct histopathological appearance of SCNs[118,119]. Genetically, SCNs exhibit greater stability compared to other PCNs. Although *RNF43* mutations are infrequent, they can impact Wnt signaling. Additional gene alterations such as *VHL, TP53*, and telomerase reverse transcriptase further shape the genomic landscape of SCNs[17,115]. Serous cystic neoplasms are strongly associated with VHL syndrome and often present at a younger age in affected individuals, indicating a hereditary predisposition[119]. While sporadic SCNs may harbor *VHL* mutations, approximately 12% occur in patients with VHL syndrome[120,121]. Loss of heterozygosity at this locus is a defining feature, with *VHL* mutations detected in approximately 50% of tissue samples and 75% of cyst fluid specimens[122,123]. Mechanistically, growth factor pathways like EGFR and MAPK signaling are frequently activated in SCNs, which play an essential role in SCNs development[124]. *VHL* mutation-driven vascular endothelial growth factor (VEGF) upregulation and angiogenesis activation represent sensitive and specific biomarkers for SCN diagnosis[125]. In summary, SCNs develop through a multistep process driven by the loss of tumor suppressor genes, particularly *VHL*, which disrupts angiogenesis and cell regulation. Additional mutations in growth and survival pathways contribute to tumor progression, with somatic and inherited alterations playing key roles in SCN pathogenesis. Nevertheless, SCNs have a low risk of malignant transformation and typically follow a benign clinical course. Rare malignant transformations are associated with mutations in *TP53, PTEN*, and *KRAS*, key regulators of cell cycle progression and apoptosis[17,126,127]. These genetic alterations may disrupt normal cellular functions, facilitating the rare progression of SCNs from benign to malignant states despite their overall benign nature (Fig. 4).

Tissue and cyst fluid sequencing of PCNs for gene mutation insights

Recent advances in liquid biopsy and high-throughput sequencing technologies have enabled detailed molecular characterization of PCNs using both cystic tissue and cyst fluid. Cyst fluid obtained via endoscopic ultrasound-guided fine needle

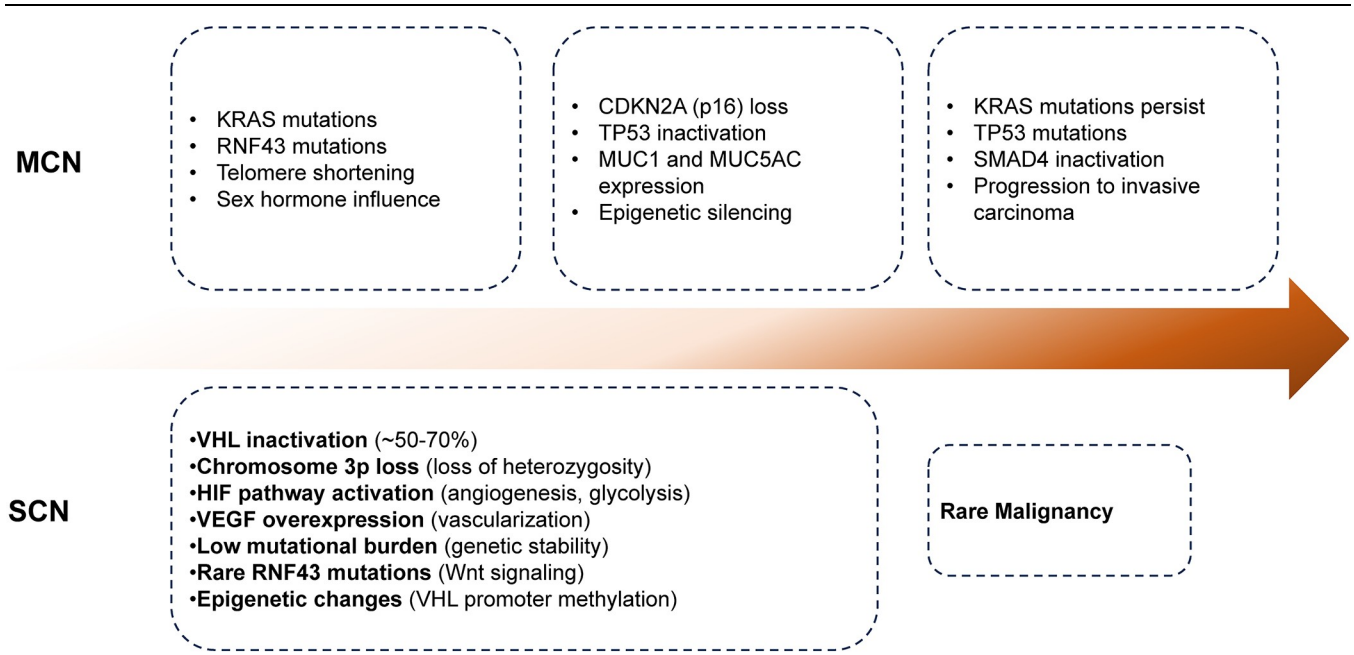


Figure 4. Genetic and molecular alteration in MCN and SCN development.

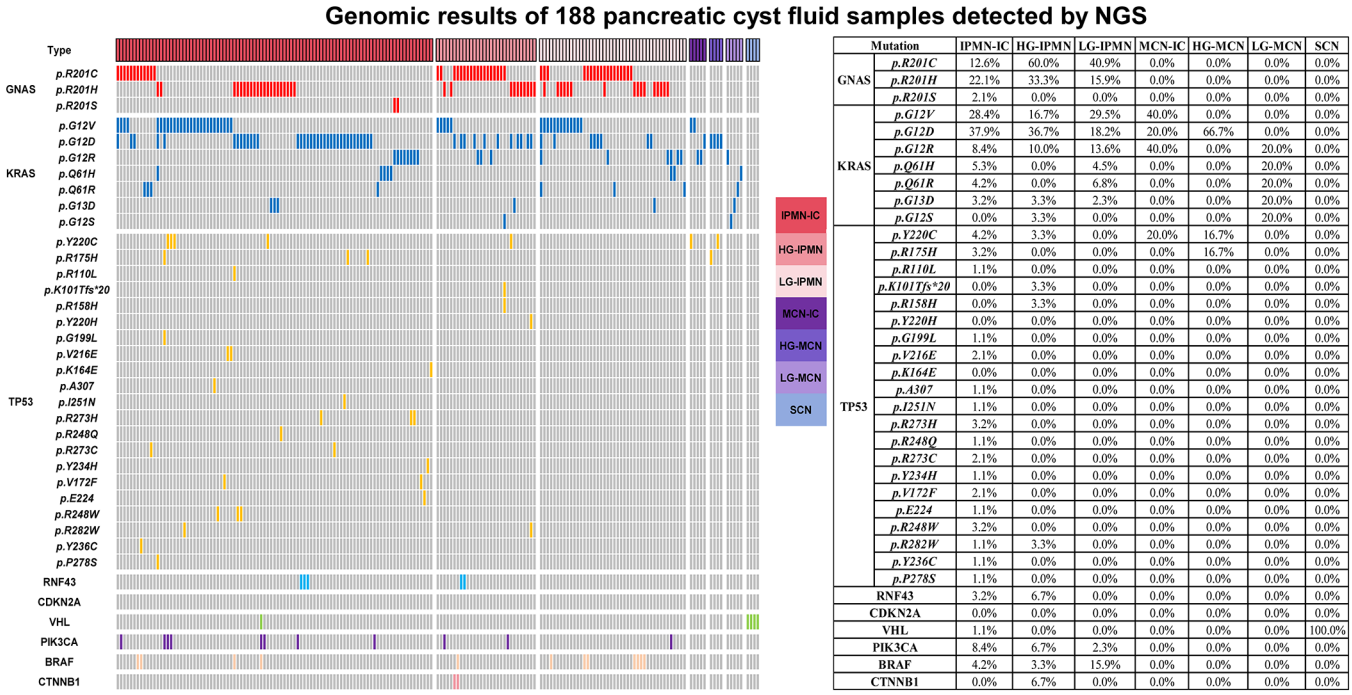
aspiration (EUS-FNA) offers a minimally invasive source of tumor-derived nucleic acids, suitable for molecular analysis before surgery. Multiple studies have employed a range of sequencing platforms, including polymerase chain reaction, NGS, whole-exome sequencing (WES), and whole-genome sequencing (WGS), to identify genetic alterations in PCNs. This review compiled data from seven studies encompassing 297 patients, including 104 cyst tissue samples and 187 cyst fluid samples after quality control. Mutational profiles from these cohorts are summarized in the accompanying heatmaps (Figs 5 and 6), offering a comparative overview of genetic alterations across major cyst subtypes, including IPMN, MCN, SCN, and PDAC[43,83,122,128].

Figure 5 illustrates the distinct mutation signatures associated with different PCN subtypes. *GNAS* and *KRAS* mutations are frequently observed in IPMNs, with *GNAS* alterations predominantly at R201C and R201H and KRAS clustered at G12V, G12D, and G12R, reflecting their strong oncogenic selection. *TP53* and *RNF43* mutations occur less frequently and are more variably distributed, suggesting a later role in neoplastic progression. In contrast, MCNs show high *KRAS* mutation rates but minimal *TP53* or *GNAS* alterations, supporting a separate molecular pathogenesis. Serous cystic neoplasms are characterized almost exclusively by *VHL* mutations, consistent with their benign and non-mucinous identity. These data support subtype-specific mutation profiles for classification and risk stratification. The mutation spectrum demonstrates apparent subtype specificity across tissue samples. IPMN-IC and HG-IPMN exhibit the highest prevalence of co-occurring *KRAS* and *GNAS* mutations, often exceeding 60%, underscoring their cooperative role in mucinous tumorigenesis. TP53 mutations, especially p.R175H, p.P152L, and p.R273C, are enriched in PDAC and high-grade IPMNs, reflecting progression toward invasive disease. MCNs show a *KRAS*-dominant profile without *GNAS* and *TP53*, while SCNs consistently harbor *VHL* mutations (100%), reinforcing their genomic and biological distinction from mucinous lesions.

Figure 6 summarizes the mutation landscape of 188 cyst fluid samples, which generally mirror tissue findings but also reveal significant differences[17,129]. *KRAS* mutations, particularly p.G12D and p.G12V, remain the most common across mucinous subtypes, while *GNAS* mutations at R201C and R201H are highly enriched in IPMNs. Notably, *TP53* mutations appear at relatively higher frequencies in fluid than in matched tissue, especially in IPMN-IC and MCN-IC, suggesting that fluid-derived DNA may more sensitively capture early neoplastic transformation. This discrepancy may be attributed to the release of DNA from apoptotic or exfoliated high-risk epithelial cells into the cystic cavity, thereby enhancing the detection of early clonal alterations. In contrast, *RNF43* mutations are markedly underrepresented in fluid samples, likely due to low allelic fractions or sampling bias. These observations highlight the value of cyst fluid as a dynamic biospecimen that reflects both clonal architecture and epithelial shedding.

Mutation		PDAC	IPMN-IC	HG-IPMN	LG-IPMN	HG-MCN	LG-MCN	SCN
GNAS	*p.R201C*	0.0%	33.3%	46.9%	25.0%	0.0%	0.0%	0.0%
	p.R201H	40.0%	0.0%	28.4%	25.0%	0.0%	0.0%	0.0%
	p.R201S	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.Q227E	0.0%	0.0%	2.5%	0.0%	0.0%	0.0%	0.0%
	p.Q870L	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.I774I	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.D464N	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
KRAS	*p.G12V*	20.0%	66.7%	28.4%	25.0%	42.9%	0%	0%
	p.G12D	40.0%	0.0%	30.9%	25.0%	14.3%	33.3%	0.0%
	p.G12R	40.0%	0.0%	13.6%	0.0%	14.3%	0.0%	0.0%
	p.G12C	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.Q61H	20.0%	0.0%	6.2%	0.0%	0.0%	0.0%	0.0%
	p.Q61R	0.0%	0.0%	2.5%	0.0%	0.0%	0.0%	0.0%
	p.G13D	20.0%	33.3%	0.0%	25.0%	0.0%	0.0%	0.0%
	p.G12S	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.A146V	0.0%	0.0%	3.7%	0.0%	0.0%	0.0%	0.0%
	*p.L120**	0.0%	0.0%	0.0%	0.0%	14.3%	0.0%	0.0%
TP53	*p.R175H*	33.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.P72R	0.0%	33.3%	2.5%	0.0%	0.0%	0.0%	0.0%
	*p.R342**	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.R273H	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.R306X	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.R248Q	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R273C	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.L369M	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.V172D	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.P152L	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.D208A	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R337L	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.S106R	0.0%	0.0%	0.0%	0.0%	14.3%	0.0%	0.0%
	p.C242fs	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	*p.E171**	20.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.H214fs	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.I195N	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.V272L	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.M237I	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
	p.R213R	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%
RNF43		0.0%	66.7%	27.2%	0.0%	28.6%	0.0%	0.0%
SMAD4		0.0%	66.7%	8.6%	0.0%	14.3%	0.0%	0.0%
CDKN2A		0.0%	66.7%	9.9%	0.0%	0.0%	0.0%	0.0%
VHL		0.0%	0.0%	0.0%	0.0%	0.0%	66.7%	100.0%
PIK3CA		0.0%	0.0%	4.9%	0.0%	14.3%	0.0%	0.0%
ATM		60.0%	0.0%	2.5%	0.0%	0.0%	0.0%	0.0%
BRAF		20.0%	0.0%	3.7%	0.0%	0.0%	0.0%	0.0%
CTNNB1		0.0%	0.0%	4.9%	0.0%	0.0%	0.0%	0.0%

Figure 5. Genomic results of 104 PCN tissue samples based on NGS detection.



Mutation		IPMN-IC	HG-IPMN	LG-IPMN	MCN-IC	HG-MCN	LG-MCN	SCN
GNAS	*p.R201C*	12.6%	60.0%	40.9%	0.0%	0.0%	0.0%	0.0%
	p.R201H	22.1%	33.3%	15.9%	0.0%	0.0%	0.0%	0.0%
	p.R201S	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
KRAS	*p.G12V*	28.4%	16.7%	29.5%	40.0%	0.0%	0.0%	0.0%
	p.G12D	37.9%	36.7%	18.2%	20.0%	66.7%	0.0%	0.0%
	p.G12R	8.4%	10.0%	13.6%	40.0%	0.0%	20.0%	0.0%
	p.Q61H	5.3%	0.0%	4.5%	0.0%	0.0%	20.0%	0.0%
	p.Q61R	4.2%	0.0%	6.8%	0.0%	0.0%	20.0%	0.0%
	p.G13D	3.2%	3.3%	2.3%	0.0%	0.0%	20.0%	0.0%
	p.G12S	0.0%	3.3%	0.0%	0.0%	0.0%	20.0%	0.0%
TP53	*p.Y220C*	4.2%	3.3%	0.0%	20.0%	16.7%	0.0%	0.0%
	p.R175H	3.2%	0.0%	0.0%	0.0%	16.7%	0.0%	0.0%
	p.R110L	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	*p.K101Tfs*20*	0.0%	3.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R158H	0.0%	3.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.Y220H	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.G199L	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.V216E	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.K164E	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.A307	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.I251N	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R273H	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R248Q	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R273C	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.Y234H	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.V172F	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.E224	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R248W	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.R282W	1.1%	3.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.Y236C	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	p.P278S	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
RNF43		3.2%	6.7%	0.0%	0.0%	0.0%	0.0%	0.0%
CDKN2A		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
VHL		1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
PIK3CA		8.4%	6.7%	2.3%	0.0%	0.0%	0.0%	0.0%
BRAF		4.2%	3.3%	15.9%	0.0%	0.0%	0.0%	0.0%
CTNNB1		0.0%	6.7%	0.0%	0.0%	0.0%	0.0%	0.0%

Figure 6. Genomic results of 187 pancreatic cystic fluid samples detected by NGS.

Despite the promising diagnostic utility of cyst fluid-based genomic profiling in PCNs, multiple technical and pre-analytical limitations challenge its reliable clinical application. The inherent biological properties of cyst fluid, such as low and variable concentrations of cell-free DNA (cfDNA), particularly in low-grade, serous, or acellular lesions, often result in insufficient input material for robust sequencing, thereby compromising assay sensitivity and increasing the likelihood of false-negative results[122,130]. Contamination during EUS-FNA procedures, including the inadvertent introduction of blood or gastrointestinal epithelial cells, further dilutes neoplastic DNA and may obscure low-frequency driver mutations. Moreover, substantial discordance between fluid- and tissue-derived genomic profiles has been observed, especially for subclonal or low-allele-frequency variants, reflecting both spatial heterogeneity and sampling bias[128,129]. Compounding these issues are the marked inter-institutional variations in sample collection techniques, DNA extraction protocols, stabilization reagents, input thresholds, and bioinformatic pipelines, all of which contribute to inconsistent mutation detection and poor cross-study reproducibility. For instance, the reported prevalence of *RNF43* mutations in IPMNs ranges from 14% to 75% across studies, underscoring the combined influence of biological variability and technical heterogeneity[44,82]. To ensure analytic validity and clinical translatability, standardized workflows are urgently needed. It includes rigorous quality control measures such as DNA quantification, replication and orthogonal validation of variants, and harmonized thresholds for variant calling. Establishing consensus protocols for cyst fluid processing and genomic interpretation will be pivotal to advancing the integration of molecular diagnostics into routine risk stratification and decision-making for PCNs.

The choice of sequencing platform also influences the analytical performance. Targeted panels focusing on *KRAS* and *GNAS* provide high specificity for mucinous cysts but may miss high-grade lesions. Broader panels incorporating *TP53, SMAD4*, or *PIK3CA* improve sensitivity for detecting advanced neoplasia but increase the risk of identifying variants of uncertain significance. Newer techniques such as digital droplet polymerase chain reaction, MASSARRAY, WES, and WGS allow greater flexibility in assay depth and coverage[128]. Therefore, platform selection should be tailored to the clinical context to optimize diagnostic yield. Equally important are robust quality control protocols, including DNA quantification, replicate testing, and orthogonal validation, to ensure reproducibility. Building on these developments, novel molecular technologies are poised to enhance the resolution and scalability of cyst-based diagnostics. The single-molecule bio-electronic smart system platform, which integrates a three-dimensional-printed sensor gate for simultaneous DNA and protein detection, represents a promising non-invasive and ultra-sensitive tool for PCN diagnostics[131]. Although still under development, early validation studies suggest its feasibility for ultrasensitive multiplex detection in cystic lesions. Integration of NGS with immunophenotyping and histopathology provides multi-dimensional insights into tumor biology[132]. Expanded sequencing panels now include both somatic and germline variants in genes such as *KRAS, TP53, CDKN2A*, and *SMAD4*[133]. Future implementation will benefit from the modular use of platforms based on diagnostic needs. As cohort sizes increase and molecular workflows become standardized, harmonized protocols and refined biomarker panels will be critical for the widespread adoption of precision diagnostics in PCNs[134].

Genetic diagnosis and risk stratification in PCNs

Diagnostic performance of genomic alterations in PCNs

The accurate preoperative distinction between low- and high-risk cysts, particularly mucinous versus non-mucinous, is essential to avoid overtreatment and missed malignancy. Given the limitations of imaging and cytology, molecular diagnostics have become a critical adjunct. Among available substrates, cyst fluid obtained via EUS-guided FNA remains the diagnostic standard, as it directly samples the epithelial source. Emerging sequencing technologies extend beyond genomics to transcriptomic and proteomic profiling, fueling the exploration of novel diagnostic biomarkers. Table 1 summarizes the diagnostic performance of key genetic markers detected in cyst fluid, although inter-study variation highlights the need for standardized reporting and validation. A single EUS-FNA-derived sample can simultaneously support molecular, biochemical, and cytologic evaluations, allowing parallel NGS, CEA quantification, and cytology[135]. Notably, NGS has reclassified up to 19% of cysts previously deemed benign as mucinous lesions harboring high-risk mutations, directly altering clinical management; however, the generalizability of these findings requires larger multicenter validation[136]. Among these, activating mutations in *KRAS* and *GNAS* serve as definitive molecular signatures of mucin-producing cysts, with reported sensitivities exceeding 65% and specificities over 70% across multiple studies[97,123,135–144]. When combined with cyst fluid CEA analysis, diagnostic performance improves substantially, raising sensitivity from approximately 71% to 92.9% while maintaining specificity around 85%, thereby enhancing mucinous classification even in CEA-negative or cytologically indeterminate cases[123,136,140,145–148]. Compared with cytology, which has limited sensitivity but moderate-to-high specificity, molecular testing of cyst fluid offers markedly greater diagnostic accuracy[17,97,130,135,140–143,145,149]. Moreover, microforceps biopsy (MFB) provides histologic confirmation with sensitivities ranging from 68% to 85.7% and specificity as high as 100%, though it remains more invasive and technically demanding[143,150,151]. Although cytology and MFB offer the advantage of direct cellular or tissue assessment, their diagnostic success depends on sampling adequacy and operator expertise, resulting in relatively low detection rates in routine practice. These methods offer high specificity and serve as key confirmatory tools in diagnosing pancreatic cysts, but their broader adoption is

Table 1

Diagnostic Performance of Cyst Fluid and Imaging Modalities in Differentiating Pancreatic Cyst Types and Malignancy Risk

Comparisons		Gene/Panel	Sample Type	Sensitivity	Specificity	PPV	NPV	Reference
Mucinous vs. Non-mucinous		CEA	Cyst fluid	42.1–72%	63–100%	83–100%	70–84%	[97,130,135,142,145]
		Cytology	Cyst fluid	38.1–61%	76–94.7%	58–88%	60–90%	[130,143,145,149]
		GNAS	Cyst fluid	36–56%	80–100%	70–96%	72–94%	[136,142]
		KRAS	Cyst fluid	43–100%	62–100%	66–98%	75–99%	[136,142–144]
		KRAS or/and GNAS	Cyst fluid	65–100%	70–100%	79–97%	81–98%	[17,97,130,135,140–142,145,149]
		KRAS or/and GNAS + CEA	Cyst fluid	71%–92.9%	87.2–96.3%	85–98%	82–97%	[123,136,145]
		Microforceps Biopsy	Cyst wall tissue	68%–85.7%	90–100%	85–99%	83–98%	[143,150,151]
		CT	Image	36–71%	64–100%	63.2–76.4%	47.2–63.2%	[205–207]
		MRI	Image	56–76%	74–90%	55–86%	47–74%	[205–207]
		EUS (morphology)	Image	75–88.9%	64.4–86.1%	80–85%	80–86%	[205–208]
		CA199	Serum	35–59%	86–91%	47–88%	48–75%	[209–211]
Advanced neoplasia vs. Benign/Low-grade cyst		Cytology	Cyst fluid	29.3–55%	90–100%	71–96%	52–78%	[17,97,123,145,153]
		KRAS or/and GNAS	Cyst fluid	42–78%	62–99%	63–93%	60–89%	[141,144,145,154]
		KRAS or/and GNAS + Advanced mutations	Cyst fluid	72–93%	80%–99%	76–98%	79–96%	[17,129,135,136,153]
		Cytology + KRAS or/and GNAS	Cyst fluid	62–92%	50–70%	64–85%	61–87%	[17,97,123,145,153]
		CT	Image	57.7–69.2%	63.9–83.3%	58.1–73.9%	70.3–76.9%	[212,213]
		MRI	Image	65.4–76.9%	58.3–88.9%	57.1–81%	74.3–78%	[212,213]
		EUS (morphology)	Image	60–81%	60–85%	55–80%	64–90%	[208,214]
		CA199	Serum	50–85%	76–90%	60–89%	65-–92%	[210,211,215]
PCN types	IPMN	CEA	Cyst fluid	47%—72%	63–100%	60–89%	55–88%	[123,143,144,159]
		KRAS	Cyst fluid	52%–70%	88–100%	70–96%	66–93%	[123,135,141,159]
		GNAS	Cyst fluid	31–51%	96–100%	80–98%	74–97%	[135,141,143,153,159]
		KRAS or/and GNAS + CEA	Cyst fluid	68.5–84%	89.9–98%	86–97%	81–94%	[135,136,141,143,159]
	MCN	KRAS or/and GNAS	Cyst Fluid	0%–65% (GNAS detection in MCN is rarely low)	65%–100%	35–70%	60–85%	[123,135,159]
	SCN	VHL	Cyst fluid	25–71%	99–100%	90–100%	78–95%	[17,160]
		Cytology	Cyst fluid	2%–3%	Not specified	-	-	[160]
		KRAS or/and GNAS	Cyst fluid	0%	0%	-	-	[160]
	CT		Image	40–68%	48–75%	36–67%	50–78%	[216,217]
	MRI		Image	54–89%	60–87%	55–84%	59–90%	[216,217]
	EUS (Morphology)		Image	60–91%	70–94%	65–92%	64–93%	[216–218]

Reported sensitivity and specificity represent the full ranges directly reported in the original publications, rather than recalculated from pooled raw data. PPV and NPV values are study- and cohort-dependent and reflect the estimated ranges under moderate disease prevalence. Advanced mutations refer to TP53, SMAD4, PIK3CA, PTEN, AKT1, mTOR, and CTNNB1 alterations as consistently associated with high-grade dysplasia or invasive carcinoma. All molecular data were obtained from cyst fluid via EUS-FNA unless otherwise noted. Combined diagnostic panels reflect multimodal approaches as reported in the original studies.

hindered by limited prospective validation and lack of standardized workflows.

Detecting advanced mutations associated with progression and malignancy offers a broader diagnostic spectrum when distinguishing benign or low-grade cysts from high-grade or invasive ones. Traditional indicators such as mural nodules, ductal dilation, and cytology exhibit limited sensitivity and variable specificity, with AGA guidelines missing up to 45% of high-grade or malignant IPMNs despite an overall sensitivity of only 62%[97,152]. Cytological analysis of cyst fluid, though precise (90–100%), suffers from low sensitivity (29.3–55%) due to frequent inadequacy in sampling atypical or malignant cells[17,97,123,145,153]. In contrast, detecting *KRAS* and/or *GNAS* mutations demonstrates moderately improved sensitivity (42–78%) and a broader specificity range (62–99%). Still, these alterations alone do not reliably distinguish between indolent and aggressive mucinous lesions[141,144,145,154]. To overcome this limitation, incorporating additional advanced mutations, such as *TP53, RNF43, SMAD4*, or *PIK3CA*, alongside *KRAS*/*GNAS* significantly enhances diagnostic performance[97,155]. This combined molecular panel achieves a 72–93% sensitivity and specificity of 80–99% for identifying advanced neoplasia[17,129,135,136,153], offering a more refined molecular stratification of cystic neoplasms. While combining cytology with *KRAS*/*GNAS* mutation analysis may raise sensitivity to as high as 92%, its specificity often declines to 50–70% due to the additive effect of less specific findings[17,97,123,145,153]. Beyond this, epigenetic markers such as methylated *TBX15* and *SOX17* have shown utility in dysplasia grading, and additional gene signatures are consistently being identified, further enhancing the future diagnostic potential of cyst fluid sequencing[95,110,156].

Beyond risk stratification, molecular profiling enables precise differentiation among PCN subtypes, offering diagnostic specificity that surpasses traditional imaging or cytology. *GNAS* mutations are particular for IPMNs, occurring in approximately 50–70% of cases but rarely in MCNs or non-mucinous lesions[153,157,158]. In contrast, *KRAS* mutations are present in both IPMNs and MCNs, indicating a mucinous lineage without subtype distinction[123,158]. *KRAS* and *GNAS* mutations are hallmark genetic alterations, detected in approximately 52–70% and 31–51% of cases, respectively, with high specificity for IPMN over non-IPMN lesions (88–100% and 96–100%)[135,141,143,153,159]. Combined with CEA analysis, the diagnostic performance improves substantially, yielding 68.5–84% sensitivities and specificities up to 98%[135,136,141,143,159]. In contrast, MCNs rarely harbor *GNAS* mutations, and the presence of *KRAS* mutations alone remains inconsistent, with reported sensitivities ranging from 0% to 65%[123,135,159], limiting the utility of these markers for reliably distinguishing MCNs from other subtypes. Conversely, *VHL* gene alterations are virtually pathognomonic for SCNs, occurring in most cases and rarely in other cyst types[17,138]. For SCNs, *VHL* mutations are the most characteristic molecular feature, with sensitivities between 25% and 71% and exceptional specificity[17,160]. A *VHL*-mutated cyst, particularly when accompanied by low CEA and glycogen-rich fluid, can be confidently diagnosed as SCN, thereby avoiding unnecessary surveillance or surgery[161]. In addition, a combination of biochemical markers, including VEGF, glucose, CEA, and amylase, achieves diagnostic accuracy approaching 93–100% sensitivity and 83.7–100% specificity for SCN identification[160]. Cytology and common oncogenic mutations (*KRAS, GNAS*) are typically absent in SCNs[160], further supporting the specificity of this molecular signature. Other cystic lesions, such as SPNs and cystic NETs, often exhibit distinct imaging features and are frequently diagnosable based on clinical and radiologic criteria alone. Solid pseudopapillary neoplasms are commonly characterized by somatic mutations in the *CTNNB1* gene, which encodes β-catenin, and this alteration is considered highly specific for this entity[17]. Cystic NETs may harbor alterations in genes such as *MEN1, DAXX*, or *ATRX*, aligning with the genomic landscape of their solid counterparts[160]. Although these subtypes are less common, incorporating such molecular profiles into the diagnostic algorithm further refines cyst classification, particularly in ambiguous or non-mucinous cases, and facilitates more targeted clinical management. Additionally, among these molecular classifiers, *GNAS* (for IPMN) and *VHL* (for SCN) have demonstrated remarkably consistent diagnostic performance across studies, with high specificity and reproducibility, even in multicenter cohorts. Their detection enables confident subtype assignment, especially when integrated with cyst fluid CEA and biochemical markers. While broader NGS panels incorporating mutations such as *TP53, SMAD4*, or *PIK3CA* offer enhanced sensitivity for high-grade dysplasia, their performance may vary depending on sample quality, sequencing depth, and interpretive criteria. Thus, despite ongoing advances, few molecular markers have yet achieved universal standardization. Our discussion and summary table emphasize those genetic alterations with the strongest evidence base, clinical reproducibility, and additive value over imaging and cytology in differentiating mucinous cysts and guiding surgical decision-making.

While cyst fluid remains the most established and informative biospecimen for molecular diagnosis of PCNs, other sample types, including pancreatic juice and peripheral blood, are being increasingly investigated. Cyst fluid allows direct access to lesion-derived DNA, yielding high sensitivity (50–80%) and specificity (up to 95–100%) for detecting *KRAS* or *GNAS* mutations in mucinous cysts[135,162,163]. When cyst fluid is unobtainable or non-diagnostic, pancreatic juice collected endoscopically after secretin stimulation offers a viable alternative. Although target DNA in pancreatic juice is more dilute due to sampling the entire ductal system rather than a specific cyst, it excels at detecting field changes associated with high-grade dysplasia or early malignancy[164,165]. In prospective surveillance cohorts, combined detection of *TP53, PIK3CA*, and *PTEN* mutations in pancreatic juice achieved sensitivities in the low 70% range and specificities exceeding 95% for advanced neoplasia[166,167]. Resected tissue provides the histological reference standard and has been instrumental in identifying driver mutations. Low-grade dysplasia is typically associated with *KRAS* and *GNAS* mutations, whereas high-grade dysplasia or invasive carcinoma often harbors alterations in *TP53, SMAD4, CDKN2A*, and *PIK3CA*[136,168,169]. However, tissue analysis is retrospective and has limited utility in preoperative decision-making. Recent advances in liquid biopsy have also enabled peripheral blood to be a minimally invasive medium for detecting circulating cfDNA and extracellular vesicles containing key mutations. Studies have demonstrated high concordance between plasma-derived and cyst fluid-derived profiles for *KRAS, GNAS*, and *TP53* mutations[170–172]. Ultra-deep sequencing of cfDNA has shown promise in identifying oncogenic mutations months before radiographic progression, potentially supporting real-time monitoring of high-risk cysts.

As validation from large-scale studies progresses, blood-based testing may supplement or even partially replace invasive procedures such as EUS-FNA in selected cases. All in all, cyst fluid, pancreatic juice, and blood represent complementary diagnostic matrices: cyst fluid offers lineage-defining information, juice enables early detection of progression, and plasma provides a minimally invasive tool for surveillance.

While traditional modalities, cross-sectional imaging, cyst fluid CEA, and cytology remain foundational in the diagnostic triage of PCNs, their limited sensitivity, interobserver variability, and subtype ambiguity constrain clinical accuracy. International guidelines such as Fukuoka (2017) and Kyoto (2024) still rely on morphological features like cyst size ≥3 cm, mural nodules ≥5 mm, and main duct dilation >5–10 mm to guide surgical decision-making, yet these features offer only moderate predictive value and suffer from considerable variability, particularly in branch duct lesions[173,174]. Similarly, cyst fluid CEA and cytology provide high specificity but limited sensitivity, often failing to detect early or subtle neoplastic changes[130,146]. In this context, NGS of cyst fluid serves as a powerful diagnostic adjunct by directly identifying key genomic alterations, thereby enabling more accurate lineage classification, subtype distinction, and dysplasia grading, clearly outperforming conventional markers such as CEA and cytology[17,129]. A systematic review further confirmed the superiority of *KRAS/GNAS* mutations over CEA in mucinous differentiation[143], while *VHL* and *CTNNB1* mutations remain highly specific for SCNs and SPNs, respectively[138,175,176]. Importantly, the presence of high-risk mutations in morphologically low-risk cysts can upstage management toward resection. At the same time, their absence in radiologically suspicious lesions may justify conservative surveillance in high-risk surgical candidates[129]. Rather than replacing traditional tools, molecular diagnostics complement and refine them, forming a biologically informed, stepwise strategy that aligns diagnostic precision with clinical management goals. As validation expands and accessibility improves, integrated molecular testing is poised to redefine standard care in PCN evaluation, minimizing overtreatment, reducing missed malignancies, and enabling truly personalized decision-making. Although several studies have reported promising sensitivity and specificity for advanced molecular panels, large-scale prospective validation across multiple centers remains limited, underscoring the need for standardized workflows before broad clinical adoption.

Genomic-guided risk stratification and clinical decision-making

Current international guidelines offer varying thresholds for surgical intervention, reflecting ongoing uncertainty and contributing to heterogeneity in the management of PCNs. The 2015 AGA guideline adopts a conservative stance, recommending resection only when a solid component and central pancreatic duct (MPD) dilation or positive cytology are present[177]. In contrast, the 2017 Fukuoka criteria, supported by ESGE, advocate for surgery in the presence of any high-risk stigmata, such as mural nodules ≥5 mm or MPD dilation >10 mm, and recommend EUS evaluation for worrisome features, including features such as cyst size ≥3 cm[2]. The 2018 ACG guideline emphasizes individualized decision-making, explicitly incorporating adjunct cyst fluid markers such as CEA and *KRAS/GNAS* mutations to improve diagnostic specificity[148,178]. The 2024 Kyoto consensus maintains the high-risk/worrisome feature model but incorporates emerging predictors such as cyst growth rate and new-onset diabetes[173]. Comprehensive genomic profiling remains inconsistently adopted despite these refinements, primarily due to concerns regarding accessibility, cost, limited prospective validation, and the lack of standardized, reproducible protocols across centers[179,180]. This divergence in recommendations has significant implications for clinical decision-making. While the Fukuoka/ESGE approach may lead to overtreatment, up to 75% of resected IPMNs harbor only low-grade dysplasia[181], and the stringent AGA criteria risk missing malignant lesions, particularly in morphologically indeterminate cysts[177,178]. Surveillance strategies also differ: the AGA allows surveillance discontinuation after 5 years of cyst stability, whereas Fukuoka, ACG, and ESGE recommend indefinite monitoring in surgically fit individuals[2,148,182]. These inconsistencies highlight the limitations of morphology-based algorithms and underscore the need for biologically informed stratification strategies.

Genomic profiling offers a more granular framework for assessing malignant potential. Lineage-defining mutations such as *KRAS* and *GNAS* reliably identify mucinous cysts and demonstrate superior diagnostic performance compared to CEA in direct comparative analyses[148,183]. In contrast, high-grade alterations, such as *TP53, SMAD4, CDKN2A, PIK3CA*, and *PTEN*, are strongly associated with high-grade dysplasia or invasive carcinoma and serve as molecular surrogates for surgical consideration[129,184]. Integrated classifiers such as the Stanford CompCyst model, which combines clinical, radiologic, cytologic, and molecular parameters, have shown the potential to reduce overtreatment while maintaining oncologic safety. However, their clinical utility still requires validation in real-world multicenter cohorts[185]. In clinical practice, discordance between imaging and molecular findings is common and often necessitates multidisciplinary adjudication. A small BD-IPMN lacking high-risk radiologic features but harboring a *TP53* mutation may still indicate the need for surgical resection. Conversely, a radiographically suspicious cyst limited to *KRAS* or *GNAS* mutations may be appropriate for surveillance. The 2018 ACG guideline explicitly endorses tumor board review in such scenarios to incorporate surgical risk, patient comorbidities, and preferences[148,178]. Registry data support the multidisciplinary approach, showing that high-risk molecular findings often guide surgical decisions, even in patients with guideline-low-risk imaging, and that many resected cases harbor histologically confirmed malignancy[186]. Conversely, patients with favorable molecular profiles may be safely observed despite resection-eligible imaging characteristics.

Molecular stratification also informs the management of non-mucinous cysts. Serous cystic neoplasms, confirmed by *VHL* mutation or classic imaging features, typically do not require long-term surveillance[161]. MCNs are considered premalignant and are generally resected if ≥4 cm (per ESGE), ≥ 3 cm (per Fukuoka), or when symptomatic[187–189]. Solid pseudopapillary neoplasms, characterized by *CTNNB1* mutations, are typically resected due to their malignant potential. Cystic pancreatic neuroendocrine tumors, frequently harboring *MEN1, DAXX*, or *ATRX* mutations, require individualized treatment strategies based on size, functionality, and clinical context[190].

This biology-informed management paradigm is schematically illustrated in Figure 7. Surgical intervention is prioritized for cysts exhibiting high-risk morphological or molecular

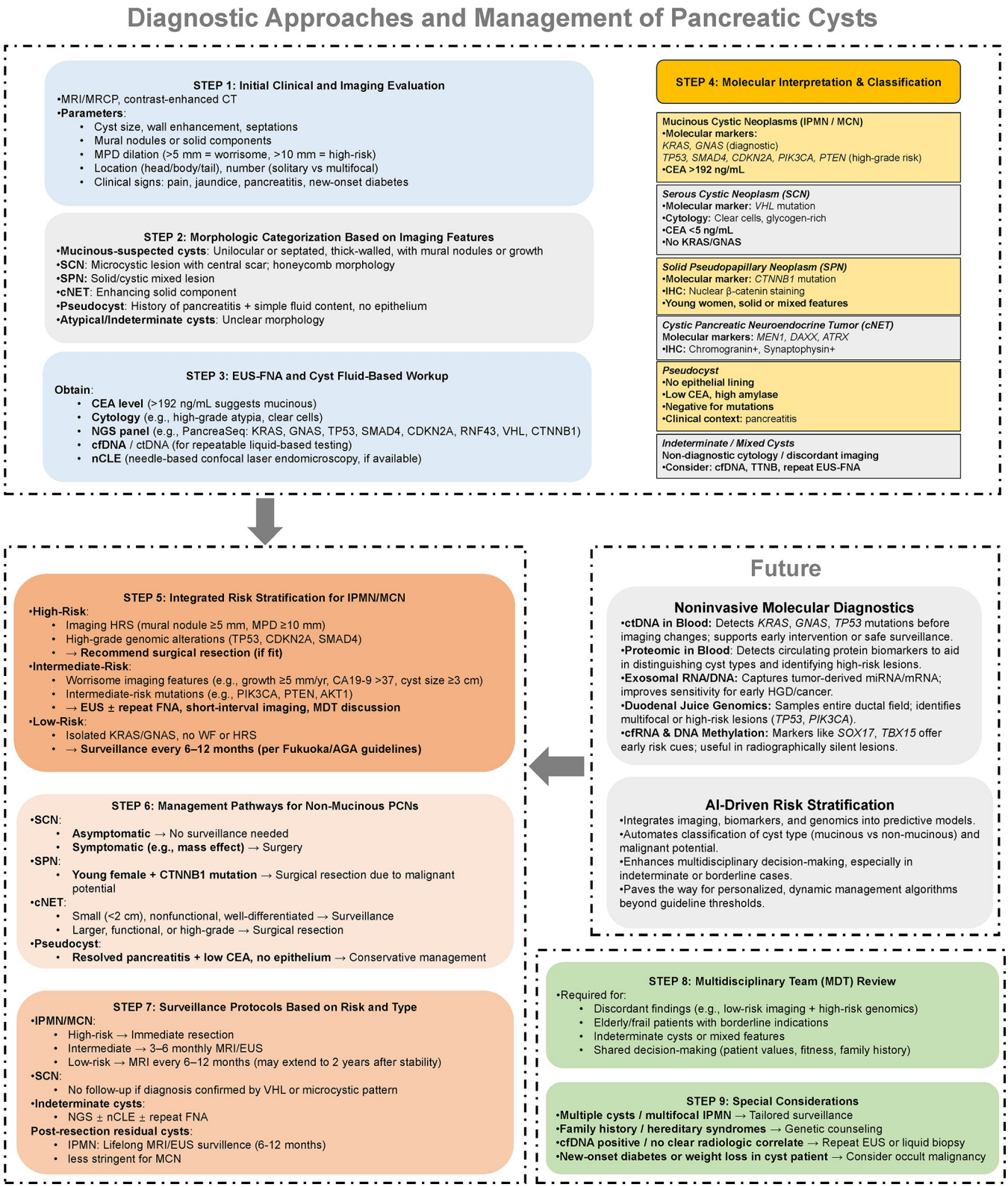


Figure 7. Diagnostic approaches and management of pancreatic cysts.

characteristics. In contrast, lesions with low-risk profiles are typically managed through surveillance protocols tailored to individual clinical contexts or determined via multidisciplinary consensus. Indeterminate cases characterized by equivocal imaging features or ambiguous molecular alterations may benefit from intensified surveillance with short-interval follow-up, repeat fluid aspiration, or expert panel adjudication. Cysts demonstrating low-grade mutational profiles and lacking high-risk clinical features are generally appropriate for long-term observation. Emerging adjunctive technologies, including confocal laser endomicroscopy, circulating tumor DNA analysis, duodenal fluid-based sequencing, and radiogenomic artificial intelligence, are expected further to enhance this risk-adapted framework[191–193]. Collectively, these developments signify a paradigm shift toward biologically informed management that facilitates early intervention in high-risk cysts while minimizing overtreatment in indolent cases. Integrating molecular diagnostics into clinical algorithms will depend on developing validated, standardized workflows supported by prospective multicenter trials to ensure reproducibility and clinical effectiveness.

Conclusions and perspectives

PCNs represent a heterogeneous group of lesions with distinct molecular trajectories and variable malignant potential, posing ongoing challenges for accurate risk stratification and individualized management. Nevertheless, significant advances have been made in characterizing the genomic landscape of PCNs; the clinical integration of genomic insights, particularly those derived from cyst fluid analysis, remains limited. Existing surveillance and clinical decision frameworks lack full integration of genotype-driven criteria, highlighting the need for prospective validation and standardized molecular diagnostic protocols.

Future research should prioritize the development of integrative diagnostic models that combine molecular, radiologic, cytologic, and clinical variables to enhance the precision of malignancy prediction. Emerging liquid biopsy technologies, such as cfDNA methylation profiling, proteins in the blood, duodenal fluid sequencing, and exosomal RNA analysis, provide minimally invasive and highly informative platforms for biomarker discovery. Furthermore, artificial intelligence has demonstrated substantial potential in the early detection of pancreatic cancer by capturing subtle imaging and clinical patterns beyond the resolution of conventional methods[194,195]. Concurrently, machine learning applied to large-scale clinical and genomic data enables more precise disease stratification and prognostic modeling[196,197]. These advances support the integration of artificial intelligence (AI)-driven, multi-platform analytics into the risk assessment and individualized management of PCNs.

Beyond diagnostic and risk-stratification applications, specific genomic alterations identified in PCNs may carry potential therapeutic implications, although their clinical utility remains mainly investigational. For example, *RNF43* loss-of-function mutations, frequently observed in IPMNs and MCNs, confer dependency on Wnt signaling and may sensitize neoplastic epithelium to Wnt pathway inhibition[198,199]. Early-phase clinical trials of PORCN inhibitors targeting Wnt/β-catenin signaling in gastrointestinal malignancies have demonstrated preliminary efficacy, providing a rationale for future exploration in high-risk PCNs harboring *RNF43* mutations[200,201]. Similarly, alterations in DNA damage response genes such as breast cancer type 1/2 susceptibility protein and ATM, while better established in pancreatic ductal adenocarcinoma, may suggest sensitivity to PARP inhibitors; extrapolation from the POLO trial and related studies supports this hypothesis, although no clinical trials have yet evaluated such agents in PCNs[202,203]. Additionally, activating mutations in PIK3CA, occasionally detected in mucinous neoplasms, engage the PI3K/AKT/mTOR axis and represent another tractable pathway for targeted intervention, supported by ongoing trials in other solid tumors[93,204]. While these therapeutic strategies are not currently integrated into PCN management algorithms, their potential reinforces the value of comprehensive molecular profiling for diagnosis and surveillance and as a foundation for future individualized treatment paradigms.

Moving forward, integrating validated molecular biomarkers into clinical algorithms, with evolving liquid biopsy platforms and AI-powered analytics, has the potential to transform PCN care. Realizing this vision will require interdisciplinary collaboration, technical standardization, and rigorous prospective validation to ensure that genomic insights translate into improved patient outcomes.

Ethical approval

This manuscript is a review article and does not involve the collection or analysis of new data from human or animal subjects. Therefore, no formal ethical approval was required.

Consent

No new patient or volunteer data were obtained for this review article. Hence, no consent was necessary or obtained.

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S.Y. and M.C.: writing – original draft. S.Y. and T.C.: writing – review and editing. M.C. and Y.H.: project administration. Y. H.: funding acquisition.

Conflicts of interest disclosure

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

Guarantor

S.Y. is the guarantor of this work and accepts full responsibility for the integrity of the manuscript and the decision to publish.

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